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Three Months of Weekly Rifapentine plus Isoniazid for Treatment of *M. tuberculosis* Infection in HIV Co-infected Persons

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- 19th International AIDS Conference. July 22-27, 2012, Washington, DC. Abstract # MOAB03
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Author Contributions

TRS: study design; acquisition, analysis, and interpretation of data; drafted the first version of the manuscript
NAS: analysis and interpretation of the data; critical revision of the manuscript
JMM: acquisition and interpretation of data; critical revision of the manuscript
GC: acquisition and interpretation of data; critical revision of the manuscript
AL: acquisition and interpretation of data; critical revision of the manuscript
RI: acquisition and interpretation of data; critical revision of the manuscript
MPC: analysis and interpretation of the data; critical revision of the manuscript
DAB: acquisition and interpretation of data; critical revision of the manuscript
FG: acquisition and interpretation of data; critical revision of the manuscript
CAB: study design; interpretation of data; critical revision of the manuscript
REC: study design; acquisition and interpretation of data; critical revision of the manuscript
MEV: study design; analysis and interpretation of data; critical revision of the manuscript

Declaration of Interests

TRS: one-day consultation for Sanofi for presentation of PREVENT TB study data to the U.S. Food and Drug Administration in 2012. Data safety monitoring board for a clinical trial sponsored by Otsuka.
NAS: employed by the CDC Foundation, which receives funds for rifapentine research from Sanofi.
JMM: Research and academic grants: Abbott, Bristol-Myers Squibb, Gilead Sciences, Merck, Novartis, ViiV Healthcare. Lectures and advisory boards: Abbott, Bristol-Myers Squibb, Gilead Sciences, Janssen-Cilag, Merck, Novartis, ViiV Healthcare
GC: no conflict
AL: no conflict
RI: no conflict
MPC: no conflict
DAB: no conflict
FG: no conflict
CAB: no conflict
REC: no conflict
MEV: no conflict

For study sites and personnel, please see the Supplement.

Data access, responsibility, and analysis

TRS and NAS had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study 26 data management team: Nigel Scott, Ruth Moro, Lorna Bozeman, Erin Bliven-Sizemore.

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Abstract

Objective—Compare the effectiveness, tolerability, and safety of three months of weekly rifapentine plus isoniazid under direct observation (3HP) vs. 9 months of daily isoniazid (9H) in HIV-infected persons.

Design—prospective, randomized, open-label non-inferiority trial

Setting—U.S., Brazil, Spain, Peru, Canada, and Hong Kong

Participants—HIV-infected persons who were tuberculin skin test positive or close contacts of tuberculosis cases.

Intervention—3HP vs. 9H.

Main Outcome Measures—The effectiveness endpoint was tuberculosis; the non-inferiority margin was 0.75%. The tolerability endpoint was treatment completion; the safety endpoint was drug discontinuation due to adverse drug reaction.

Results—Median baseline CD4+ counts were 495 (IQR:389–675) and 538 (IQR:418–729) cells/mm^3 in the 3HP and 9H arms, respectively (P=0.09). In the modified intention to treat analysis, there were two tuberculosis cases among 206 persons (517 person-years (p-y) of follow-up) in the 3HP arm (0.39 per 100 p-y) and six tuberculosis cases among 193 persons (481 p-y of follow-up) in the 9H arm (1.25 per 100 p-y). Cumulative tuberculosis rates were 1.01% vs. 3.50% in the 3HP and 9H arms, respectively (rate difference: −2.49%; upper bound of the 95% confidence interval (CI) of the difference: 0.60%). Treatment completion was higher with 3HP (89%) than 9H (64%) (P<0.001), and drug discontinuation due to an adverse drug reaction was similar (3% vs. 4%; P=0.79) in 3HP and 9H, respectively.

Conclusions—Among HIV-infected persons with median CD4+ count of approximately 500 cells/mm^3, 3HP was as effective and safe for treatment of latent *M. tuberculosis* infection as 9H, and better tolerated.

Trial Registration—ClinicalTrials.gov (identifier: NCT00023452)

Keywords

M. tuberculosis; latent tuberculosis; HIV; rifapentine; isoniazid

Introduction

The human immunodeficiency virus (HIV) epidemic has worsened tuberculosis control in many countries.[1] HIV infection is the strongest risk factor for progressing from *Mycobacterium tuberculosis* infection to tuberculosis disease, and globally tuberculosis is the leading cause of death among people with HIV infection.[2–6] Treatment of *M. tuberculosis* infection is an important strategy for preventing active tuberculosis, and could have a significant impact on decreasing the global tuberculosis burden if implemented broadly.[7, 8] While treatment of active tuberculosis is highly effective, many patients die without being diagnosed or offered therapy, and transmission of *M. tuberculosis* to contacts is ongoing from those not on treatment.

Three months of once-weekly rifapentine and isoniazid given under direct observation (3HP) is at least as effective as 9 months of daily self-administered isoniazid (9H) in HIV-uninfected persons,[9] and is comparable to isoniazid given for 6 months or continuously in persons with HIV infection.[10] We sought to further evaluate the effectiveness, tolerability, and safety of 3HP in HIV-infected persons by extending enrollment of this patient group in the PREVENT TB trial.[9] The HIV study population has not previously been assessed, and effectiveness, tolerability, and safety endpoints in this population have not previously been reported.

Methods

Study design and patient population

The details of the PREVENT TB trial have been described previously.[9] This was a prospective, open-label, randomized trial of 3 months of once-weekly rifapentine 600–900 mg (adjusted by weight above or below 50 kg) plus isoniazid 15 mg/kg (25 mg/kg in children; rounded up to nearest 50 mg; 900 mg maximum) given under direct observation (3HP) compared to 9 months of daily self-administered isoniazid 5 mg/kg (15 mg/kg in children; rounded up to nearest 50 mg; 300 mg maximum)(9H). It was recommended that participants receive vitamin B6 50 mg with each dose of isoniazid. HIV testing was recommended, but not required, for enrollment into the PREVENT TB trial.

HIV-infected persons ≥ 2 years old who were tuberculin skin test positive (≥ 5 mm induration) or who had close contact with a tuberculosis case were eligible for enrollment, and were included in this analysis. Participants were enrolled in the United States, Spain, Brazil, Canada, and Hong Kong (all countries with low to moderate tuberculosis incidence rates, and settings in which treatment of latent *M. tuberculosis* infection is logistically feasible and a high public health priority) between June 2001 and December 2010. Participants were enrolled from Peru, and additional sites in Brazil, between February 2008 and December 2010. Follow-up was through September 2013.

Sample size

We tested the hypothesis that there would be no significant difference in the rates of treatment discontinuation due to adverse drug reaction (ADR) between the two treatment arms. We considered a ≤ 5% difference in the rates of treatment discontinuation due to ADR

to be clinically equivalent. Assuming 15% loss to follow-up, 80% power, type 1 error rate of 0.05 and 1% rate of discontinuation due to ADR in the standard treatment arm, the sample size estimate for testing the main safety hypothesis was 322 persons per arm. However, enrollment was discontinued prior to achieving this sample size due to slow enrollment over the study period.

Randomization

Treatment allocation was based on unrestricted randomization, except in some group settings (e.g., households), where all participants could be allocated to the same regimen as the first person in the group (cluster); in these situations, only the first person in the group was randomized.

Exclusion criteria included confirmed or suspected tuberculosis, resistance to isoniazid or rifampin in the source case, treatment with a rifamycin or isoniazid during the previous 2 years, sensitivity/intolerance to isoniazid or rifamycins, serum aspartate aminotransferase >5 times the upper limit of normal, pregnancy or breastfeeding, weight <10.0 kg, or receiving (or planning to initiate within 90 days of enrollment) HIV-1 protease inhibitor-or non-nucleoside reverse transcriptase inhibitor-based antiretroviral therapy. The study was approved by the institutional review boards of the Centers for Disease Control and Prevention (CDC) and all study sites. Written informed consent was obtained from all study participants.

The treatment effectiveness endpoint was culture-confirmed tuberculosis in persons ≥18 years old and culture-confirmed or clinical tuberculosis in persons <18 years old. The secondary effectiveness endpoint was culture-confirmed or clinical tuberculosis regardless of age. All suspected tuberculosis cases were reviewed by an external, blinded 3-person expert committee; final diagnoses were by consensus.

Tolerability and safety endpoints included completion of study therapy, permanent discontinuation of therapy, permanent discontinuation for adverse drug reaction, any grade 3 or 4 drug-related toxicity, all-cause mortality (grade 5 toxicity), and resistance to study medications in *M. tuberculosis* isolated from subjects who developed tuberculosis. Adverse events were graded by local investigators using common toxicity criteria;[11] investigators also determined attribution to study drug. The definition of flu-like and other systemic drug reactions is provided in the Supplement; this syndrome is described in detail elsewhere.[12]

Trial participants were followed for 33 months from enrollment and evaluated monthly during treatment. Baseline CD4+ lymphocyte counts were those reported closest to enrollment, from <6 months before to ≤3 months after enrollment. Adverse events were reported if they occurred up to 60 days after last dose of study medication. After treatment completion, study visits occurred every 3 months until the 21st month, then at months 27 and 33. Persons lost to follow-up before 33 months were cross-matched with local and state tuberculosis databases. Participants who discontinued study therapy early could be treated with alternative therapy at the discretion of the local investigator, and follow-up continued.

Quality Assurance

Quality assurance was ensured at all study sites through adherence to a common study protocol, standardized training of study investigators and study coordinators, external monitoring performed at least annually (by Westat), and quality assurance review of data by the study data center at the Centers for Disease Control and Prevention.

Statistical Analysis

We sought to assess whether 3HP was non-inferior to 9H. Without treatment, tuberculosis risk in persons with HIV and *M. tuberculosis* co-infection is estimated to be 5% annually.[3] Overall, twelve months of isoniazid is 55–83% effective in the general population; 68% has been estimated for a 9–12 month course.[13] In persons with HIV infection, treatment of *M. tuberculosis* infection is 11–62% effective, depending on the tuberculin skin test result.[14] Assuming a conservative estimate of 68% effectiveness, there would be (1.0–0.68) x 5%=1.6% tuberculosis cases annually in the 9H arm. We defined non-inferiority as 17% of the expected case rate in the 9H arm (17% × 1.6% × 2.75 years = 0.75%) in 33 months (2.75 years), which corresponds to an absolute non-inferiority margin (delta) of 0.75%. This margin was selected for the end of follow-up (33 months).[9] See the Supplement for a detailed justification of the non-inferiority margin.

The analysis groups were defined as follows: modified intention-to-treat (MITT) included all persons enrolled who were eligible. The per-protocol population (PP) included all eligible persons enrolled who completed the assigned study regimen (defined as ≥11 of 12 HP doses within 16 weeks or ≥240 of 270 H doses within 52 weeks), or persons who developed tuberculosis or died but completed ≥75% of the expected number of doses prior to the event. Tuberculosis rates were assessed 33 months after enrollment. In the MITT and PP analysis all follow-up time contributed was included. The MITT population, followed up to 33 months from enrollment, was considered the primary analysis population for effectiveness. The PP population was used to evaluate efficacy. The safety analysis was performed among all persons who received ≥ 1 dose of study drug. The 95% confidence interval (CI) of the difference of the rates of discontinuation due to ADR was calculated and then compared with the equivalence range (−5% , 5%). P-values were calculated with Fisher's exact test to determine whether the rates were significantly different. 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. See Supplement Table 1 for the study populations.

A Cox regression analysis was performed to assess demographic and clinical risk factors for tuberculosis. The proportional hazards assumption was verified by plotting the negative log of the survivor functions versus the log of time, and for suspect factors, an interaction with time was analyzed. Participants who initiated antiretroviral therapy during the study did so at different times. Antiretroviral therapy was therefore examined as a time-dependent variable, with the initiation of antiretroviral therapy being measured from enrollment date. For all analyses, statistical significance was achieved with a p-value < 0.05, unless stated otherwise.

Enrollment began in June 2001. Although enrollment into the parent study ended in February 2008, the trial was kept open through December 2010 for enrollment of HIV-infected persons. AIDS Clinical Trial Group (ACTG) and International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) sites in Peru, Brazil, and the U.S. started enrollment during this extended period. A flow-chart of enrollment and follow-up of study participants is presented in Supplement Figure 1, and enrollment sites are at the end of the Supplement.

Results

There were 403 persons with HIV enrolled in the study, of whom 4 were subsequently found to be ineligible (see Supplement Table 2). Therefore, 399 persons were included in the MITT study population: 206 in the 3HP arm and 193 in the 9H arm. The clinical and demographic characteristics of the MITT study population are shown in Table 1. There were no statistically significant differences by study arm in median age, sex, race, region of enrollment, history of alcohol, injection drug, or tobacco use, hepatitis C virus infection, body mass index (BMI), or median baseline CD4+ lymphocyte count. The numbers (%) of participants with > 350 CD4+ lymphocytes/mm^3 were 158 (84%) and 140 (84%) in the 3HP and 9H arms, respectively. There was no significant difference in the cumulative loss to follow-up rate by treatment arm (log-rank P = 0.34) and fewer than 16% of enrolled participants from either arm were lost through day 800 after enrollment. (Supplement Figure 2). There were 67 participants (33%) in the 3HP arm and 58 (30%) in the 9H arm who received antiretroviral therapy during the study (P = 0.67) at a median time after enrollment of 284 days (IQR 179–544) in the 3HP arm vs. 186 days (IQR 89–392) in the 9H arm (P = 0.06). Of the 403 persons enrolled, 5 were children < 18 years old; all were ≥ 12 years old.

In the MITT population, two tuberculosis episodes occurred during 517 person-years (p-y) of follow-up in the 3HP arm (0.39 episodes per 100 p-y) and six tuberculosis episodes during 481 p-y of follow-up in the 9H arm (1.25 episodes per 100 p-y) (Figure 1 and Table 2). Cumulative tuberculosis rates were 1.01% vs. 3.50% in the 3HP and 9H arms, respectively (difference in cumulative tuberculosis rate: −2.49%; upper bound of the 95% CI of the difference: 0.60%). In the per-protocol analysis, cumulative tuberculosis rates were 0.56% and 1.81% in the 3HP and 9H arms, respectively (rate difference: −1.25%; upper bound of the 95% CI of the difference: 1.47%). See Supplement Figure 3.

There were 14 participants who received little or no study treatment (< 2 doses of HP or < 31 days of H); one developed tuberculosis (cumulative tuberculosis rate: 12.5%; 4.4 per 100 p-y).

Of the eight tuberculosis cases, three received antiretroviral therapy prior to developing active tuberculosis. All three participants were in the 9H arm, and the times from antiretroviral therapy initiation to tuberculosis diagnosis were 143, 181, 221 days.

Among those participants with CD4+ lymphocyte counts at study entry, the median CD4+ count was 366 (IQR 338–460; n=6) in those who developed tuberculosis vs. 513 (IQR 404–710; n=348) in those who did not (P = 0.1). Of the eight tuberculosis cases, resistance

testing was performed on all: six had no resistance to first-line anti-tuberculosis drugs, one isolate identified as *M. bovis* had resistance to rifampin and pyrazinamide (3HP arm; participant enrolled in the United States) and one isolate had resistance to isoniazid, rifampin, and streptomycin (9H arm; participant enrolled in Peru).

Treatment completion was significantly higher in the 3HP arm than the 9H arm (Table 3). Treatment discontinuation due to ADR was similar in both study arms, and the 95% CI of the difference was −4.7 to 2.9, which was within the equivalence range of −5% to 5% (Table 3). Rates of drug discontinuation due to grade 3 or higher adverse drug reactions were low and similar in the two arms. Drug discontinuation due to hepatotoxicity was significantly higher in the 9H arm (4%) than the 3HP arm (1%; P = 0.05). Flu-like/systemic drug reactions occurred in two patients in the 3HP arm and none in the 9H arm. All grade 3 and 4 adverse events are summarized in Supplement Table 3. Eleven patients died: five in the 3HP arm and six in the 9H arm. None of the deaths were attributable to tuberculosis and only two were AIDS-related (Supplement Table 4).

Treatment effectiveness was compared among HIV-infected participants to the HIV-uninfected participants in the PREVENT TB study (Supplement Table 5). In the MITT population, the difference in cumulative tuberculosis rate between HIV-infected and –uninfected persons who received 3HP was 0.83%. Since the confidence interval of the difference contained zero, there was no statistical evidence that the 3HP tuberculosis rates differed by HIV status. The difference in cumulative tuberculosis rate by HIV status in the 9H arm was 2.97%. The cumulative tuberculosis rate among HIV-infected participants was significantly higher than the rate among HIV-uninfected participants (3.50% vs. 0.53%; P = 0.018).

The tolerability of the two regimens in HIV-infected vs. –uninfected participants is summarized in Supplement Table 6. In the 3HP arm, rates of treatment completion were higher (88.8% vs. 80.2%; P = 0.002) and rates of flu-like/systemic drug reactions were lower (1.0% vs. 4.6%; P = 0.01) among HIV-infected persons. In the 9H arm, rates of grade 3 and 4 toxicity, hepatotoxicity, and serious adverse events were higher in HIV-infected than –uninfected persons. In both study arms, the risk of death was higher in HIV-infected than –uninfected persons, though it was not statistically significant in the 9H arm.

The univariate and multivariate analyses for risk factors associated with developing tuberculosis are described in Supplement Table 8. All factors were independently examined, and met the proportional hazard assumption. Factors independently associated with tuberculosis risk were baseline CD4+ lymphocyte count < 350 cells/mm^3, and low BMI. There were no statistically significant 2 by 2 interaction terms among these factors, nor any interactions of them with treatment regimen. After adjusting for these variables, participants randomized to 3HP were less likely to progress to tuberculosis compared to participants randomized to 9H, but the difference was not statistically significant (adjusted HR, 0.27; 95% CI, 0.05 to 1.44; P = 0.13).

Discussion

In the primary effectiveness population (MITT), 3HP was non-inferior to 9H for treatment of *M. tuberculosis* infection in persons with HIV infection. In addition, the 3HP regimen had a higher treatment completion rate and was as well-tolerated as 9H, with similar rates of grade 3, 4, and 5 toxicity in the two arms. Compared to 9H, the 3HP regimen had a significantly lower rate of drug discontinuation due to hepatotoxicity, and the risk of flu-like and other systemic drug reactions was also low. Although non-inferiority was not achieved in the PP analysis (likely due to the low number of events), the PP results were consistent with the MITT results, as well as with previous findings in the PREVENT TB trial, and with a study among persons with HIV infection in South Africa.[9, 10] Taken together, these clinical trials demonstrate that 3HP is effective and safe to treat latent *M. tuberculosis* infection in persons with HIV infection and high CD4+ lymphocyte counts (median CD4+ in this study approximately 500 cells/mm^3) who have not started antiretroviral therapy.

Study recruitment was limited to persons who did not plan to receive antiretroviral therapy within 90 days of enrollment because at the time the study was designed there were no data on the drug interactions between rifapentine and HIV-1 protease inhibitors or non-nucleoside reverse transcriptase inhibitors. However, recent studies have demonstrated that rifapentine, given either once-weekly or daily, has minimal interaction with daily efavirenz.[15, 16] Furthermore, additional studies have demonstrated that once-weekly rifapentine may be given with the integrase strand transfer inhibitor raltegravir.[17] Although studies of the effectiveness of 3HP when given with efavirenz-or raltegravir-based antiretroviral therapy are needed, these pharmacokinetic studies suggest that such regimens can be given concomitantly. Such effectiveness studies would likely include persons with lower CD4+ lymphocyte counts.

The requirement that participants not receive antiretroviral therapy for at least 90 days after enrollment likely contributed to the slow enrollment. Because of the slow pace, it was decided to stop enrollment before reaching the target sample size.

There were different numbers of participants in each study arm. This could be due to minor imbalances related to unrestricted randomization. In addition, study participants living in the same household received the same treatment as the first person in the household. Thus, only the first person in the household was randomized, and there were differences by regimen in the number of persons in households. Early in the study, household members did not have to provide informed consent before the first member was randomized, and this may have influenced participation by arm.

The multivariate risk factor analysis identified several factors that were independently associated with tuberculosis risk, including baseline CD4+ lymphocyte count < 350 cells/mm^3. This is consistent with prior studies demonstrating the strong association between low CD4+ lymphocyte count and tuberculosis risk.[18, 19] Antiretroviral therapy decreases tuberculosis risk independent of treatment of latent *M. tuberculosis* infection with daily isoniazid, presumably due to both increases in CD4+ lymphocyte count and decline in HIV-1 RNA.[20–24] In this study, approximately 30% of the participants received

antiretroviral therapy during the study period, but the risk factor analysis did not find antiretroviral therapy to be significantly associated with tuberculosis risk (Supplement Table 8). We did not have information on the number of participants who achieved virologic suppression. To accurately assess the role of changes in CD4+ lymphocyte count on tuberculosis risk, repeated measures of this time-varying variable would be needed; which was not available in this study. In addition, antiretroviral therapy use was not randomized, so the analysis of time-dependent antiretroviral therapy is subject to indication bias.

Low baseline BMI was also independently associated with tuberculosis risk. Although it has been known that low BMI is associated with increased tuberculosis risk,[24–26] it is unclear whether interventions specifically to increase BMI during treatment of latent *M. tuberculosis* infection further decrease the risk compared to medication alone; antiretroviral therapy is also associated with weight gain.

In this study, active tuberculosis at baseline was excluded by clinical evaluation and chest X-ray. HIV-infected persons with active tuberculosis who receive once-weekly rifapentine plus isoniazid in the continuation phase of treatment are at increased risk of acquired rifamycin resistance.[27] Although there is no evidence that treatment of latent *M. tuberculosis* infection in persons with HIV infection leads to development of drug-resistant tuberculosis, ruling out disease prior to starting preventive therapy is important. In the study of 3HP in Soweto, South Africa, a setting with high rates of tuberculosis and multidrug-resistant tuberculosis, there was no clear evidence that preventive treatment selected for resistance. [10] In this study, two of the eight tuberculosis cases had rifampin resistance, but one occurred in the 9H arm, in a participant from Peru, which has high background rates of drug resistance. The second case was due to *M. bovis*, which was resistant to pyrazinamide as expected, plus rifampin. Given the low number of tuberculosis cases in these studies, development of resistance will be important to assess as the 3HP regimen is used more widely.

In the comparison between HIV-infected persons in this analysis vs. HIV-uninfected persons in PREVENT TB, tuberculosis rates among persons receiving 3HP were similar regardless of HIV status. However, among persons receiving 9H, HIV-infected persons had higher tuberculosis rates than HIV-uninfected persons. This suggests that 3HP may provide greater protection than 9H among HIV-infected persons, which should be confirmed in studies designed for such a comparison. Such a finding is consistent with the multivariate risk factor analysis (adjusted HR for tuberculosis in the 3HP arm: 0·24; 95% CI, 0.05 to 1.27; P-value=0.09). Regarding tolerability, 3HP was at least as well-tolerated in HIV-infected as in HIV-uninfected persons. Among persons receiving 9H, the risk of toxicity was greater in HIV-infected than HIV-uninfected persons.

Although there were possible discrepancies at Site A regarding receipt of study drug and directly-observed therapy, participants from this site were retained in the primary analyses because they met the criteria of the modified intention to treat study population (i.e., eligible for the study and randomized). All randomized participants should be included in intention to treat analyses.[28, 29] However, additional analyses with these participants removed did not change the direction of the associations for effectiveness, efficacy, or safety, though the

confidence intervals were wider due to the smaller sample size (Supplement Table 7/Figure 4).

There were several limitations of this study. First, the sample size was small. However, there was sufficient statistical power to demonstrate that 3HP was as safe as 9H, based on the criteria that were established before the study started (equivalence region of −5%, 5%) for the difference in drug discontinuation due to ADR). In addition, the number of tuberculosis cases was sufficiently high to be able to establish non-inferiority of 3HP in the MITT analysis. Second, there were few children enrolled. Children were retained in the analysis as we are unaware of substantial differences in *M. tuberculosis* pathogenesis in HIV-infected children compared to adults. Although a recent analysis of predominantly HIV-uninfected children demonstrated good safety and effectiveness of 3HP, [30] additional data are needed in HIV-infected children. Third, the study had an open-label design, with both participants and clinicians aware of the regimen received. There were also differences in dosing frequency and duration between the two study arms. The higher treatment completion rates in the 3HP arm were likely due to both direct observation and the shorter treatment course.

Our study indicates that 3HP is as effective as 9H for the treatment of latent *M. tuberculosis* infection in HIV-infected persons with high CD4+ lymphocyte counts (median approximately 500 cells/mm^3) who have not initiated antiretroviral therapy. 3HP is safe, well-tolerated, and associated with higher treatment completion rates than 9H; this regimen should be used for treatment of latent *M. tuberculosis* infection in appropriately selected persons with HIV. Further studies of 3HP in advanced HIV disease, including with concurrent antiretroviral therapy, are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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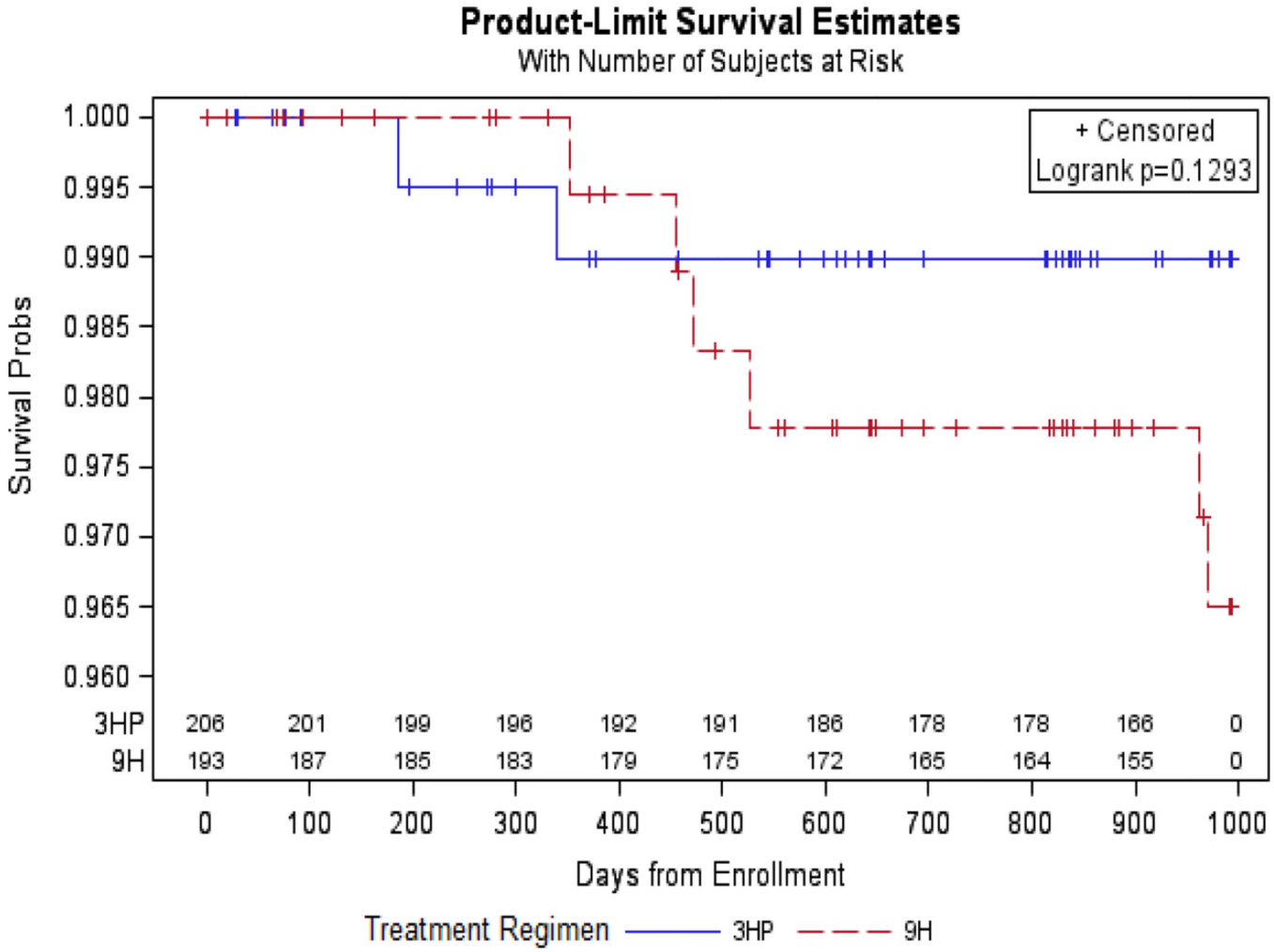

Figure 1. Kaplan-Meier curve of time to tuberculosis by study arm in the MITT study population

The number of persons at risk at 100-day increments from enrollment are provided.

Table 1
Characteristics of the modified intention to treat (MITT) study population

This includes all participants who enrolled in the study and met eligibility criteria.

Characteristic	3HP N=206 n (%)	9H N=193 n (%)	P-value
Median age-years (IQR)[#]	36 (30–44)	36 (29–44)	0.85
Median CD4+ lymphocyte count—baseline (IQR)[*]	495 (389–675)	538 (418–729)	0.09
ART reported[//]	67 (33)	58 (30)	0.67
Male sex	146 (71)	131 (68)	0.59
Race			
White	76 (37)	73 (38)	0.92
Black	75 (36)	75 (39)	0.68
Asian/Pacific Islander	6 (3)	3 (2)	0.50
North American Indian	5 (2)	4 (2)	1.00
Multiracial	44 (21)	38 (20)	0.71
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 (22–28)	25 (22–28)	0.75
Underweight	4 (2)	4 (2)	1.00
Normal	94 (46)	83 (43)	0.62
Overweight	79 (38)	68 (35)	0.53
Obese	29 (14)	38 (20)	0.14
Region of enrollment			
U.S. / Canada	91 (44)	95 (49)	0.32
Brazil/Peru/Spain/ Hong Kong[@]	115 (56)	98 (51)	0.32
Indication for LTBI			
Contact	195 (95)	188 (97)	0.20
TST converter	11 (5)	5 (3)	0.20
History EtOH use[**]	113 (55)	120 (62)	0.16
History IDU	33 (17)	27 (13)	0.33
Current smoker (at enrollment)	82 (40)	90 (47)	0.19
High School	123 (60)	118 (61)	0.84
Jail/Prison	16 (8)	24 (12)	0.14
Unemployed	37 (18)	47 (24)	0.14
Homeless	22 (11)	22 (11)	0.87
Methadone[^]	9 (4)	15 (8)	0.21

Characteristic	3HP N=206 n (%)	9H N=193 n (%)	P-value
Hepatitis C virus	22 (11)	26 (13)	0.44

3HP: three months of weekly rifapentine plus isoniazid under direct observation
9H: nine months of daily isoniazid, self-administered
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 188 participants in the 3HP arm and 166 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.

[@]By country: a: 3HP – 34 (17%), 9H – 42 (22%); b: 3HP – 35 (17%), 9H – 30 (16%); c: 3HP – 45 (22%), 9H – 25 (13%); d: 3HP – 1 (0.5%), 9H – 1 (0.5%).

[**]Alcohol use: by participant self-report; answered “yes” to ≤1 CAGE question. CAGE: cut-annoyed-guilty-eye (alcohol questionnaire)

[^]In a methadone maintenance program at study enrollment.

Table 2

Tuberculosis cases and event rates by treatment arm

Modified intention to treat population						
Treatment arm	**N**	**# TB cases**	**TB rate per 100 p-y**	**Cumulative TB rate (%)**	**Difference in Cumulative TB rate[a]**	**Upper bound of the 95% CI (%)**
9H	193	6	1.25	3.50	−2.49	0.60
3HP	206	2	0.39	1.01		

Per protocol population						
Treatment arm	**N**	**# TB cases**	**TB rate per 100 p-y**	**Cumulative TB rate (%)**	**Difference in Cumulative TB rate[a]**	**Upper bound of the 95% CI (%)**
9H	123	2	0.63	1.81	−1.25	1.47
3HP	183	1	0.21	0.56		

9H: nine months of daily isoniazid, self-administered

3HP: three months of weekly rifapentine plus isoniazid under direct observation

[a]The difference is the rate for 3HP minus the rate for 9H.

Table 3
Safety and tolerability of the study regimens

Among participants who received ≥ 1 dose of study medications, except as noted. Percentages are in parentheses.

Characteristic	3HP N=207 n (%)	9H N=186 n (%)	P-value	% Difference (95% C.I.)[a]
Treatment completion (MITT)	183/206 (89)	123/193 (64)	<0.001	25.0 (17.0, 33.0)
Discontinuation due to adverse drug reaction	7 (3)	8 (4)	0.79	−1.0 (−4.7, 2.9)
Grade 3 toxicity	14 (7)	18 (10)	0.36	−3.0 (−8.4, 2.5)
Grade 4 toxicity	4 (2)	10 (5)	0.10	−3.0 (−7.2, 0.3)
Grade 5 (death)	6 (3)	5 (3)	1.00	0.2 (−3.0, 3.5)
Discontinuation due to hepatotoxicity[b]	2 (1)	8 (4)	0.05	−3.0 (−6.5, −0.1)
Flu-like/systemic drug reaction	2 (1)	0 (0)	0.50	1.0 (−0.4, 2.3)

3HP: three months of weekly rifapentine plus isoniazid under direct observation.
9H: nine months of daily isoniazid, self-administered.

[a] 95% CI for the difference in proportions using the Wilson Score Interval method.

[b] Neither of the two persons in the 3HP arm and three of the eight persons in the 9H arm had underlying hepatitis C virus infection.