**Supplement**

**Table of Contents**

1. **Study Method Details**
2. **Dosing of Study Drugs**
3. **Study Definitions**
4. **Justification of the Non-inferiority Margin**
5. **Rationale for Exclusion of Participants from Site A**
6. **Supplement Table 1. Study populations.**
7. **Supplement Figure 1. Flow Diagram of Study Participants—CONSORT Criteria.**
8. **Supplement Table 2. Reasons for Study Ineligibility.**
9. **Supplement Figure 2. Comparison of Cumulative Lost to Follow-up by Treatment Regimen.**
10. **Supplement Figure 3. Difference of 3HP Arm from Active Control 9H Arm in Cumulative TB Rates and the 95% C.I. by MITT and PP Populations.**
11. **Supplement Table 3. All Grade 3 and 4 Adverse Events by Treatment Regimen and System Organ Classification.**
12. **Supplement Table 4. All Deaths by Treatment Regimen and ICD-9 Code.**
13. **Supplement Table 5. Tuberculosis cases and event rates by treatment arm and HIV serostatus.**
14. **Supplement Table 6. Tolerability by treatment arm and HIV serostatus.**
15. **Supplement Table 7/Figure 4. Results of the effectiveness, efficacy, and safety analyses with participants from one study site removed.**
16. **Supplement Table 8. Univariate and Multivariate Risk Factor Analysis for the Development of Tuberculosis (MITT Population)**
17. **Study Sites (Number of patients enrolled), Principal Investigators and Study Coordinators of the Tuberculosis Trials Consortium and the AIDS Clinical Trials Group for the PREVENT TB Trial (TBTC Study 26 / ACTG 5259)**

**Study Method Details**

Statistical analysis details:

Categorical variables were compared with the Pearson’s chi-squared test and continuous variables with the Wilcoxon rank-sum test. Tuberculosis rates were determined per 100 p-y of follow-up and as a cumulative rate (percentage). The difference in the cumulative tuberculosis rate by study arm, and the 95% confidence interval of the difference, were determined. The proportion of adverse events among all persons who received > 1 dose of study drug were compared by arm; for persons with > 1 event, only the first event was included. The average adverse event rate was also determined (number of events per 100 persons; included all adverse events). Univariate and multivariate risk factor analyses were performed to assess predictors of tuberculosis risk.

**Dosing of Study Drugs**

**3HP arm**

*Rifapentine:*

Persons weighing > 50.0 kg received rifapentine 900 mg once-weekly

Persons weighing < 50.0 kg were dosed once-weekly according to the following scale:

Weight Dose

10.0-14.0 kg 300 mg

14.1-25.0 kg 450 mg

25.1-32.0 kg 600 mg

32.1-50.0 kg 750 mg

*Isoniazid:*

Persons 2-11 years old received isoniazid 25 mg/kg (rounded up to the nearest 50 or 100 mg; 900 mg max) once-weekly

Persons > 12 years old received isoniazid 15 mg/kg (rounded up to nearest 50 or 100 mg; 900 mg max) once-weekly

**9H arm**

Persons 2-11 years old received isoniazid 10-15 mg/kg (round up to nearest 50 or 100 mg, 300 mg max) daily

Persons > 12 years old received isoniazid 5 mg/kg (rounded up to nearest 50 or 100 mg; 300 mg max) daily

Pyridoxine (vitamin B6) 50 mg with each dose of isoniazid was recommended for participants in both study arms but not required.

**Study Definitions**

Close contact with a tuberculosis case was defined as > 4 hours (by participant self-report or in the estimation of the site investigator) in a shared airspace during a one-week period.

A broad definition of flu-like and other systemic drug reactions was used: a) hypotension, urticaria, angioedema, acute bronchospasm, or conjunctivitis that occurred in relation to study drug; or b) > 4 of the following (one of which had to be > grade 2) that occurred in relation to study drug: weakness, fatigue, nausea, vomiting, headache, fever, aches, sweats, dizziness, shortness of breath, flushing, or chills.

**Justification of the Non-inferiority Margin**

The judgment of the protocol team was that an absolute non-inferiority margin of 0.75% was clinically appropriate, given an expected annual event rate in the 9H arm of 1.6%. The relative non-inferiority margin of 17% was felt to be appropriate because the absolute expected event rate (1.6%) was low.

The non-inferiority margin also was appropriate statistically, and consistent with guidelines of the U.S. Food and Drug Administration (FDA).1 The key aspect was to ensure that the event rate in the experimental arm (3HP) was better than placebo, under many possible scenarios. A sensitivity analysis was performed as described below.

The first step was to assume the largest acceptable margin (noted here as M1), which is defined as the effect of the active control (9H) over placebo (no-treatment), based on historical studies.

In this study, 9H was assumed to be 68% effective and the tuberculosis event rate without treatment was assumed to be 5% per year. Both assumptions were the best estimates available at the time the trial started in 2001. Therefore, the expected HIV/tuberculosis rate in the 9H arm was (1.0 – 0.68) x 5% = 1.6% annually. M1 is the improvement that the 9H arm would make over no treatment: 5% - 1.6% = 3.4% per year or 9.35% (3.4% x 2.75 years) in 33 months (2.75 years).

The second step was to select a non-inferiority margin (M2) that was not only clinically meaningful, but also preserved a large proportion of M1. A non-inferiority margin of 0.75% means that the tuberculosis rate in the 3HP arm could be 5.15% (1.6% x 2.75 years + 0.75% = 5.15%) in 33 months and still be able to claim non-inferiority. In that scenario, the improvement that 3HP would make over no treatment would be 8.6% (5% x 2.75 - 5.15%). This preserves 92% of M1, since 8.6 / 9.35 = 0.92. This was also determined from the following equation: 1 – (0.75 / 9.35) = 0.92

Large values of “preservation” are preferred. A value of 92% provides confidence that M1 was preserved. Therefore, the non-inferiority margin of 0.75% preserves 92% of M1.

We then conducted a sensitivity analysis, varying the effectiveness of 9H from 60% to 90% and the tuberculosis rate without treatment from 2% to 5%. There was still substantial preservation of M1, using a non-inferiority margin (M2) of 0.75%.

**Rationale for Exclusion of Participants from Site A**

Analyses were also performed with participants from one study site (Site A; n = 70) excluded due to possible discrepancies at that site regarding receipt of study drug and directly-observed therapy. Study populations with Site A participants removed are shown in Supplement Table 1. The CONSORT criteria as shown in Supplement Figure 1, uses ‘m’ to represent the number of participants excluded from Site A. Supplement Table 7/Figure 4 shows effectiveness, efficacy and safety analyses when participants from Site A are removed.

**Supplement Table 1. Study populations.**

*All persons enrolled.*

|  |  |  |  |
| --- | --- | --- | --- |
| **Study population** | **Assessment** | **3HP** | **9H** |
| Enrolled (intention to treat; ITT)a |  | 208 | 195 |
| Enrolled + eligible(modified intention to treat; MITT)b | Effectiveness | 206 | 193 |
| Per protocol(PP)b | Efficacy | 183 | 123 |
| Received > 1 dosea | Safety | 207 | 186 |

1. 3HP: 4 persons < 18 years old; 9H: 1 person < 18 years old.
2. 3HP: 3 persons < 18 years old; 9H: 1 person < 18 years old

*After excluding the participants enrolled from Site A (45 participants in the 3HP arm and 25 in the 9H arm).*

|  |  |  |  |
| --- | --- | --- | --- |
| **Study population** | **Assessment** | **3HP** | **9H** |
| Enrolled (intention to treat; ITT)a |  | 163 | 170 |
| Enrolled + eligible(modified intention to treat; MITT)b | Effectiveness | 161 | 168 |
| Per protocol(PP)b | Efficacy | 140 | 112 |
| Received > 1 dosea | Safety | 162 | 165 |

1. 3HP: 4 persons < 18 years old; 9H: 1 person < 18 years old.
2. 3HP: 3 persons < 18 years old; 9H: 1 person < 18 years old.

**Characteristics of the modified intention to treat (MITT) study population, after removal of participants from Site A.** This includes participants who enrolled in the study and met eligibility criteria.

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristic** | **3HP****N=161****n (%)** | **9H****N=168****n (%)** | **P-value** |
| Median age-years (IQR)# | 36 (29 – 44) | 37 (28 – 45) | 0.54 |
| Median CD4+ lymphocyte count—baseline (IQR)\* | 473 (376 – 641) | 535 (418 – 722) | 0.04 |
| ART reported|| | 50 (31) | 51 (30) | 0.91 |
| Male sex | 106 (66) | 108 (64) | 0.82 |
| Race |  |  |  |
|  White | 40 (25) | 50 (30) | 0.33 |
|  Black | 68 (42) | 73 (43) | 0.91 |
|  Asian/Pacific Islander | 6 (4) | 3 (2) | 0.33 |
|  North American Indian | 5 (3) | 4 (2) | 0.75 |
|  Multiracial | 42 (26) | 38 (23) | 0.52 |
| Ethnicity (U.S. / Canada) |  |  |  |
|  Hispanic | 27/91 (30) | 22/95 (23) | 0.32 |
|  Non-Hispanic | 64/91 (70) | 73/95 (77) | 0.32 |
| Median BMI—baseline (IQR)  | 25 (23 – 28) | 25 (23 – 29) | 0.74 |
|  Underweight | 4 (2) | 3 (2) | 0.72 |
|  Normal | 67 (42) | 66 (39) | 0.74 |
|  Overweight | 65 (40) | 62 (37) | 0.57 |
|  Obese | 25 (16) | 37 (22) | 0.16 |
| Region of enrollment |  |  |  |
|  U.S. / Canada | 91 (57) | 95 (57) | 1.00 |
|  Brazil/Peru/Spain/  Hong Kong | 70 (43) | 73 (43) | 1.00 |
| Indication for LTBI |  |  |  |
|  Contact | 150 (93) | 163 (97) | 0.13 |
|  TST convertor | 11 (7) | 5 (3) | 0.13 |
| History EtOH use | 97 (60) | 109 (65) | 0.43 |
| History IDU | 28 (17) | 16 (10) | 0.08 |
| Current smoker (at enrollment) | 60 (37) | 75 (45) | 0.18 |
| High School | 101 (63) | 107 (64) | 0.91 |
| Jail/Prison | 14 (9) | 24 (14) | 0.12 |
| Unemployed | 30 (19) | 45 (27) | 0.09 |
| Homeless | 17 (11) | 21 (13) | 0.61 |
| Methadone^  | 7 (4) | 13 (8) | 0.25 |
| Hepatitis C virus | 14 (9) | 20 (12) | 0.37 |

ART: antiretroviral therapy

IQR: inter-quartile range

EtOH: alcohol

IDU: injection drug use

BMI: body mass index

# 3HP: 3 persons < 18 years old; 9H: 1 person < 18 years old.

\*CD4+ lymphocyte counts were available at baseline for 143participants in the 3HP arm and 141 participants in the 9H arm. The range was 55 to 1,988 in the 3HP arm and 9 to 1,406 in the 9H arm. HIV-1 RNA levels were not obtained.

**||** ART: participants were considered being on ART when ART was reported on the concomitant medication form during the study.

^In a methadone maintenance program at study enrollment.

**Supplement Figure 1. Flow Diagram of Study Participants—CONSORT Criteria.**

## Enrollment

* **Eligible for Safety analysis (n=207)** **(m=45)**
* Did not receive intervention (n=1) (m=0)
* Did not receive per protocol (n=9)
* **Eligible for Safety analysis (n=186) (m=21)**
* Did not receive intervention (n=9) (m=4)

**Eligible for PP analysis (n= 183) (m=43)**

* Excluded from analysis (n=23) (m=2)

**Eligible for PP analysis (n= 123) (m=11)** - Excluded from analysis (n= 70) (m=14`)

**Eligible for MITT analysis (n= 206) (m=45)**
Ineligible for study; excluded from analysis (n=2)(m=0)^:

 - Source case resistant to INH or RIF (n=0) (m=0)

 - Source case culture-negative for M. tb (n=1) (m=0)

 - Positive TST not confirmeda (n=0) (m=0)

 - Source case missing DST results (n=0) (m=0)

 - TB at enrollment (n=1) (m=0)

**Eligible for MITT analysis (n= 193) (m=25)**
Ineligible for study; excluded from analysis (n=2)(m=0)^:

 - Source case resistant to INH or RIF (n=0) (m=0)

 - Source case culture-negative for M. tb (n=1) (m=0)

 - Positive TST not confirmeda (n=1) (m=0)

 - Source case missing DST results (n=0) (m=0)

 - TB at enrollment (n=0) (m=0)

## Analysis

**Completed regimen per protocol (n=183) (m=43)**

Did not receive intervention (n= 1) (m=0)

Did not complete regimen per protocol (n=23) (m=2) - Incorrect duration or number of doses (n=7) (m=0)

- Withdrew consent (n=0) (m=0)

- AE with discontinuation (n=7) (m=2)

- Lost during study phase (n=7) (m=0)

- Treatment discontinued by clinician (n=0) (m=0)

- Refused treatment (n=1) (m=0)

- Incarcerated (n=1) (m=0)

**Completed regimen per protocol (n=123) (m=11)**

Did not receive intervention (n= 9) (m=4)

Did not complete regimen per protocol (n=70) (m=14) - Incorrect duration or number of doses (n=28) (m=3)

- Withdrew consent (n=2) (m=2)

- AE with discontinuation (n=8) (m=3)

- Lost during study phase (n=16) (m=2)

- Treatment discontinued by clinician (n=7) (m=1)

- Refused treatment (n=3) (m=3)

- Incarcerated (n=6) (m=0)

**3HP (n=208) (m=45)**

 - Eligible for study (n=206) (m=45)

 - Ineligible for study (n=2; see below)

**9H (n=195) (m=25)**

 - Eligible for study (n=193) (m=25)

 - Ineligible for study (n=2; see below)

-

**Assessed for eligibility\*** *June 2001 – March 2005* **(n=unknown)**

**Assessed for eligibility\*** *March 2005 – December 2010* **(n=519)**

**Enrolled** June 2001 – March 2005 **(n=106)**

Excluded (n= 222)

 - Did not meet inclusion criteria (n=176)

 - Declined to participate (n=26)

 - Other reasons (n= 20)

**Enrolled** March 2005 – December 2010 **(n=297)**

**Total Enrolled (n= 403)**

## Allocation

## Treatment

\* Eligibility screening data were obtained after March 2005, with implementation of an eligibility screening log. This was implemented in response to CONSORT reporting criteria, which were updated after the study began.2

^ Enrollment of participants was allowed before tuberculosis culture and susceptibility data were available in the source case. Participants ineligible because the source case was culture-negative for *M. tuberculosis*, had *M. tuberculosis* resistant to INH or RIF, or did not have susceptibility testing performed, were identified after enrollment.

a Positive TST not confirmed on repeat testing.

Abbreviations:

m: number of participants excluded from Site A

9H: 9 months of self-administered daily isoniazid

3HP: 3 months of directly-observed once-weekly rifapentine and isoniazid

DST: drug susceptibility testing

AE: adverse event

MITT: modified intention to treat

PP: per protocol

INH: isoniazid

RIF: rifampin

M. tb: *M. tuberculosis*

TST: tuberculin skin test

Participants were eligible for the safety analysis if they received > 1 dose of study medication

|  |
| --- |
| **Supplement Table 2. Reasons for Study Ineligibility.** Among 403 participants randomized, 4 were ineligible for the study.  |
| **Reason** | **N** | **% of Ineligible Participants** |
| Source TB case resistant to INH or RIF | 0 | 0 |
| Source TB case culture-negative for *M. tuberculosis* | 2 | 50 |
| Positive tuberculin skin test not confirmed | 1 | 25 |
| *M. tuberculosis* drug susceptibility test results not available for the source TB case | 0 | 0 |
| TB at enrollment | 1 | 25 |
| Total | 4 | 100 |

Enrollment of participants was allowed before tuberculosis culture and susceptibility data were available in the source case. Participants ineligible because the source case was culture-negative for *M. tuberculosis*, had *M. tuberculosis* resistant to INH or RIF, or did not have susceptibility testing performed, were identified after enrollment.

**Supplement Figure 2. Comparison of Cumulative Lost to Follow-up by Treatment Regimen.** Modified intention to treat study population. Follow-up was from the time of enrollment. Log-rank P-value = 0.34.



**Supplement Figure 3. Difference of 3HP Arm from Active Control 9H Arm in Cumulative TB Rates and the 95% C.I. by MITT and PP Populations.**

****

**Supplement Table 3. All Grade 3 and 4 Adverse Events by Treatment Regimen and System Organ Classification.** Among participants who received at least 1 dose of study treatment (the safety population). Adverse events were classified by the MedDRA (Medical Dictionary for Regulatory Activities) System Organ Class (SOC). They are presented in the order of frequency of total number of events. The number of events in each SOC are provided.

|  | **9HN=186** | **3HPN=207** |
| --- | --- | --- |
|  | **Non-SAE** | **SAE\*** | **Non-SAE** | **SAE\*** |
| **System Organ Class** | **System Organ ClassPreferred Term** | **N**  | **(%)** | **N**  | **(%)** | **N**  | **(%)** | **N**  | **(%)** |
| ALL BODY SYSTEM | OVERALL | 16 | (8.60) | 16 | (8.60) | 13 | (6.28) | 6 | (2.90) |
| Infections and infestations | Infections and infestations | 2 | (1.08) | 2 | (1.08) | 1 | (0.48) | 0 | (0.00) |
|   | Cellulitis | 0 | (0.00) | 1 | (0.54) | 0 | (0.00) | 0 | (0.00) |
|   | Dengue fever | 1 | (0.54) | 0 | (0.00) | 0 | (0.00) | 0 | (0.00) |
|   | Hepatitis B | 0 | (0.00) | 0 | (0.00) | 1 | (0.48) | 0 | (0.00) |
|   | Herpes simplex | 1 | (0.54) | 0 | (0.00) | 0 | (0.00) | 0 | (0.00) |
|   | Syphilis | 1 | (0.54) | 0 | (0.00) | 0 | (0.00) | 0 | (0.00) |
|   | Wound infection | 0 | (0.00) | 1 | (0.54) | 0 | (0.00) | 0 | (0.00) |
| Psychiatric disorders | Psychiatric disorders | 0 | (0.00) | 3 | (1.61) | 1 | (0.48) | 1 | (0.48) |
|   | Confusional state | 0 | (0.00) | 0 | (0.00) | 1 | (0.48) | 0 | (0.00) |
|   | Depression | 0 | (0.00) | 0 | (0.00) | 0 | (0.00) | 1 | (0.48) |
|   | Hallucination, visual | 0 | (0.00) | 0 | (0.00) | 1 | (0.48) | 0 | (0.00) |
|   | Restlessness | 0 | (0.00) | 0 | (0.00) | 1 | (0.48) | 0 | (0.00) |
|   | Suicidal ideation | 0 | (0.00) | 1 | (0.54) | 0 | (0.00) | 0 | (0.00) |
|   | Suicide attempt | 0 | (0.00) | 2 | (1.08) | 0 | (0.00) | 0 | (0.00) |
| Gastrointestinal disorders | Gastrointestinal disorders | 0 | (0.00) | 3 | (1.61) | 0 | (0.00) | 1 | (0.48) |
|   | Abdominal pain upper | 0 | (0.00) | 1 | (0.54) | 0 | (0.00) | 0 | (0.00) |
|   | Diverticulum | 0 | (0.00) | 1 | (0.54) | 0 | (0.00) | 0 | (0.00) |
|   | Pancreatitis | 0 | (0.00) | 0 | (0.00) | 0 | (0.00) | 1 | (0.48) |
|   | Periodontal disease | 0 | (0.00) | 1 | (0.54) | 0 | (0.00) | 0 | (0.00) |
| Hepatobiliary disorders | Hepatobiliary disorders | 11 | (5.91) | 2 | (1.08) | 3 | (1.45) | 0 | (0.00) |
|   | Cholecystitis acute | 1 | (0.54) | 0 | (0.00) | 0 | (0.00) | 0 | (0.00) |
|   | Hepatitis | 10 | (5.38) | 2 | (1.08) | 2 | (0.97) | 0 | (0.00) |
|   | Hypertransaminasaemia | 0 | (0.00) | 0 | (0.00) | 1 | (0.48) | 0 | (0.00) |
| Vascular disorders | Vascular disorders | 0 | (0.00) | 2 | (1.08) | 2 | (0.97) | 0 | (0.00) |
|   | Deep vein thrombosis | 0 | (0.00) | 1 | (0.54) | 0 | (0.00) | 0 | (0.00) |
|   | Hypertension | 0 | (0.00) | 0 | (0.00) | 2 | (0.97) | 0 | (0.00) |
|   | Hypertensive crisis | 0 | (0.00) | 1 | (0.54) | 0 | (0.00) | 0 | (0.00) |
| Blood and lymphatic system disorders | Blood and lymphatic system disorders | 2 | (1.08) | 2 | (1.08) | 3 | (1.45) | 0 | (0.00) |
|   | Anaemia | 0 | (0.00) | 2 | (1.08) | 0 | (0.00) | 0 | (0.00) |
|   | Neutropenia | 2 | (1.08) | 0 | (0.00) | 3 | (1.45) | 0 | (0.00) |
| Cardiac disorders | Cardiac disorders | 0 | (0.00) | 2 | (1.08) | 0 | (0.00) | 0 | (0.00) |
|   | Cardiac failure congestive | 0 | (0.00) | 1 | (0.54) | 0 | (0.00) | 0 | (0.00) |
|   | Myocardial infarction | 0 | (0.00) | 1 | (0.54) | 0 | (0.00) | 0 | (0.00) |
| Metabolism and nutrition disorders | Metabolism and nutrition disorders | 0 | (0.00) | 0 | (0.00) | 2 | (0.97) | 0 | (0.00) |
|   | Gout | 0 | (0.00) | 0 | (0.00) | 1 | (0.48) | 0 | (0.00) |
|   | Hypokalaemia | 0 | (0.00) | 0 | (0.00) | 1 | (0.48) | 0 | (0.00) |
| Musculoskeletal and connective tissue disorders | Musculoskeletal and connective tissue disorders | 0 | (0.00) | 0 | (0.00) | 1 | (0.48) | 1 | (0.48) |
|   | Myositis | 0 | (0.00) | 0 | (0.00) | 0 | (0.00) | 1 | (0.48) |
|   | Osteoarthritis | 0 | (0.00) | 0 | (0.00) | 1 | (0.48) | 0 | (0.00) |
| Nervous system disorders | Nervous system disorders | 1 | (0.54) | 1 | (0.54) | 1 | (0.48) | 1 | (0.48) |
|   | Convulsion | 1 | (0.54) | 0 | (0.00) | 1 | (0.48) | 0 | (0.00) |
|   | Syncope | 0 | (0.00) | 1 | (0.54) | 0 | (0.00) | 1 | (0.48) |
| Surgical and medical procedures | Surgical and medical procedures | 0 | (0.00) | 1 | (0.54) | 0 | (0.00) | 1 | (0.48) |
|   | Ankle operation | 0 | (0.00) | 0 | (0.00) | 0 | (0.00) | 1 | (0.48) |
|   | Inguinal hernia repair | 0 | (0.00) | 1 | (0.54) | 0 | (0.00) | 0 | (0.00) |
| General disorders and administration site conditions | General disorders and administration site conditions | 0 | (0.00) | 0 | (0.00) | 0 | (0.00) | 1 | (0.48) |
|   | Pyrexia | 0 | (0.00) | 0 | (0.00) | 0 | (0.00) | 1 | (0.48) |
| Immune system disorders | Immune system disorders | 0 | (0.00) | 0 | (0.00) | 1 | (0.48) | 0 | (0.00) |
|   | Hypersensitivity | 0 | (0.00) | 0 | (0.00) | 1 | (0.48) | 0 | (0.00) |
| Injury, poisoning and procedural complications | Injury, poisoning and procedural complications | 1 | (0.54) | 0 | (0.00) | 0 | (0.00) | 0 | (0.00) |
|   | Tooth fracture | 1 | (0.54) | 0 | (0.00) | 0 | (0.00) | 0 | (0.00) |

\* SAE – Serious Adverse Event

**Supplement Table 4. All Deaths by Treatment Regimen and ICD-9 Code.**

|  |  |  |  |
| --- | --- | --- | --- |
| **ICD9 Category** | **9H**n=5  | **3HP**n=6  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| Malignant neoplasms (cancer) |  | 1 |  | 1 |  |  |
|  |  |  |  |  |  |  |
| Intentional injuries |  | 0 |  | 1 |  |  |
|  |  |  |  |  |  |  |
| Chronic liver disease or cirrhosis\* |  | 1 |  | 0 |  |  |
|  |  |  |  |  |  |  |
| Hypertension (with or w/o renal disease) |  | 1 |  | 0 |  |  |
|  |  |  |  |  |  |  |
| AIDS |  | 1 |  | 1 |  |  |
|  |  |  |  |  |  |  |
| Septicemia |  | 1 |  | 1 |  |  |
|  |  |  |  |  |  |  |
| Unknown |  | 0 |  | 1 |  |  |
|  |  |  |  |  |  |  |
| All other causes |  | 0 |  | 1 |  |  |
|  |  |  |  |  |  |  |

\*The 1 death that occurred on therapy or within 60 days of last dose is among this category.

**Supplement Table 5. Tuberculosis cases and event rates by treatment arm and HIV serostatus.** In the modified intention to treat study population.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Treatment arm** | **HIV Status** | **N** | **# TB cases** | **TB rate per 100 p-ya** | **Cumulative TB rate and its 95% CI (%)** | **Difference in cumulative TB rate (%)b** | **95% CI of the difference in cumulative TB rate (%)** |
| 9H | HIV-infected | 193 | 6 | 1.25 | 3.50(0.74, 6.26) | 2.97 | (0.18, 5.76) |
| HIV- uninfected | 1826 | 9 | 0.19 | 0.53(0.19, 0.87) |
| 3HP | HIV-infected | 206 | 2 | 0.39 | 1.01(-0.38, 2.40) | 0.83 | (-0.57, 2.24) |
| HIV- uninfected | 1837 | 3 | 0.06 | 0.18(-0.02, 0.37) |

H: isoniazid P: rifapentine; p-y: person-years; CI: confidence intervals

a Follow-up was up to 33 months from the time of study enrollment.

b The difference in cumulative TB disease rate, within arms, is the rate among HIV-infected persons minus the rate among HIV-uninfected persons.

**Supplement Table 6. Tolerability by treatment arm and HIV serostatus.** This includes all participants who enrolled in the study and received at least 1 dose of study treatment (the safety population).

|  |  |  |
| --- | --- | --- |
| **Characteristic** | **3HP** | **9H** |
|  | **HIV- infected****n=207****n (%)** | **HIV-uninfected****n=1861****n (%)** | **P-valuea** | **HIV- infected****n=186****n (%)** | **HIV-uninfected****n=1824****n (%)** | **P-valuea** |
| Treatment completion (MITT)b | 183 (88.8) | 1473 (80.2) | 0.002 | 123 (63.7) | 1230 (67.4) | 0.33 |
| Discontinuation due to adverse drug reaction | 7 (3.4) | 99 (5.3) | 0.32 | 8 (4.3) | 63 (3.5) | 0.53 |
| Grade 3 toxicity | 14 (6.8) | 110 (5.9) | 0.64 | 18 (9.7) | 110 (6.0) | 0.06 |
| Grade 4 toxicity | 4 (1.9) | 20 (1.1) | 0.29 | 10 (5.4) | 24 (1.3) | <0.0001 |
| Grade 5 (death) | 6 (2.9) | 17 (0.9) | 0.02 | 5 (2.7) | 20 (1.1) | 0.07 |
| Discontinuation due to hepatotoxicity  | 2 (1.0) | 9 (0.5) | 0.30 | 8 (4.3) | 34 (1.9) | 0.05 |
| Flu-like/systemic drug reaction | 2 (1.0) | 85 (4.6) | 0.01 | 0 (0.0) | 10 (0.6) | 0.61 |
| Serious Adverse Eventsc | 8 (3.9) | 41 (2.2) | 0.15 | 21 (11.3) | 59 (3.2) | <0.0001 |

H: isoniazid P: rifapentine

a P-value based on Fisher’s exact test.

b MITT: Modified Intention to Treat. 9H: HIV infected = 193, Non-HIV infected = 1826; 3HP: HIV infected = 206, Non-HIV infected = 1837.

c Serious Adverse Events include deaths while receiving a study drug or within 60 days after the last dose, life-threatening events, hospitalization, disability or permanent damage, and congenital anomalies or birth defects.

**Supplement Table 7/Figure 4. Results of the effectiveness, efficacy, and safety analyses with participants from Site A removed.**

**Kaplan-Meier curve of time to tuberculosis by study arm in the MITT study population.**  The number of persons at risk at 100-day increments from enrollment are provided.



**Tuberculosis cases and event rates by treatment arm.** All participants from Site A removed.

Modified intention to treat population

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Treatment arm | N | # TB cases | TB rate per 100 p-y | Cumulative TB rate (%) | Difference in cumulative TB rate | Upper bound of the 95% CI (%) |
| 9H | 168 | 5 | 1.19 | 3.36 | -2.06 | 1.35 |
| 3HP | 161 | 2 | 0.50 | 1.30 |

Per protocol population

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Treatment arm | N | # TB cases | TB rate per 100 p-y | Cumulative TB rate (%) | Difference in cumulative TB rate | Upper bound of the 95% CI (%) |
| 9H | 112 | 2 | 0.69 | 2.01 | -1.28 | 1.82 |
| 3HP | 140 | 1 | 0.28 | 0.73 |

**Safety and tolerability of the study regimens.** Among participants who received > 1 dose of study medications, except as noted. Percentages are in parentheses. All participants from Site A removed.

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristic | 3HPN=162 | 9HN=165 | P-value |
| Treatment completion (MITT) | 140/161 (87%) | 112/168 (67%) | <0.001 |
| Discontinuation due to adverse drug reaction | 5 (3) | 5 (3) | 1.00 |
| Grade 3 toxicity | 10 (6) | 18 (11) | 0.17 |
| Grade 4 toxicity | 4 (2) | 8 (5) | 0.38 |
| Grade 5 (death) | 5 (3) | 5 (3) | 1.00 |
| Discontinuation due to hepatotoxicity\*  | 2 (1) | 5 (3) | 0.45 |
| Flu-like/systemic drug reaction | 1 (0.6) | 0 (0) | 0.50 |

\*Neither of the two persons in the 3HP arm and one of the five persons in the 9H arm had underlying hepatitis C virus infection.

|  |
| --- |
| **Supplement Table 8. Univariate and Multivariate Risk Factor Analysis for the Development of Tuberculosis (MITT Population).** |
| Characteristic (N) | Reference Group (N) | **Univariate Analysis** | **Multivariate Analysis** |
| HR(95% CI) | p-value | Adjusted HR(95% CI) | P-value |
| Regimen (3HP) (206) | 9H (193) | 0.31 (0.06, 1.54) | 0.15 | 0.27 (0.05, 1.44) | 0.13 |
| Age (> 35 years) (208) | Age (≤ 35 years) (191) | 0.30 (0.06, 1.49) | 0.14 |  |
| Baseline CD4+a  | CD4+ < 350 (56) | CD4 ≥ 350 (298) | 5.14 (1.04, 25.48) | 0.04 | 6.22 (1.16, 33.42) | 0.03 |
| CD4+ Unknown (45) | 4.31 (0.72, 25.82) | 0.11 | 3.19 (0.51, 20.13) | 0.22 |
| ART reportedb (125) | No ART (274) | 0.48 (0.12, 1.91) | 0.29 |  |
| Male sex (277) | Female sex (122) | 3.16 (0.39, 25.70) | 0.28 |
| Race | Black (150) | White (149) | 1.03 (0.14,7.29) | 0.98 |
| North American Indian (9) | 0.00 | NA |
| Asian (9) | 0.00 | NA |
| Multiracial (82) | 3.72 (0.68, 20.31) | 0.13 |
| BMIc  | Underweight (8) | Normal (177) | 14.39 (2.40, 86.14) | 0.004 |  17.77 (2.54, 124.34) | 0.0037 |
| Overweight (147) | 1.17 (0.24, 5.80) | 0.85 | 1.51 (0.27, 8.34) | 0.64 |
| Obese (67) | 0.00 | NA | NA | NA |
| Region | Brazil (76) | US/Can(186) | 0.79 (0.08, 7.54) | 0.83 |  |
| Spain (70) | 0.86 (0.09, 8.22) | 0.89 |
| Peru (65) | 2.86 (0.58, 14.18) | 0.20 |
| Hong Kong (2) | 0.00 | NA |
| Indication for LTBI | TST converter (16) | Contact (383) | 3.77 (0.46, 30.66) | 0.21 |
| Alcohol use | Abused (39) | No Abuse (360) | 1.27 (0.16, 10.31) | 0.82 |
| Usee (233) | No Use (166) | 1.15 (0.28, 4.82) | 0.85 |
| IDU  | (Yes) (60)  | No (339) | 0.00 | NA |
| Current smoker | Yes (172) | No (227) | 0.81 (0.19, 3.40) | 0.77 |
| High School | No (158) | Yes (241) | 1.52 (0.38, 6.08) | 0.55 |
| Jail/prison | Yes (40) | No (359) | 0.00 | NA |
| Unemployed | Yes (84) | No (315) | 1.27 (0.26, 6.29) | 0.77 |
| Homeless | Yes (44) | No (355) | 0.00 | NA |  |
| Methadone | Yes (23) | No (376) | 0.00 | NA |
| Hepatitis C virus | Yes (48) | No (351) | 0.93 (0.11, 7.55) | 0.93 |
| Abbreviations: 9INH: 9-month (270-dose) regimen of daily isoniazid; 3HP: 3-month (12-dose) regimen of weekly rifapentine and isoniazid; HR: hazard ratio; NA: not applicable; ART: antiretroviral therapy; CD4: ;US: United States; Can: Canadian; BMI: body mass index; TST: tuberculin skin test; IDU: injection drug use; CAGE: cut-annoyed-guilty-eye (alcohol questionnaire); HIV: human immunodeficiency virus aBaseline CD4 counts: reported less than 6 month before enrollment and up to 3 months after enrollmentbART start times are calculated from enrollment date. ART start dates are based on evaluation date reported on concomitant medication form. For patients with multiple reports, the earliest report date was used.cBMI categories: Underweight (below 18.5); Normal (18.5 to <25.0); Overweight (25.0 to <30.0); Obese (30.0 and above).dAlcohol abuse: participant self-report of alcohol use and answered “yes” to ≥2 CAGE questions.eAlcohol use: by participant self-report; answered “yes” to ≤1 CAGE question.A p-value ≤ 0.20 in the univariate analysis, led to inclusion in the multivariate analysis. A p-value < 0.05 indicated overall significance. Regimen was allowed to stay in the model regardless of p-value.The model was checked for all combinations of 2 \* 2 interactions that included study arm, baseline CD4<350, multiracial, Hispanic ethnicity, and underweight BMI. Using the backward elimination method and allowing treatment arm to remain in the model, there were no significant interactions.  |

**Study Sites, Principal Investigators and Study Coordinators**

Tuberculosis Trials Consortium (TBTC) (266 participants enrolled):

TB Investigation Unit of Barcelona, Barcelona, Spain and UNTHSC

Joan A. Cayla, MD, PhD, Jose M. Miró, MD, PhD, Maria Antonia Sambeat, MD, PhD, Jose L. López Colomés, MD, José A. Martinez, MD, Xavier Martinez-Lacasa MD, PhD, Angels Orcau, MD, Paquita Sanchez, MD, Cecilia Tortajada, MD, PhD, Imma Ocana, MD, PhD,  Juan P. Millet, MD, MPH, Antonio Moreno, MD, Jeanne Nelson, MPH, Omar Sued, MD, Mª Luiza de Souza, MD, María A. Jiménez, MD, Lucía del Baño RN, Laia Fina MSc, Celia Milá, MD, Christian Manzardo, MD, PhD.

Johns Hopkins University, Baltimore, MD

Richard Chaisson MD, Susan Dorman, MD, Jim Fisher, Gina Maltas, RN, Judith Hackman, RN.

University of North Texas Health Science Center at Ft. Worth

Stephen E. Weis, D.O., Michel Fernandez, MD, Barbara King, RN, Lee Turk, RN, Norma Shafer, Gloria Stevenson, RN, Guadalupe Bayona, MD, Randy Dean, RN, Joseph Helal, MS, RPh, Gerry Burgess, RN, Edgar Vecino, M.D., Philip Slocum, D.O., John Podgoe, D.O., George Samuel, M.D.

Emory University

Susan M. Ray, MD , David P. Holland, MD, Deirdre Dixon, Omar Mohamed, Kanoa Folami, Jane Bush, MA, Cheryl D. Simpson, BS, Gibson Barika, Wenona N. Favors, Nicole Snow.

University of California at San Diego

Antonino Catanzaro, MD, Philip LoBue, MD, Kathleen Moser, MD, Mark Tracy, MD, Peach Francisco, RN, Judy Davis.

Hospital Universitario Clementino Fraga Filho, Rio de Janeiro, Brazil, Johns Hopkins University

Marcus B. Conde, MD, Fernanda C. Q. Mello, MD, Anne Efron, MSN, MPH, Carla Loredo, RN, Millene Barty S. Fortuna, Michelle Cailleaux-Cezar, MD, Renata L. Guerra, MD, Gisele Mota, RN, Cristina Felix, RN, Valéria de Oliveira, Claudeci dos Santos Sacramento.

Boston University Medical Center, Boston, MA

John Bernardo, MD, Jussi Saukkonen, MD, Claire Murphy, NP-C, Denise Brett-Curran, RN.

University of Southern California/Los Angeles County

Brenda E. Jones, MD, Patricio Escalante, MD, Peregrina Molina, RN, Claudia Silva, RN, Angela Grbic, RN, Maria Brown, MPH, Bonifacia Oamar, RN, Ermelinda Rayos, CW, Celia Luken.

Denver Department of Public Health, Denver, CO

William Burman, MD, Randall Reves, MD, Robert Belknap, MD, David Cohn, MD, Jan Tapy, RN, Grace Sanchez, CCA, Laurie Luna, RN.

Duke University / Family Health International (FHI) 360 / Durham Veterans Administration Hospital

Carol Dukes Hamilton, MD, MHS, Jason Stout, MD, MHS, Ann Mosher, RN, MPH, FNP-BC, Emily J. Hecker, RN, MSN, Brenda Ho, LPN, Elle Rich, RN, MPH.

CP Felton National TB Center at Harlem Hospital Center, New York, NY

Wafaa M. El-Sadr, MD, MPH, Mary Klein, RN, Cyrus Badshah, MD, John Salazar Schicchi, MD, Yael Hirsch-Moverman, PhD, MPH.

Vanderbilt University/Nashville Metro Public Health Department

Timothy Sterling, MD, Linda R. Hammock RN, Amy Kerrigan, RN MSN, Diedra Freeman, RN,FNP-C, Guat-Siew McKee, M.D.

University of California at San Francisco

Payam Nahid, MD, MPH, Philip Hopewell, MD, Charles Daley, MD, Robert Jasmer, MD, Cindy Merrifield, RN, William Stanton, RN, Irina Rudoy, MD, Jill Israel, RN.

Metro-DC Consortium - Washington DC Veterans Affairs Medical Center

Debra A. Benator, MD, Donna Conwell, RN, Shirley Cummins, Fred Gordin, MD.

Prince Georges County, Maryland Health Department: Walter Karney MD, Thomas Walsh, MD.

National Naval Medical Center:  Kyle Petersen, DO, Timothy Whitman, DO.

New Jersey School of Medicine

Bonita T. Mangura, MD, Lee B. Reichman, MD, George McSherry MD, Alfred Lardizabal, MD, Maria Corazon Leus, RN, Marilyn Owens, RN, Eileen Napolitano, Laurie Kellert, RN, Veronica Anokute, RN.

Montreal Chest Institute, Montreal, Canada

Dick Menzies, MD, Kevin Schwartzman, MD,  Christina Greenaway, MD, Larry Lands, MD, Sharyn Mannix, MD, Paul Brassard, MD, Bérénice Mortezai, MD, Barry Rabinovitch, MD, Marthe Pelletier, Chantal Valiquette, Joanne Tremblay, Paul Anglade Plaisir, Rebecca Binet.

University of Manitoba, Manitoba, Canada

Wayne Kepron, MD, Earl Hershfield, MD, Marian Roth, RN, Gerry A. Izon, RN.

Public Health – Seattle & King County

Masahiro Narita, MD, Charles M. Nolan, MD, Stefan Goldberg, MD, Debra Schwartz, RN, Linh Le, Marcia Stone, RN, MPH, Connie Friedly, RN.

TB and Chest Service of Hong Kong China

Chi-Chiu Leung, MBBS, Kwok-Chiu Chang, MBBS, MSc, Sik-Wai Tam, Cheuk-Ming Tam, Kenny Chi-Wai Chan, Sau-Yin Tam, Ida Ka-Yun Mak,  Ka-Lin Fong, Nai-Chung Lee, May Kwai-Foon Chan, Suk-Yee Ko, Kai-Man, Kam, Chi-Wai Yip, Judy Yee-Man Lam, Chi-Wai Ng, Oi-Wah Fong, Edman Tin-Keung Lam, Chung-Ying Wong.

VA Houston Texas – Ben Taub General Hospital

Elizabeth Guy, MD, Christopher Lahart, MD, Terry Scott, RN, Ruby Nickson, RN.

Columbia University College of Physicians and Surgeons and New York City Department of Health and Mental Hygiene

Neil W. Schluger, MD, Joseph Burzynski, MD, Vilma Lozano, RN, Magda Wolk, RN.

University of British Columbia, Vancouver, Canada

J. Mark Fitzgerald, MD, Kevin Elwood, MD, Edwardo Hernandez, MD, Banafsheh Peyvandi, MD, Kadria Alasaly, MD.

VA Little Rock, Arkansas – Arkansas Department of Health

Iram Bakhtawar, MD, Frank Wilson, MD, Pauline Wassler, RN, Annette Arnold, RN, Kathy Haden, RN, Jamie Owen, RN.

Edward Hines Jr. VA Medical Center Chicago

Constance T. Pachucki, MD, Anna Lee, MD, Susan Marantz MD, Mary Poly Samuel, RN, Ana Zulaga BS, MPH.

Chicago-Lakeside Veterans Administration Hospital/The Chicago Department of Public Health

Mondira Bhattacharya, MD, William Clapp, MD, Susan Lippold, MD, MPH, Julie Fabre, RN, MPH.

Audie L. Murphy VA Hospital, San Antonio, TX

Marc Weiner, MD, Melissa Engle, CRT, CCRC, Jose A. Jimenez, BS, Hipolito Pavon, MPH, Victoria Rodriguez, RN, Col. Kevin B. West, MD, Col. David Dooley, MD, Col. Duane Hospenthal, MD, PhD.

AIDS Clinical Trials Group (ACTG) (133 participants enrolled):

Asociacion Civil Impacta Salud y Educacion, Lima, Peru

Jorge Sanchez, MD, MPH, Alberto La Rosa, MD, Fanny Rosas, RN.

Investigaciones Médicas en Salud-Inmensa, Peru

Javier Lama, MD, MPH, Rosa Infante, MD, Fanny Garcia, RN.

Instituto de Pesquisa Clínica Evandro Chagas, Rio de Janeiro, Brazil

Beatriz Grinsztejn, MD, PhD, Valdilea Gonçalves Veloso, MD, PhD, Guilherme Calvet, MD, PhD, Sandra Wagner Cardoso, MD, PhD, Thiago Silva Torres, RPH, PhD, Ronaldo Ismério Moreira, MSc, Deise Faria, MD, Lidiane Tuler, Janaina Vieira, Alexandre Souza, Paula Leite Cruz dos Santos.

Hospital Nossa Senhora da Conceicao Porto Alegre, Brazil

Breno Riegel Santos, MD, Marineide Gonçalves de Melo, MD, MS, Rita de Cássia Alves Lira, MD, Teresinha Joana Dossin, MD, Marcelo Edison Vieira de Almeida, RN/MS, Maria Lourdes Somagal Turella, RN, Kelin Roberta Zabtoski Piovesana, MS.

Denver Department of Public Health, Denver, CO

William Burman, MD, Randall Reves, MD, Robert Belknap, MD, David Cohn, MD, Jan Tapy, RN, Grace Sanchez, CCA, Laurie Luna, RN, Diane States, RN.

University of Texas Health Sciences Center-Houston

Roberto C. Arduino, MD, Maria Laura Martinez, BS.

The Miriam Hospital, Providence, Rhode Island

Pamela Poethke, RN, Karen T. Tashima, MD.

International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT; 4 participants enrolled)

Universidade de Sao Paulo de Rebeirao Preto, Brazil

Marisa Márcia Mussi-Pinhata, MD, Adriana Tiraboschi Barbaro, MD, Fernanda Tomé Sturzbecher, MD, Márcia de Lima Isaac, MD, Julio Cesar Gabaldi, Pharm, Camila Carolina Correia, Pharm.

Instituto de Infectologia Emilio Ribas, Brazil

Marinella Della Negra,MD, PhD, Wladimir Queiroz, MD, Denise Peluso Pacola, MD, Yu Ching Lian, MD, Roberio Alves Carneiro,MD.

Hospital Federal Dos Servidores Do Estado, Brazil

Maria Leticia Santos Cruz , MD, PhD, Esau Joao, MD , PhD, Leon Sidi, MD, José Carlos Cruz, BS, Fellipe Lattanzi , Pharm, Elaine Santos, RN, Deisi S Torgecki, Pharm.

Reference List

 1. Food and Drug Administration. Guidance for industry non-inferiority clinical trials. Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) 2010;<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140.pdf>.

 2. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. Ann Intern Med 2001;134(8):657-662.