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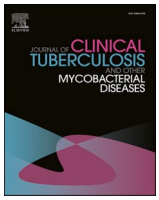

Latent TB treatment regimens in 2023: Wetmore TB clinic in New Orleans

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ABSTRACT

The USPSTF has updated Latent TB Infection (LTBI) screening and treatment recommendations in 2023; describing treatment courses, side effects and benefits associated with each regimen. Overall, rifampin-containing shortened regimens are the preferred modality for LTBI treatment. A recent study in 2023 evaluated adherence and tolerance of the isoniazid(INH) + rifapentine(RPT), or "3HP" regimen and identified patient groups that may be at higher risk for non-completion of this regimen. It emphasized the need for targeted education at the beginning of treatment, to avoid early discontinuation. Our experience in New Orleans demonstrated that the 3HP is well-tolerated, with higher completion rates than other LTBI regimens. Utilizing a retrospective chart review model, we reviewed 756 patients who were treated for LTBI over a two-year period from 1/2021—12/2022. The three possible treatment regimens included isoniazid (INH) alone, rifampin (RIF) alone, or INH + RPT (3HP). Of these regimens, the highest completion rate was in the 3HP group, despite literature suggesting this regimen is difficult to tolerate. Our experience suggests that this may still be an efficacious regimen that is well-tolerated if there is good access to clinicians to discuss mitigating side effects. More data is needed to determine factors that led to the success or failure for each regimen. Our clinic does have increased availability of nursing and medical staff to discuss side effects and answer questions, which may have contributed to our relatively higher success rate. In addition, we applied the review recommendations to our patient population, and would recommend the consideration of diabetes, heavy alcohol use, and tobacco use as risk factors for patients that would benefit from LTBI screening and treatment.

1. Introduction

1.1. Background/Rationale

Recently, the United States Preventive Services Task Force (USPSTF) commissioned a systemic review on latent tuberculosis infection (LTBI) screening and treatment in asymptomatic adults, to update prior recommendations in 2016 [1]. To set the landscape, the estimated prevalence of LTBI in the US is five percent, or 13 million people; about five to ten percent of those will progress to active TB at some point in their lives. Thirty percent of people exposed to TB will develop LTBI. Because of the role of LTBI in producing cases of active TB in low-prevalence areas, one effective strategy for reducing transmission of TB in the US is to identify and treat LTBI [2].

This USPSTF review delineates updated recommendations on screening and identifies who may be considered to be at increased risk, based on country of origin, high-risk living situations, medical comorbidities such as immunosuppression/immunodeficiency and silicosis, or those with social/workplace contact with persons with TB. There is insufficient evidence on screening for and treatment of LTBI in persons with diabetes to make a separate recommendation. The panel that convened to author this review also investigated the evidence for, benefits, and harms of LTBI screening and treatment [3].

The objective of our study was to determine if frequently described issues of intolerance and discontinuation with the 3HP regimen were observed in our patient population. Our hypothesis was that our population has had better success with the 3HP regimen than what is reported in the literature.

1.2. Shortened treatment courses

A network *meta*-analysis in 2023 that included 53 studies found that

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the shorter-duration recommended regimens are efficacious for preventing active TB (including RIF for 3 to 4 months daily, RPT plus INH for 3 months weekly, and INH for 6 months daily) and may have fewer side effects and subsequently higher completion rates. That analysis included studies on a diverse population including children; HIV-infected persons; household or close contacts of persons with active tuberculosis; and persons with renal transplant, silicosis, or rheumatoid arthritis who were taking immunosuppressive biologic medication. Both of the regimens that are now considered preferred are shortened courses; 4 months of rifampin daily and 3 months of rifapentine + isoniazid weekly [7].

1.3. Hepatotoxicity

Overall, the findings of the above review related to harms and benefits of LTBI screening can be summarized to include the following: higher incidence of hepatotoxicity is found with isoniazid (INH) as opposed to placebo or rifampin (RIF); the observation that treatment of LTBI reduced the risk of progression to active TB, and the observation that there is no data evaluating the benefits or harms of LTBI screening as compared to no screening.

Hepatotoxicity from INH remains a frequent clinical problem, with multiple mechanisms and risk factors [8]. Hepatotoxicity from INH has been found to increase with the number of weeks of treatment. When comparing INH daily to RPT plus INH weekly (the 3HP regimen), again there appeared to be higher rates of hepatotoxicity with treatment by INH alone than in a combined therapy course, perhaps because of the prolonged course. However, as described below, there were higher rates of discontinuation in the RPT plus INH group, along with more hypersensitivity, systemic drug reactions, and flu-like symptoms. In areas where INH is the only option, a 6 month course may be preferable to a 9 month course for this reason, and either length is still considered a recommended alternative regimen [7].

1.4. 3HP practical concerns

In mid 2023, Sadowski et all published an article [9] in *Clinical Infectious Diseases* to look more closely into clinical issues with the 3HP regimen, which consists of three months of weekly RPT and INH. They were able to review just over 1000 patients and identified the symptoms that were most likely to lead to discontinuation. One advantage of this study was the diversity of patients included, who were 48 % female, 52 % white, 25 % Black, 20 % Asian, and 39 % Latino. The authors found that 77 % reported 1 or more symptom at any time; among these 81 % completed treatment. 19 % did not complete treatment. They found the most common pattern for discontinuation were symptoms of weakness, dizziness, anorexia, headache, fever, chills, or mood changes developing in the first month. They identified 1.6 % with severe systemic drug reactions which included hypotension, angioedema, wheezing/bronchospasm, or conjunctivitis.

Interestingly, the study identified several subgroups with a higher risk of systemic drug reactions and subsequent discontinuation; these were people who were female sex, age > 45 years, had use of concomitant medications, and potentially those who had a history of liver disease. They conclude that individuals who fall into these groups may benefit from targeted education, at baseline and on treatment, to ensure they understand and can identify the patterns and severity of reactions with 3HP. This approach may improve rates of treatment completion if this regimen is available.

2. Objective

The objective of our study was to determine if the described issues (of intolerance and discontinuation) with the 3HP regimen were observed in our patient population. Our hypothesis was that our population has had better success with the 3HP regimen than what is reported in the literature.

3. Methods

3.1. Study design

Using a retrospective observational data design, we reviewed the charts of each patient who was treated in our clinic for LTBI during the time period from 1/2021 until 12/2022. This typically included a clinical diagnosis of patients based on: 1) positive IGRA, 2) chest X-ray without concern for active TB, and 3) no symptoms concerning for active TB. Occasionally patients were initially classified as “TB under investigation” if particularly high risk. In those cases, we waited for negative AFB smear, culture, and PCR before moving them to the designation of LTBI. We identified the number of patients who were treated with one of three possible regimens: INH daily alone, RIF daily alone, or 3HP weekly. We then identified how many patients in each group completed therapy.

3.2. Setting

Our study was conducted in the Wetmore Tuberculosis clinic, which is a clinic operated by the Louisiana Department of Public Health in collaboration with teaching faculty from Louisiana State University and Tulane University Medical Schools. This clinic operates at no cost to the patients and provides video interpreting services to any patient whose primary language is one other than English.

3.3. Participants

Patients were included in the study if they had a diagnosis of LTBI in the two calendar years specified. The clinic population is fairly diverse; patients were 16 % Black, 64 % white, 39 % Latino, 14 % Asian, 45 % female, and 12 % had a primary language other than English in a random 19-month sampling of clinic visits.

3.4. Variables

Variables assessed were the rates of enrollment and discontinuation for each of 3 regimens for LTBI treatment.

4. Data sources/measurement

Data sourcing was conducted via manual chart review, assessing each patient chart for duration of therapy.

4.1. Bias

Potential sources of bias include selection bias and confounding bias. Selection bias was mitigated by the nature of this study; which was a retrospective review of every patient offered treatment for LTBI. We did not exclude any patients from this review; therefore, this bias is unlikely to affect our results. Confounding bias may be relevant in terms of the cause of discontinuation of regimen, but we did not examine rates of specific causes of discontinuation in this paper. This study has the benefit of including a diverse population of patients in terms of age, sex, race, primary language, and risk factors.

5. Statistical methods

One-way ANOVA testing was utilized to determine test significance by calculating confidence intervals.

6. Results

The study population included 756 individual patients (see Fig. 1). In

Year	Total patients	INH #, % started	INH #, % completed	3HP #, % started	3HP #, % completed	RIF #, % started	RIF #, % completed
2021	335	173 (52%)	107 (62%)	123 (37%)	98 (80%)	24 (7%)	20 (83%)
2022	421	177 (42%)	117 (66%)	163 (39%)	132 (81%)	64 (15%)	39 (61%)

Fig. 1. Table of Initiation and Completion rates of LTBI Regimens.

2021, 335 patients were identified with LTBI infection; 320 (98.5 %) started treatment and 227 (68 %) completed treatment with either INH, RIF, or 3HP. 80 % of the patients on 3HP completed their treatment. Initially in 2021, the highest completion success rate was with RIF at 83 %; however, with many fewer patients than the 3HP group. INH was the least completed course, with 62 %.=.

The next year in 2022, 421 patients were identified with LTBI; 404 (95.9 %) started treatment and 293 (70 %) completed treatment with either INH, RIF, or 3HP. 81 % of the patients on 3HP completed treatment that year. RIF completion dropped that year, with only a 61 % completion success rate. INH completion success improved slightly to 61 %. In both years, the patients that didn't receive treatment either declined therapy or were lost to follow-up after initial laboratory testing was done.

7. Discussion

Multiple courses of LTBI therapy were compared in the above USPSTF review. When reviewing shortened courses of therapy, 3 months of a rifapentine (RPT) plus isoniazid (INH) combo regimen has been found to be noninferior to 9 months of INH therapy [4,5]. In addition, 4 months of RPT has been found to be noninferior to 9 months of INH therapy [6]. Concerns have been reported that 3HP has a higher discontinuation rate than other regimens, with one large study of > 1000 patients reporting only a 48 % completion rate [9]. A recent study in 2023 found the trend towards shorter-course treatment for LTBI to be increasing dramatically between 2013 and 2016 [11].

In reviewing study data, we had quite a different result. We found that while approximately a third of our patients were treated with 3HP, this was the most likely regimen to be completed overall, and much more likely to be prescribed than RIF alone. INH was the most prescribed treatment, with lower completion rates than 3HP. We used a one-way ANOVA post-hoc analysis to measure Fig. 2 the difference in the significance of two means of the groups, and to obtain p-values to verify if our findings were statistically significant in terms of treatment completion. We obtained p values of less than 0.01 for 3HP treatment completion and less than 0.05 for RIF treatment completion; both statistically significant. Our findings on INH treatment completion, while numerically notable, did not achieve statistical significance.

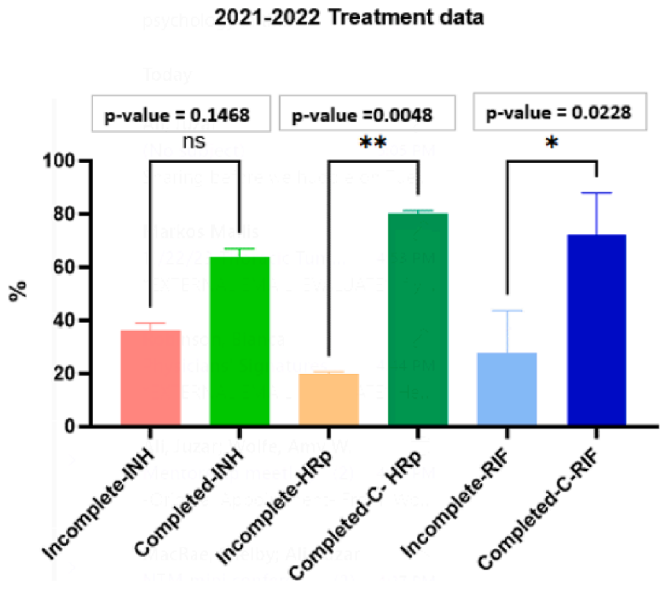

Fig. 2. Treatment Data with p-values.

The success of 3HP in our population is likely due to the scheduling of medications only once weekly, and the availability of clinic visits to discuss any side effects and make a shared plan for tolerance of meds leading to higher completion. Our clinic hours typically include 3 days a week in which doctor's visits can be scheduled, and two additional days for nursing visits. In addition, 3HP is the only LTBI regimen in which our clinic requires directly observed therapy (DOT) due to limited access to rifapentine, which likely improves treatment completion, and is recommended by the CDC. From visits with patients in clinic, we have observed that while many patients do have side effects, the ability to discuss these with a provider in clinic or a DOT worker in the field leads to improved completion of this regimen. However, we did not formally collect data regarding side effects and specific reasons for discontinuation.

In 2021, 86 incident cases of TB disease were counted in Louisiana, or a case rate of 1.9 cases per 100,000 population [10], which is in the top 25 states in the US for case rates. Many of our patients are at risk for drug-drug interactions due to high rates of diagnosis of and treatment for HIV, diabetes, chronic kidney disease, and hypertension. They are also at risk for conversion from latent to active TB due the above diagnoses, as well as high rates of alcohol use, drug use, and smoking. From our perspective working in a public health TB clinic in Louisiana, which is a low incidence area, but with higher comorbidities and greater risk of drug-drug interactions in the patients seen, the USPSTF recommendations must be adapted to population and resources available. Thus, based on our local pattern of patients seen in our clinic and in the rest of Louisiana we would suggest that uncontrolled diabetes, heavy alcohol use, and tobacco use be added to the USPTF high risk groups for LTBI screening, and subsequent treatment [10]. These are important large populations that may be at higher risk for conversion to active TB.

7.1. Limitations

This study did not collect demographic data associated with or specific reasons for discontinuation of each regimen, which would have helped us understand more detailed patterns behind discontinuation.

7.2. Interpretation and generalizability

These results suggest that despite other trials, the 3HP regimen may be more well-tolerated than previously thought. It is still unclear which populations are ideal for this regimen. Our study has moderate generalizability, as our results describe a population that includes adults, children, immunocompromised/immunosuppressed people, people with comorbidities such as HIV, cardiovascular disease, and T2DM. Our population is fairly diverse; for example, in a 19-month demographic sampling of all clinic visits in 2021–2023, our patients were 16 % Black, 64 % white, 39 % Latino, 14 % Asian, 45 % female, and 12 % had a primary language other than English.

Ethics statement

This research was conducted in accordance with the principles embodied in the Declaration of Helsinki and in accordance with local statutory requirements.

This human study was approved by Louisiana State IRB. Adult participant consent was not required because data was deidentified and this was a retrospective chart review, determined to consist of minimal risk to patients.

CRediT authorship contribution statement

Amy Wolfe: Writing – review & editing, Writing – original draft, Supervision, Project administration, Conceptualization. **Priyanka Jadhav:** Writing – review & editing, Validation, Formal analysis, Conceptualization. **Amber May:** Writing – review & editing, Validation, Methodology, Investigation, Data curation. **Shandrica Seymour:** Methodology. **Angela Blanchard:** Writing – review & editing, Resources, Conceptualization. **Juzar Ali:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jctube.2024.100443.

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