

ICAP's Journal Club is designed to inform ICAP staff and colleagues of the latest scientific literature by providing a succinct summary and critical analysis of important studies, and by discussing the implications of the research on clinical work.

Article

Swindells S, Ramchandani R, Gupta A, et al for the BRIEF TB/A5279 Study Team. **One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis.** *N Engl J Med.* 2019;380(11):1001–1011. <https://doi.org/10.1056/NEJMoa1806808>.

Study Summary

This randomized, open-label, non-inferiority trial compared the efficacy and safety of a 1-month regimen of daily rifapentine plus isoniazid to nine months of isoniazid alone as tuberculosis preventive treatment (TPT) in HIV-positive adults and adolescents.

Study Setting

- Forty-five sites in 10 countries in Africa, Asia, South America, North America, and the Caribbean.

Methods

- Eligible participants had confirmed HIV infection, were ≥ 13 years of age and either lived in an area with a tuberculosis (TB) prevalence of ≥ 60 cases per 100,000 or had a positive test for latent TB.
- Individuals were excluded from the study if they were pregnant or breastfeeding, had elevated liver enzymes, weighed < 30 kilograms, had known or suspected active TB, or had recently received treatment for TB.
- Participants were stratified by antiretroviral therapy (ART) status and CD4 cell count at baseline, and randomized (1:1) to receive either four weeks of daily rifapentine (dosed at 300 milligrams for a weight of < 35 kilograms, 450 milligrams for 35–45 kilograms, and 600 milligrams for > 45 kilograms) plus 300 milligrams of isoniazid daily (1-month group) or 36 weeks of isoniazid alone at a dose of 300 milligrams daily (9-month group). All participants received pyridoxine with each dose of trial medication.
- Participants were followed for at least three years and trial visits were conducted at weeks 2, 4, 8, 12, 16, 20, 24, 36, and every 12 weeks thereafter.
- Treatment completion was defined as self-reported adherence to the trial regimen. Participants in the 1-month group were given eight weeks to complete treatment, whereas participants in the 9-month group were allowed 54 weeks to accommodate possible interruptions.
- The primary end point was a diagnosis of active TB, death from TB, or death of unknown cause.
- Secondary end points included adverse events and drug-related side-effects.

- The non-inferiority margin was set at 1.25 for the upper limit of the 95% confidence interval (CI) for the between-group difference in the number of events per 100 person-years.
- A modified intention-to-treat method was used for the primary analysis, which included all participants who had received at least one dose of a trial medication.

Study Population and Follow-up

- From May 2012 to November 2014, 3,696 individuals were assessed for eligibility, of which 3,000 underwent randomization.
- Of those randomized, 14 never received a dose of medication and were excluded from the analysis, with 1,498 included in the 9-month group and 1,488 in the 1-month group analysis.
- More participants were female (54%) and were from Africa (52%). The median age was 35 years (interquartile range [IQR] 28–43).
- Participants had a median CD4 count of 470 cells per cubic millimeter (IQR, 346–635). Fifty percent were receiving ART on study entry and 77% of those on ART had an undetectable viral load (<40 copies/milliliter).
- The majority of participants (97%) were from areas with a high prevalence of TB, and 23% had a positive tuberculin skin test and/or a positive result on the interferon- γ release assay.
- Self-reported adherence to treatment was $\geq 90\%$ in each group; treatment was completed in 97% of the participants in the 1-month group and in 90% of those in the 9-month group ($p < 0.001$).
- A total of 18% of the participants in each group were lost to follow-up and the median time of trial participation was approximately 3.3 years.

Primary Outcome

- The primary end point occurred in 2% (32/1,488) of participants in the 1-month group and in 2% (33/1498) of participants in the 9-month group, with incidence rates of 0.65 and 0.67 per 100 person-years (py), respectively, for a between-group difference of -0.02 per 100 py (95% CI, -0.35 to 0.30).
- Active TB accounted for 91% (29/32) of events in the 1-month group and for 79% (26/33) of events in the 9-month group.
- The primary end point incidence rate was higher among those with evidence of latent TB infection (0.90 per 100 py in the 1-month group and 0.97 per 100 py in the 9-month group), and among those who were not on ART at enrollment (0.75 per 100 py and 0.72 per 100 py in the 1- and 9-month groups, respectively), although these differences were not statistically significant.
- Among participants with a CD4 count ≤ 250 cells per cubic millimeter at baseline, the incidence of the primary end point was higher in the 1-month group than in the 9-month group (1.93 per 100 py and 1.28 per 100 py, respectively), whereas among those with a CD4 count > 250 cells per cubic millimeter, the incidence was lower in the 1-month group than the 9-month group (0.47 per 100 py and 0.59 per 100 py, respectively), however neither of these differences were statistically significant.

Secondary Outcomes

- Discontinuation of treatment because of toxic effects occurred in 1% (n = 16) of participants in the 1-month group and in 2% (n = 25) in the 9-month group.
- The proportional odds ratio for discontinuing or withholding a trial regimen was 2.09 (95% CI 1.32–3.33), favoring the 1-month regimen.
- Serious adverse events of any grade occurred in 6% (n = 83) of participants in the 1-month group and in 7% (n = 108) in the 9-month group (p = 0.07).
- Elevations in liver enzymes of grade 3 or greater and neurologic toxicity were less common in the 1-month group than in the 9-month group (2% vs. 3% and 1% vs. 2%, respectively), whereas neutropenia of grade 3 or higher was more common in the 1-month group (2% vs. 1%).
- An analysis of the rates of combined grade 3 and 4 serious adverse events and targeted safety events (nausea and vomiting, rash, drug-associated fever, elevated liver enzymes, and peripheral neuropathy) showed that fewer events occurred in the 1-month group than in the 9-month group (2.9 vs. 4.6 events per 100 py, p = 0.01).

Critical Analysis

This randomized, open-label, non-inferiority trial demonstrated that one month of daily rifapentine plus isoniazid was non-inferior to nine months of daily isoniazid for the prevention of TB in HIV-positive adults and adolescents. Participants receiving the 1-month regimen had a lower incidence of adverse events and were more likely to complete treatment than those receiving the 9-month regimen.

The following points should be considered when interpreting the study findings:

- Pregnant and breastfeeding women, as well as children under the age of 13 years, were excluded from this trial; therefore, the efficacy and safety of the 1-month trial regimen remains unclear in these groups.
- This trial was started before global policy shifted to treat all people living with HIV, regardless of CD4 cell count. Consequently, only half of participants were receiving ART at the time of enrollment in the trial, but over 90% were on ART by trial completion.
- Despite low ART use at baseline, overall TB incidence was lower than expected, which limited ability to perform sub-group analyses.
- Only a small proportion of participants (13%) had a CD4 count ≤ 250 cells per cubic millimeter at baseline, and only 2% had a CD4 count < 100 cells per cubic millimeter, limiting the generalizability of these findings in those with more advanced HIV disease.
- The majority of those receiving ART at baseline were on an efavirenz-based regimen (86%); therefore, it remains unclear if similar results would be seen with the 1-month regimen and integrase inhibitor-based ART regimens, such as those containing dolutegravir. However, there is preliminary evidence that weekly rifapentine is safe and does not affect viral load suppression in those on a dolutegravir-based ART regimen.¹

Implications

This randomized, open-label trial showed that a 1-month regimen of daily rifapentine plus isoniazid (also known as “1HP”) was non-inferior to daily isoniazid for nine months as TPT in HIV-positive individuals. The 1-month regimen was also found to be safe, with fewer adverse events and a better completion rate than the traditional 9-month regimen. This study provides strong evidence that national programs should consider the 1-month regimen used in this study as an option for TPT in people living with HIV. However, cost of the 1HP regimen may be a barrier and there still remain gaps in evidence around its use with pregnant and breastfeeding women, children, and those on a dolutegravir-based regimen.

This article synopsis was written by Cassia Wells. Share your thoughts on this article or suggest an article for Journal Club by emailing her at can2208@columbia.edu.

References

1. Dooley, KE, Churchyard, G, Savic, RM et al. Safety and PK of Weekly Rifapentine/Isoniazid (3HP) In Adults with HIV on Dolutegravir. Oral abstract presented at Conference on Retroviruses and Opportunistic Infections, March 2019, Seattle, Washington. Available at: <http://www.croiconference.org/sessions/safety-pk-weekly-rifapentineisoniazid-3hp-adults-hiv-dolutegravir>