Published in final edited form as:

*J Infect Dis*. 2024 November 15; 230(5): 1271–1278. doi:10.1093/infdis/jiae180.

# Assessment for Antibodies to Rifapentine and Isoniazid in Persons Developing Flu-Like Reactions During Treatment of Latent Tuberculosis Infection

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## Abstract

**Background.—**Flu-like reactions can occur after exposure to rifampin, rifapentine, or isoniazid. Prior studies have reported the presence of antibodies to rifampin, but associations with underlying pathogenesis are unclear.

**Methods.—**We evaluated PREVENT TB study participants who received weekly isoniazid plus rifapentine for 3 months (3HP) or daily isoniazid for 9 months (9H) as treatment for *Mycobacterium tuberculosis* infection. Flu-like reaction was defined as a grade ≥2 of any of flu-like symptoms. Controls (3HP or 9H) did not report flu-like reactions. We developed a competitive enzyme-linked immunosorbent assays (ELISA) to detect antibodies against rifapentine, isoniazid, rifampin, and rifapentine metabolite.



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***Author contributions.*** T. R. S. and A. S. B. conceived the study protocol, which was a substudy of the parent clinical trial. K. M. D., C. M., and P. D. conducted laboratory methodology procedures and conceptualization. R. N. M., T. R. S., C. M., and K. M. D. contributed to methodology, conceptualization, and writing of the original draft manuscript. A. S. B. contributed to conceptualization, data collection, and data curation. R. N. M. contributed to data collection, data curation, and analysis. E. P. provided substantial contributions to clinical and immunological concepts. All authors contributed to the writing, critical review, and editing of the manuscript, and approved the final version.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

***Financial support.*** No financial support was received for this work.

**Results.—**Among 128 participants, 69 received 3HP (22 with flu-like reactions; 47 controls) and 59 received 9H (12 with flu-like reactions; 47 controls). In participants receiving 3HP, anti-rifapentine IgG was identified in 2 of 22 (9%) participants with flu-like reactions and 6 of 47 (13%) controls ($P = .7$), anti-isoniazid IgG in 2 of 22 (9%) participants with flu-like reactions and 4 of 47 (9%) controls ($P = .9$). Among participants receiving 9H, IgG and IgM anti-isoniazid antibodies were each present in 4 of 47 (9%) controls, but none among participants with flu-like reactions; anti-rifapentine IgG antibodies were not present in any participants with flu-like reactions or controls.

**Conclusions.—**We detected anti-rifapentine, anti-isoniazid, and anti-rifapentine metabolite antibodies, but the proportions of participants with antibodies were low, and did not differ between participants with flu-like reactions and those without such reactions. This suggests that flu-like reactions associated with 3HP and 9H were not antibody mediated.

**Clinical Trials Registration.—**NCT00023452.

## Keywords

rifapentine; isoniazid; antibodies; latent tuberculosis; *M. tuberculosis*

Rifamycins (eg, rifampin and rifapentine) and isoniazid are effective antituberculosis drugs that have been used to treat and prevent tuberculosis for approximately 7 decades. Among the adverse events (AEs) associated with these drugs, flu-like reactions have been described, including in persons receiving rifampin [1, 2], isoniazid [3–6], and once-weekly rifapentine and isoniazid [7, 8].

The flu-like syndrome, characterized by fever, chills, malaise, headache, and joint and bone pain, was first described in association with intermittent, high doses of rifampin given alone or in combination with other antituberculosis drugs (eg, isoniazid or ethambutol) [1, 2, 9–13]. Several organ systems can be involved, including cutaneous, abdominal, and/or respiratory [1, 14, 15]. Although this reaction has been associated with the presence of antibodies to rifampin, antibodies to rifampin do not closely correlate with the development of flu-like reactions [16]. Antibodies against rifampin were reported in 55% of those who developed flu-like reactions, compared to 22% among those who did not [14]. In another study, rifampin-dependent antibodies were reported in only 23% of patients who developed flu-like reactions while receiving antituberculosis treatment [17]. Antibodies to rifampin are neither sensitive nor specific for flu-like reactions [18].

In 1973, Worlledge described a method to detect rifampin-dependent antibodies based on an indirect assay showing positive reactions to complement [18]. This method relies on complement fixation of the drug-antibody complex; the result is usually nonquantitative (eg, agglutination of red blood cells). Subsequent studies have used this and similar techniques. However, the method we developed is based on a quantitative indirect enzyme-linked immunosorbent assay (ELISA).

The Tuberculosis Trials Consortium PREVENT TB trial demonstrated that a 12-dose once-weekly regimen of isoniazid (900 mg) plus rifapentine (900 mg) (3HP), the maximum doses used for the study, was as effective as the standard 9-month daily isoniazid (300

mg) (9H) regimen for the treatment of latent tuberculosis infection (LTBI) [19]. In this trial, a higher proportion of participants who received 3HP developed flu-like reactions compared to participants receiving 9H (3.8% vs 0.5%, respectively; $P < .001$). In a separate substudy, as part of a more in-depth evaluation of the AEs developed by PREVENT TB participants, flu-like reactions were thought to be nonimmunologically mediated because some characteristics (eg, the successful completion of treatment despite drug reactions) were different from known immunologically mediated drug reactions (eg, intensification of symptoms with continued dosing and severe reactions after rechallenge) [7].

The objectives of this study were to (1) assess serum antibodies against rifapentine, isoniazid, rifampin, and rifapentine metabolite in participants treated with 3HP or 9H for LTBI; and to (2) determine whether the presence of antibodies was more frequent in participants who developed flu-like reactions than controls.

## METHODS

### Study Population

This study was an observational, post hoc analysis of data nested within the PREVENT TB trial, a phase 3, multicenter, open-label, randomized trial registered at https://clinicaltrials.gov/ (NCT00023452) [19]. This substudy was designed after possible flu-like reactions and hypotensive events were reported in participants receiving either 3HP or 9H. All participants enrolled in the trial provided written informed consent, which included evaluation of potential drug toxicity; controls for this substudy provided additional informed consent. Institutional review boards at the Centers for Disease Control and Prevention and at all participating clinical sites approved the protocols for the PREVENT TB study and this substudy.

At enrollment into the PREVENT TB trial, all participants denied a history of treatment for more than 14 consecutive days with a rifamycin (rifampin, rifabutin, rifapentine), treatment for more than 30 consecutive days with isoniazid within 2 years prior to enrollment, treatment of LTBI or tuberculosis disease in the past, or history of sensitivity/intolerance to isoniazid or rifamycins.

Flu-like reactions were defined as any participant enrolled in the trial who developed a grade 2, 3, or 4 AE of flu-like related symptoms, based on the Common Toxicity Criteria version 2.0 [20] , that was felt to be definitively, probably, or possibly study drug-related and for which there was no other known explanation. Serum samples were collected only for the substudy. Participants with flu-like reactions had samples collected at up to 4 time points based on the development or recovery from symptoms: (1) acute phase severe, if episodes of any of the following occurred, hypotension, urticaria, angioedema, or acute bronchospasm; (2) acute phase nonsevere, if at least 4 of the following symptoms occurred (at least 1 of which was reported as an AE of ≥grade 2): weakness, fatigue, nausea, vomiting, headache, fever, aches, sweats, dizziness, shortness of breath, flushing, or chills; (3) asymptomatic, no symptoms and <10 days after recovery from symptoms; and (4) convalescent, 10–35 days after recovery from symptoms (Supplementary Material). The sampling scheme in the protocol was based on the severity of symptoms rather than the grade (eg, hypotension,

urticaria, angioedema, bronchospasm). Potential controls were identified and enrolled into the substudy after enrollment into the parent study but prior to taking any study medicine. Controls and participants who developed flu-like reactions were enrolled in US sites. Controls were a convenience sample randomly selected from participants at the 5 highest-enrolling sites who received either study regimen but did not develop flu-like reactions, even after completion of treatment. Identified controls had samples collected at up to 2 time periods: at baseline and after 12 weeks of therapy (eg, 12 doses of 3HP or 84 doses of 9H). The estimated sample size was 52 participants with flu-like reactions and 104 controls (Supplementary Material). Power calculations were adjusted to account for the possibility that there was a low incidence of antibody development among participants with flu-like reactions in this study. It was conservatively assumed that no more than 25% of controls would have antibodies to rifapentine (Supplementary Material). Controls were randomly selected.

### Specimen Collection

For acute severe reactions, specimens were collected within 6 hours of onset of the reaction; for acute nonsevere reactions, specimens were obtained at the first opportunity after onset of symptoms. Laboratory specimens during the convalescent phase were collected 10–35 days after symptom resolution.

### Laboratory Methods

Blood specimens were collected and clotted for 30–60 minutes at room temperature, then centrifuged 10 minutes at 1000g (2000–3000 rpm). Serum was then frozen at −70°C within 60 minutes of centrifugation. Samples were labeled and delivered to Colorado State University for the development of the immunological assays to detect anti-rifapentine, anti-isoniazid, anti-rifampin, and anti-rifapentine metabolite antibodies. Laboratory personnel were blinded to the flu-like reaction/control status of the samples.

### Development of Immunoassay to Detect Antibodies Against Rifamycin

An indirect ELISA was developed to detect human antibodies against rifapentine, rifampin, and rifapentine metabolite. For this purpose, rifamycin S [21], which has the core structure of all rifamycins, was conjugated to carrier proteins ovalbumin (OVA), keyhole limpet hemocyanin (KLH), or streptavidin (STR). The methodology used in the ELISA assay was originally developed for this study. Subsequently, the same ELISA and conjugation methods were used by Brooks et al to detect antibodies against rifapentine, isoniazid, and rifapentine metabolite [22].

Briefly, rifamycin-S-KLH was injected into New Zealand white rabbits to obtain polyclonal antirifamycin-S serum (rabbit polyclonal), which was used as a positive control. Immunizations were carried out at Pierce Custom Antibody Services (Thermo Scientific). Pooled clean human serum (AB blood type; Sigma Aldrich) was used as a negative control. Rifamycin-S-OVA and OVA were used as antigens during ELISA optimization.

Human serum samples were initially tested at a dilution of 1:10. Samples with a resulting absorbance of more than 3 times the read for the negative control were tested again at a

dilution of 1:50 and 1:100 using rifamycin-S-STR as antigen. This was performed to rule out possible cross-reactivity to OVA. Samples with a resulting absorbance of more than 3 times the read for the negative control were considered potential positives for the presence of antibodies against rifamycins and subsequently subjected to isotyping.

Isotyping of potential positive samples was performed using antibodies against human immunoglobulin E (IgE), IgA, IgG, and IgM isotypes. Human serum samples were tested at a dilution of 1:50. Samples with a resulting absorbance of more than 3 times the read for the negative control were considered potential positives for the presence of the respective isotype. To confirm antibody specificity against rifapentine, rifampin, or rifapentine metabolite, samples with a positive isotype were confirmed by a competitive ELISA using rifapentine, rifampin, and rifapentine metabolite as competitors.

### Development of Immunoassay to Detect Isoniazid Antibodies

An indirect ELISA was developed to detect human antibodies against isoniazid. For this purpose, isoniazid was conjugated to carrier proteins OVA or KLH The ELISA and conjugation methods have been published elsewhere [22].

Briefly, New Zealand white rabbits were immunized with isoniazid-OVA conjugate to develop an anti-isoniazid ELISA and with isoniazid-KLH conjugate to generate rabbit sera to use as a positive control. The final ELISA parameters were defined as those resulting in the largest difference among isoniazid-OVA versus OVA. Serum samples were run in an initial screening assay for anti-isoniazid responses, followed by confirmation of reactivity in 2 subsequent validation assays. Pooled clean human serum (AB blood type; Sigma Aldrich) was used as a negative control. A negative control was tested at the same dilution as the participant samples. Human serum samples were initially tested at a dilution of 1:10. Samples with a resulting absorbance of more than 3 times the read for the negative control were tested again at a dilution of 1:200. At this dilution, the presence of human antibodies against both isoniazid-OVA and OVA were tested. Only samples with a positive signal (more than 3 times the absorbance of the negative control) for isoniazid-OVA but negative when tested against OVA alone (less than 3 times the absorbance of the negative control) were considered potential positives and subjected to isotyping.

Isotyping of potential positive samples was performed by an indirect ELISA using goat anti-human IgA, IgE, IgG, or IgM conjugated to alkaline phosphatase (Sigma Adrich) at a dilution of 1:2500 as secondary/detection antibodies. Human serum samples were tested at a dilution of 1:200. Samples with a resulting absorbance of more than 3 times the read for the negative control were considered potential positives for the presence of the respective isotype. To confirm the specificity of the antibodies to the tested drug, a competitive ELISA was developed.

### Statistical Analysis of Competitive ELISA Results

Negative controls, represented by 10 human serum samples from BioreclamationIVT (https://bioivt.com/) were tested in both rifapentine/rifampin/rifapentine metabolite and isoniazid competitive ELISAs as outlined above. There was no clinical information regarding these controls. All samples were tested at the same dilution as participants'

samples. Results were plotted in Excel. The delta optical density (OD) at 30 minutes was calculated as: delta OD = 405 nM OD sample without excess free drug − 405 nM OD sample with excess free drug. Percent binding from 0–30 minutes was calculated as: percent binding = b/b0 × 100, where b0 is the slope of the curve of sample with excess free drug and b is the slope of the curve of the sample tested without addition of drug. Confidence intervals (CIs) at 90% and 99% for both delta OD and percent binding results of the 10 negative samples for IgG and IgM were calculated using GraphPad Prism. Results from participant samples were compared to these cutoffs. Results with a delta OD higher than the 90% CI or a percent binding lower than the 90% CI were considered positives.

### Data Analysis

The median number of doses received by trial participant and the median duration of drug exposure in days were calculated among participants with flu-like reactions and controls and by regimen. The proportion of participants who developed IgG and/or IgM antibodies to the different antituberculosis drugs among participants with flu-like reactions and controls, and by regimen were calculated. *P* values were calculated with the use of $\chi^2$ tests for comparison of proportions of participants with flu-like reactions and controls who received the treatment regimen and in whom anti-rifapentine IgG, anti-isoniazid IgG, and anti-rifapentine metabolite IgG were identified.

## RESULTS

One hundred twenty-eight participants from the PREVENT TB trial were selected for clinical assessment and exploration of their immune response to rifapentine, isoniazid, rifampin, or rifapentine metabolite, of whom 69 received 3HP (22 participants with flu-like reactions and 47 controls) and 59 received 9H (12 participants with flu-like reactions and 47 controls). One participant, enrolled as a control, developed a flu-like reaction during treatment with 3HP and was analyzed as a participant with flu-like reaction in the ELISA testing. There were 3 children among participants with flu-like reactions, aged 2, 3, and 5 years, who received 3HP, 9H, and 3HP, respectively (Figure 1). In participants who received 3HP, the median number of doses among participants with flu-like reactions was 5 compared to 12 among controls; the median duration of drug exposure among participants with flu-like reactions was 29 days compared to 83 days among controls. In participants who received 9H, the median number of doses was 54 in participants with flu-like reactions versus 264 in controls; the median duration of drug exposure among participants with flu-like reactions was 59 days versus 286 days in controls. The shorter duration of treatment among participants with flu-like reactions was due to the development of the AE (Table 1).

Among participants who received 3HP, anti-rifapentine IgG antibodies were identified in 2 of 22 participants with flu-like reactions (9%) sampled during the convalescent phase (Table 2) and in 6 of 47 controls (13%) ($P = .7$); anti-rifapentine IgG were also observed in 3 of these 6 participants at baseline (Supplementary Table 1).

In the same group (3HP), anti-isoniazid IgG antibodies were identified in 2 of the 22 participants with flu-like reactions (9%) and in 4 of 47 controls (9%) ($P = .9$). No IgG anti-rifampin or anti-rifapentine metabolite antibodies were present among participants with

flu-like reactions; however, IgM anti-rifampin antibodies were found in 4 participants and IgM anti-rifapentine metabolite antibodies were found in 6 participants among 47 controls. Anti-rifapentine metabolite IgG was identified in 2 of 47 (4%) controls but not among participants with flu-like reactions ($P = .9$).

Among participants who received 9H, IgG anti-rifapentine antibodies were not present among participants with flu-like reactions or controls. However, IgM anti-rifapentine antibodies were present in 1 control after therapy. IgG anti-isoniazid antibodies were not detected in participants who experienced an AE while receiving 9H, whereas IgG and IgM anti-isoniazid antibodies were present in 4 of 47 controls (9%), of which 2 of the IgM antibodies were observed at baseline (Supplementary Table 2). No IgG anti-rifampin or anti-rifapentine metabolite antibodies were present among participants with flu-like reactions or controls.

Concurrent presence of antibodies was identified among participants with flu-like reactions and controls. Thus, among participants in the 3HP group, IgG anti-rifapentine and IgG anti-isoniazid antibodies were identified in 2 participants with flu-like reactions. IgG anti-rifapentine, IgM anti-isoniazid, IgM anti-rifampin, and IgM anti-rifapentine metabolite antibodies were identified in the serum of 2 controls. Among participants in the 9H group, IgM anti-rifapentine and IgM anti-isoniazid antibodies were found in 1 control (Supplementary Table 3 and 4). IgA or IgE were not detected.

IgM antibodies against rifampin were also present in 3 participants in the control group of the 9H cohort, including the 1 individual who also had IgM antibodies against rifapentine. IgM antibodies against both rifampin and rifapentine metabolite were also present in 1 participant in this control group.

## DISCUSSION

Our study population was nested within a prospective, randomized controlled clinical trial, the PREVENT TB study. We implemented an innovative, accurate antibody assay, the competitive ELISA, to detect antibodies against rifapentine, isoniazid, rifampin, and rifapentine metabolite. The advantages of using this newly developed test include the ability to confirm antibody specificity to highly similar antibiotics (ie, rifampicin, rifapentine, and rifapentine metabolite), and the ability to identify specific antibody isotypes. This method is different from other methods reported in previous studies, in which the presence of antibodies was tested through complement fixation assays. The complement fixation assay relies on antibody binding to complement. Different antibody isotypes have varying degrees of binding to complement [23], which may result in false negatives (if the isotype in serum does not bind complement efficiently). Blajchman et al in 1970 described a positive direct antiglobulin test due to antibodies complement-fixed on the red cells' surface of a patient with suspected rifampin-induced immune thrombocytopenia [24]. Worlledge et al in 1973 reported the detection of rifampin-dependent antibodies by complement-fixed reactions in patients who developed flu symptoms [18]. Similarly, other studies reported positive reactions to complement in serum of patients receiving rifapentine, mostly receiving intermittent doses of rifampin [25–28]. This ELISA was used to detect rifapentine, isoniazid,

and rifapentine metabolite in patients receiving dolutegravir with 3HP. While antibodies against isoniazid and rifapentine were identified in a few participants, similar to our results here, antibodies were not detected in a high proportion of participants who developed symptoms [22].

Previous studies using indirect laboratory methods (eg, reactions to the complement) reported the detection of anti-rifampin antibodies in about half of the persons who developed flu-like symptoms during the course of tuberculosis treatment. The presence of these antibodies has also been reported in other events such as thrombocytopenia, hemolytic anemia, and hepatitis, which are thought to be immunologically mediated. Although at a lower frequency of seropositivity, our laboratory method detected antibodies against the 4 drugs. For instance, among persons who received 3HP, 9% and 13% of IgG anti-rifapentine antibodies were identified among participants with flu-like reactions and controls, respectively; and 9% of IgG anti-isoniazid antibodies were identified among participants with flu-like reactions as well as among controls. Similar to previous reports, we identified antibodies in participants who had not developed an AE. The low proportion of antibodies against rifapentine or isoniazid detected in participants with flu-like reactions versus controls suggests that flu-like reactions associated with 3HP is not antibody mediated.

Although there was not sufficient power in the sample, the absence of IgG anti-rifapentine antibodies among participants who received 9H indirectly supports the specificity of the test. IgM antibodies against rifapentine metabolite and rifampin were detected in the serum of a participant who did not develop a flu-like reaction. This may indicate that the IgM assay against these 2 drugs may not be as specific. However, we identified rifapentine antibodies in participants without prior exposure to rifamycins and identified isoniazid antibodies in participants without prior exposure to isoniazid, which might indicate cross reaction with other substances of similar chemical structure or could indicate false-positive results.

Isoniazid is another important antituberculosis drug for treatment of both active tuberculosis disease and LTBI. Its most frequent AE is hepatitis; however, systemic reactions such as flu-like symptoms, fever, and hypersensitivity have also been reported [3–6, 29, 30]. The pathogenesis of these events is unclear. It has been proposed that the bioactivation of isoniazid can result in reactive metabolites that can form covalent adducts to liver proteins, which can eventually trigger an immune response [31]. Although at a low proportion, our study identified anti-isoniazid antibodies among participants with flu-like reactions who received 3HP and among controls who received 3HP or 9H, but not among participants with flu-like reactions who received 9H.

One of the main limitations was that sample collection at the time of the event, either severe or nonsevere, was not performed for every participant with flu-like reactions due to delays in notification of the study staff regarding the AE. In addition, 7 controls who received 3HP and 12 controls who received 9H missed the sample at baseline. Controls were selected from a subset of the sites, which may not be fully representative of all the sites. Another limitation was low statistical power; the number of participants with flu-like reactions and controls equal or higher to the calculated sample size were needed to statistically confirm

the lack of association between the development of symptoms and the development of drug antibodies. However, with the study sample size there was no suggestion of an association. These negative findings also raise the possibility that the flu-like reactions associated with 3HP and 9H are not antibody mediated. An alternative hypothesis that should be considered is that these are T-cell mediated reactions, leading to activation of T cells either through direct pharmacological interaction or an adaptive process previously described for drugs like abacavir. In the past, reactions to small-molecule medications like abacavir and even trimethoprim-sulfamethoxazole were associated with flu-like symptoms that occurred after only a few doses; these reactions have been shown to be HLA class I restricted T-cell dependent reactions [32, 33]. Given the noncovalent/reversible binding of the drug to HLA in these reactions, we would not expect to see the development of an antibody to a conformational epitope and hence there would be no correlation between antibody formation and flu-like symptoms [34]. Individuals of different geographic/racial and ethnic backgrounds could also be expected to differ pharmacogenomically in their predisposition to these T-cell mediated reactions, as has been seen with specific HLA class I associations with hypersensitivity reactions to abacavir, sulfa antibiotics, and antiepileptic medications; however, this was not examined in this study [32].

In summary, we detected anti-rifapentine, anti-isoniazid, anti-rifampin, and anti-rifapentine metabolite antibodies, but the proportions of participants with antibodies were low, and not different in participants with flu-like reactions or controls. This suggests that the flu-like reaction associated with 3HP is not antibody mediated.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments.

The following investigators are recognized for their valuable contribution in conceptualization and guidance during the development of this study: N. Franklin Adkinson, MD, Johns Hopkins University School of Medicine, Baltimore, MD; Robert G. Hamilton, PhD, MS, Johns Hopkins University School of Medicine, Baltimore, MD; and M. Elsa Villarino, MD, MPH, Centers for Disease Control and Prevention.

### Disclaimer.

The findings and conclusions in this article are those of the authors and do not necessarily represent the official positions of the Centers for Disease Control and Prevention or the authors' affiliated institutions.

### Potential conflicts of interest.

E. P. reports grant contracts from National Institute of Health and National Health and Medical Research Council (NHMRC) of Australia; and consulting fees, outside the submitted work: active: UpToDate (Royalties and consulting fees), Jansen, Verve; within the last 3 years: Biocryst, Esperion/Ramboll, Novavax, AstraZeneca. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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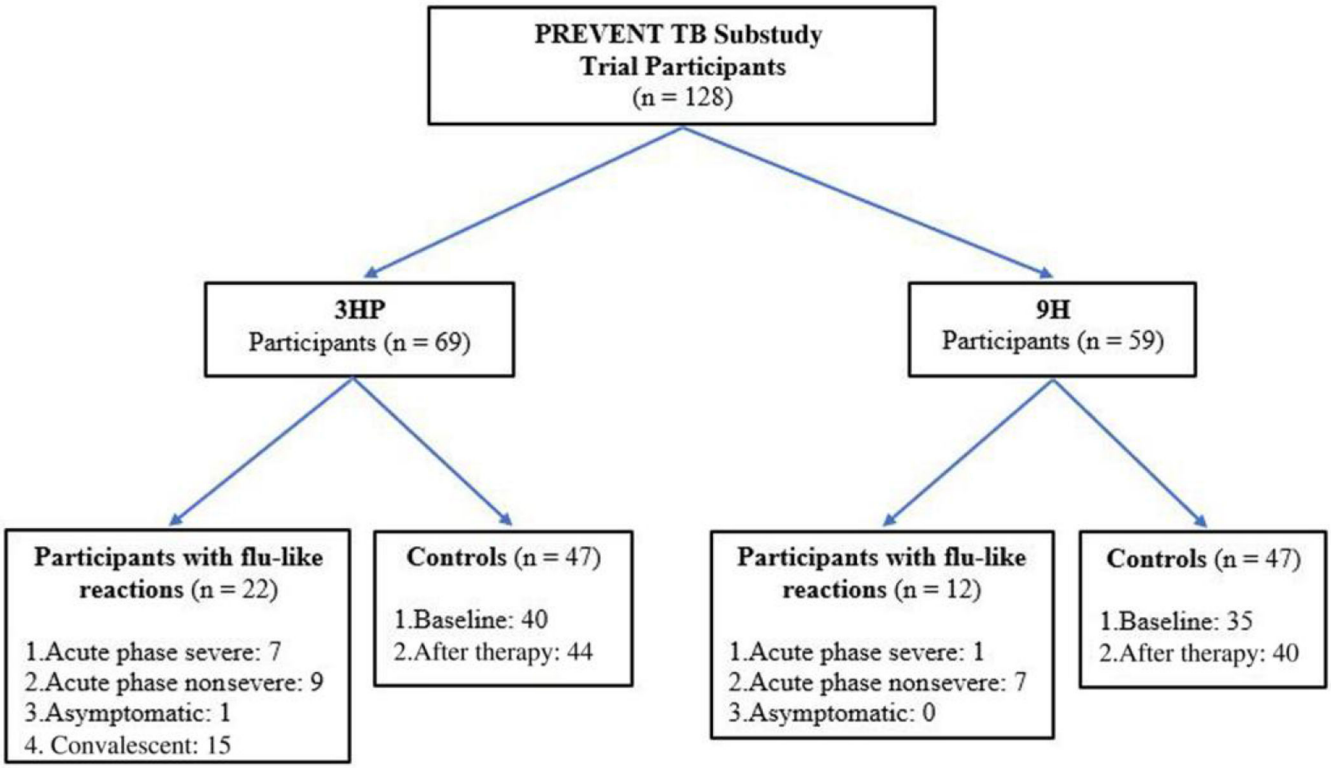


**Figure 1.**

PREVENT TB substudy trial participants evaluated for antibodies against rifapentine, isoniazid, rifampin, and rifapentine metabolite. Participants with flu-like reactions had samples collected at up to four time points (1) acute phase, severe reaction; (2) acute phase, nonsevere reaction; (3) asymptomatic, less than 10 days after recovery from symptoms; and (4) convalescent, 10–35 days after recovery from symptoms. Controls had samples collected at up to two time points (1) baseline and (2) after 12 weeks of therapy (12 doses of isoniazid plus rifapentine or 84 doses of isoniazid). Some samples were lost which might explain that numbers at baseline and total number of participants do not match. Abbreviations: 3HP, 3 months of directly observed once-weekly rifapentine (maximum dose, 900 mg) plus isoniazid (maximum dose, 900 mg); 9H, 9 months of daily self-administered isoniazid (maximum dose, 300 mg).

**Table 1.**

Doses Received and Time of Drug Exposure Among 128 Participants of the PREVENT TB Substudy, by Regimen

| | 3HP (n = 69) | | 9H (n = 59) | |
|---|---|---|---|---|
| | Participants With Flu-Like Reactions (n = 22) | Controls (n = 47) | Participants With Flu-Like Reactions (n = 12) | Controls (n = 47) |
| No. of doses received, median (IQR) | 5 (3–8) | 12 (12–12) | 54 (20–161) | 264 (252–270) |
| Drug exposure, d, median (IQR) | 29 (14–50) | 83 (77–89) | 59 (23–190) | 286 (273–314) |

Abbreviations: 3HP, 3 months of directly observed once-weekly rifapentine (maximum dose, 900 mg) plus isoniazid (maximum dose, 900 mg); 9H, 9 months of daily self-administered isoniazid (maximum dose, 300 mg); IQR, interquartile range.

**Table 2.**

Antibodies Against Rifapentine, Isoniazid, Rifampin, and Rifapentine Metabolite Among Participants of the PREVENT TB Substudy, by Regimen

| | Rifapentine Antibodies | | Isoniazid Antibodies | | Rifampin Antibodies | | Rifapentine Metabolite Antibodies | |
|---|---|---|---|---|---|---|---|---|
| | Participants With Flu-like Reactions, % (n/N) | Controls, % (n/N) | Participants With Flu-Like Reactions, % (n/N) | Controls, % (n/N) | Participants With Flu-Like Reactions % (n/N) | Controls,% (n/N) | Participants With Flu-Like Reactions % (n/N) | Controls,% (n/N) |
| 3HP treatment received | | | | | | | | |
| IgG | | | | | | | | |
| Anti-IgG delta 90% | 9 (2/22) | 13 (6/47) | 9 (2/22) | 9 (4/47) | 0 | 2 (1/47) | 0 | 4 (2/47) |
| IgM | | | | | | | | |
| Anti-IgM delta 90% | 0 | 4 (2/47) | 0 | 9 (4/47) | 5 (1/22) | 9 (4/47) | 0 | 13 (6/47) |
| 9H treatment received | | | | | | | | |
| IgG | | | | | | | | |
| Anti-IgG delta 90% | 0 | 0 | 0 | 9 (4/47) | 0 | 0 | 0 | 0 |
| IgG | | | | | | | | |
| Anti-IgM delta 90% | 0 | 2 (1/47) | 0 | 9 (4/47) | 0 | 6 (3/47) | 0 | 2 (1/47) |

Abbreviations: 3HP, 3 months of directly observed once-weekly rifapentine (maximum dose, 900 mg) plus isoniazid (maximum dose, 900 mg); 9H, 9 months of daily self-administered isoniazid (maximum dose, 300 mg); Ig, immunoglobulin; n, number of participants in whom drug antibodies were identified; N, number of participants who received 3HP or 9H and either developed flu-like reactions or participated as controls (3HP: participants with flu-like reactions (22), controls (47); 9H: participants with flu-like reactions (12), controls (47)).