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Claire Sadowski Date

Incidence and Prediction of Symptoms and Drug Sensitivity Reactions in Persons Receiving Weekly Rifapentine Plus Isoniazid (3HP) for Treatment of Latent Tuberculosis Infection

By

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Master of Public Health

Epidemiology

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By

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An abstract of

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Abstract

Incidence and Prediction of Symptoms and Drug Sensitivity Reactions in Persons Receiving Weekly Rifapentine Plus Isoniazid (3HP) for Treatment of Latent Tuberculosis Infection

By Claire Sadowski

Background: Approximately a quarter of the world is latently infected with *Mycobacterium tuberculosis*, the causative agent of tuberculosis disease. Three months of once weekly rifapentine plus isoniazid therapy for latent tuberculosis infections is now recommended in a wide variety of populations, however, the development of signs and symptoms and possible hypersensitivity reactions have not been fully characterized. We sought to describe the patterns of sign and symptom development, characterize possible hypersensitivity reactions, and identify risk factors for hypersensitivity in patients on 3HP therapy.

Methods: We analyzed the signs and symptom data on the 1002 participants undergoing 3HP therapy in TBTC Study 33. We examined the patterns of symptom development across all participants from baseline up to 4 monthly visits. A modified definition of hypersensitivity from the PREVENT TB trial was used to characterize possible hypersensitivity reactions across all study visits. Bivariate analyses and multivariate logistic regression were used to identify possible sociodemographic predictors of hypersensitivity in this population.

Results: We found that symptoms commonly reported as developing during 3HP treatment include headache (27%), nausea (20%), and fatigue (22%). The most common pattern of symptom progression was development during the first month, followed by resolution. Reported symptoms during 3HP treatment tended to be mild in nature and did not affect treatment completion in most cases. We identified 56 out of 1002 (5.6%) participants who had possible hypersensitivity reactions. Factors that were associated with hypersensitivity reactions in multivariate logistic regression included older age (>=45 years) (OR=2.02 [1.14, 3.56]) and use of any concomitant medications 14 days prior to treatment start (OR=3.82 [1.66, 8.81]). Hypersensitivity reactions were a treatment limiting factor in this population.

Conclusions: Our findings suggest that if patients develop symptoms while on 3HP treatment, these symptoms tend to be mild and resolve after the first month of treatment. We suggest close monitoring of patients undergoing 3HP treatment who are older in age and who take concomitant medications, especially during the first month of treatment. Increased education of physicians and patients regarding the signs and symptoms associated with possible hypersensitivity reactions as well as the potential risk factors is recommended.

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CHAPTER 1: LITERATURE REVIEW

The Global Tuberculosis Epidemic

Tuberculosis is a deadly infectious disease that affects nearly 10.4 million individuals worldwide each year (1). Tuberculosis disease is caused by infection with *Mycobacterium tuberculosis* and most often affects the lungs. In 2016, the disease caused nearly 1.3 million deaths in HIV-negative individuals and an additional 374,000 deaths in HIV-positive individuals (1). According to the World Health Organization (WHO), *Mycobacterium tuberculosis* (*Mtb*) infections that result in tuberculosis disease are the leading cause of death worldwide from a single infectious agent (1).

Tuberculosis is spread through the inhalation of droplet nuclei, which are 1-5 microns in diameter (2). These droplet nuclei are expelled by individuals with active tuberculosis disease through behaviors such as coughing, sneezing, and shouting (2). Once inhaled, the droplet nuclei make their way through either the mouth or nasal passage to the upper respiratory tract and bronchi, finally arriving in the alveoli in the lungs (2). While it is possible for some *Mtb* bacilli to get into the blood stream and travel to other parts of the body, known as extrapulmonary tuberculosis, most often *Mtb* affects the lungs (2). Once *Mtb* bacilli reach the alveoli of the lungs, they are ingested and surrounded by macrophages from the body's immune system to form a granuloma shell, which keeps the bacteria from spreading or causing disease. This is called a latent tuberculosis infection, which is not considered a case of tuberculosis and individuals latently infected are incapable of passing the infection on to others (2). In persons with LTBI, disease occurs if the immune system cannot keep the bacteria under control in the lungs, causing the bacteria to then begin to rapidly multiply and spread (2).

After infection, conversion to tuberculosis disease can occur at any point: 10% of individuals with healthy immune systems are expected to develop tuberculosis disease

after infection during their lifetime, with 5% of individuals getting the disease within the first two years of infection (2). Symptoms of pulmonary tuberculosis disease include coughing with or without sputum production, hemoptysis, chest pain, loss of appetite, unexplained weight loss, night sweats, fever, and fatigue (2). Individuals who are only latently infected with the *Mtb* do not show symptoms of disease.

As with many infectious diseases, the severity of the global tuberculosis epidemic varies greatly across different parts of the world. WHO states that the regions with the highest burden of disease in 2016 were the Southeast Asia region (45% of global cases), the Africa region (25%), the Western Pacific region (17%), the Eastern Mediterranean region (7%), the European region (3%), and the region of the Americas (3%) (1). Tuberculosis disproportionately affects certain areas of the world, with 87% of all cases seen in the 30 countries with the highest tuberculosis burden (1). Overall, the case fatality ratio in 2016 was 16% according to WHO, but 44 million deaths were averted through adequate treatment (1). Because the prevalence of tuberculosis disease varies greatly in different parts of the world, the epidemiology of low-incidence and high-incidence areas are very different for tuberculosis, making the global epidemic difficult to overcome.

Epidemiology of Tuberculosis in the United States

Areas with a low burden of tuberculosis disease, such as the United States, follow a different epidemiologic pattern than high burden countries and have different strategies for management and elimination. Tuberculosis monitoring in the United States has recently adopted strategies to genotype strains of confirmed cases through the National Tuberculosis Genotyping Service (NTGS). Surveillance for cases is managed by the U.S National Tuberculosis Surveillance System (NTSS) (3). These organizations are

tasked with determining whether cases of TB are due to a “reactivation” of a previously acquired latent infection, or from recent transmission. If a TB case is due to recent transmission, it is more likely to share a genotype with other confirmed cases (3), which represents the possibility of ongoing transmission from other unrecognized cases. This also means that the presence of recently infected contacts of the case would benefit from preventative antibiotic therapy (3). There is currently no diagnostic test that can differentiate cases of tuberculosis due to reactivation of a latent infection or cases due to a recent infection, causing epidemiologists to rely on genotypic data to make inferences. A growing body of genotypic evidence in the United States indicates that transmission of tuberculosis is not a major driver in the overall tuberculosis epidemic.

Out of the 26,586 genotyped cases of tuberculosis between January 2011 and September 2014, a study found that only 14% of cases were attributable to recent transmission, and of these cases 29% were due to extensive recent transmission (3). This same study also found large amounts of heterogeneity across states and even across counties of states. Five out of the 8 states with the lowest levels of tuberculosis incidence had counties where greater than 20% of cases were attributable to recent transmission (3). Therefore, in low burden countries, incidence of tuberculosis alone is not necessarily a good predictor of transmission risk. A similar study conducted from 2005 to 2009 also found that only 1 in 4 cases of tuberculosis disease could be attributable to recent transmission (4).

Although tuberculosis transmission is not the most important factor for incidence in the United States, there are still some factors that are associated with a much higher risk of disease and transmission. Known risk factors in the United States for tuberculosis cases due to recent infection include American Indian/Alaska native race, being a Native Hawaiian/Pacific Islander, black race, Asian race, homelessness, and being under the

age of 4 (3, 4). Some studies have found cases of recent transmission tend to cluster by factors such as male sex, being born in the U.S, being a substance abuser, and having a history of homelessness (4). Individuals born in the United States are at a significantly higher risk of developing tuberculosis due to recent transmission, as 33% of cases in this group are estimated to be due to recent transmission compared to the overall proportion of approximately 25% (4). Overall, in low-incidence, high resource countries such as the United States control efforts are typically based on contact investigations that are usually thought not to be sufficiently comprehensive, due to their high complexity and length. Contact investigations require many steps and involve interviews by health departments and TST testing, which many times results in not all contacts being found (5). Despite these factors, the vast majority of cases of tuberculosis in low incidence countries are due to the reactivation of a latent infection and not transmission. The United States is also met with a set of unique challenges as the total number of cases of tuberculosis declines.

Overall, TB cases in the United States have been declining for several years. In the U.S-born population, cases declined approximately 5.9% annually from 2002-2008 with about 20 cases/million reported in 2008 (6). Cases also declined in the foreign-born population although not as drastically, with a 3.8% annual decline in cases between 1993-2008 resulting in approximately 202 cases/million reported in 2008 (6). Some projection models have shown that elimination of tuberculosis could occur by 2100 in the United States if transmission had stopped in 2008 within the U.S born population (6). However, given that the overall transmission of the disease has not been eliminated, this goal may not be met in the United States. A slightly more pessimistic model suggests that under current control efforts there is less than a 50% chance that elimination in the any U.S population will occur by 2100 (7).

Studies suggest that in the U.S, the current high levels of treatment for active tuberculosis disease does not greatly accelerate the decline in incidence (6). However, one modeling study suggests that incidence rates could be reduced through targeted testing and treatment of latent tuberculosis infections (LTBI) (6). In this study modeling tuberculosis trends in the United States, it was found that treatment rate of LTBI was influential on the incidence rate among foreign-born individuals and the hypothetical elimination year in the U.S-born population was reduced by 20 years if treatment for chronic LBTI was doubled (6). Due to the low levels of cases from recent transmission, focus has recently shifted towards the management of latent tuberculosis infections in the United States.

Latent Tuberculosis in the United States and Other Low Incidence Countries

As seen in previous studies, most cases of active tuberculosis disease in low incidence areas are a result of the reactivation of a previously existing latent tuberculosis infection. Recently, the rate of U.S tuberculosis cases has levelled off, with epidemiologic and modeling data suggesting the need to address latent tuberculosis infections in order to eliminate disease (8). The World Health Organization defines a latent tuberculosis infection as "a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of clinically manifested active tuberculosis" (9). WHO estimates that approximately a third of the world is latently infected with *Mtb*, and only 5-10% of these individuals will go on to develop active disease (9). Based on NHANES data from 2011-2012, 4.7% of the United States population had a positive tuberculin skin test (TST), which was not significantly different from 1999-2000, where 4.3% of the population were TST positive (10).While this indicates that the levels of latent infections may not be changing, the overall rate of tuberculosis disease has

declined to 3 cases per 100,000 as of 2014 (11). Due to the relatively low levels of TB cases from recent transmission and given the amount of suspected LTBI cases is not declining, it is important to understand the risk factors for reactivation of latent infections to active disease.

A major risk factor for reactivation of a latent infection to active disease is having an HIV infection, as this weakens the immune system and allows the bacteria to proliferate (12). Other risk factors include having old, healed tuberculosis disease, chronic renal failure, poorly controlled diabetes, and use of tumor necrosis factor alpha-inhibitor therapy (12). The overall rate of reactivation in the U.S has been estimated at 0.084 cases per 100 person-years, however, this rate increases to 1.82 cases per 100 person-years in individuals with an HIV infection (13). The results of some studies support targeted testing and treatment of LTBI in high risk groups, especially within the foreign born population where the risk is even higher (13). This is necessary because if only 5-10% of LTBI patients go on to develop disease, treating all infected individuals would be expensive and not a cost-effective use of resources (14). In the United States especially, much of the focus on reactivation risks is in the foreign-born population.

Exposure to *Mtb* is relatively uncommon in most parts of the U.S, so many tuberculosis cases among the foreign-born population are a result of the reactivation of a latent TB infection that was acquired prior to arrival in the U.S (15). One modeling study suggests that LTBI prevalence is estimated to decline slower among non-U.S born individuals compared to U.S born individuals (7). In a separate study linking pre-immigration records to California tuberculosis reports, it was found that the rate of likely reactivation among immigrants with a normal pre-immigration examination was 31.6 per 100,000 person-years during the first 9 years in the U.S (16). This suggests that the

current targeted testing and screening should not be limited to the first 5 years post-immigration, as the risk for reactivation remains after this time period (16, 17).

In low incidence areas WHO recommends either a tuberculin skin test or an interferon-gamma release assay for diagnosis of LTBI (18). In addition to the risk groups already mentioned, healthcare workers, prisoners, immigrants from high incidence countries, illicit drug users, and homeless individuals should be considered at high risk for a latent tuberculosis infection (18). To exclude active disease, WHO recommends symptomatic screening and a chest X-ray (9). As of 2015, WHO recommended treatment regimens of either 6-9 months of daily isoniazid, 3-4 months of daily isoniazid plus rifampicin, or 3-4 months of daily rifampicin (9), although different regimens such as 3 months of weekly isoniazid plus rifapentine have been shown to be effective and are recommended in the United States.

Epidemiology of Tuberculosis in High Incidence Countries

Due to higher levels of ongoing transmission, the epidemiology of tuberculosis is much different in countries with a high burden of disease, such as South Africa. In 2016, the majority of cases occurred in the WHO South-East Asia region (45%), Africa region (25%), and Western-Pacific region (17%) (1). In general, a higher burden of tuberculosis disease is typically associated with lower resource countries. Most high-income countries average 10 cases per 100,000, however, on average there are 150-300 cases per 100,000 in low- and middle-income countries. In South Africa, this rate is as high as 500 cases per 100,000 (1). In addition, although the global case fatality ratio for tuberculosis in 2016 was 16%, it was more than 20% in the WHO African region (1).

South Africa serves as an example of the broader epidemiology of tuberculosis in high burden areas. A main obstacle to tuberculosis control and prevention in high incidence, low income areas is the high prevalence of HIV infections. In South Africa, the population prevalence of HIV infection is 17%, with 70% of all tuberculosis cases occurring in individuals who are HIV positive (19). An analysis of microbiologically confirmed cases of tuberculosis from 2004-2012 in South Africa showed that the median age for pulmonary tuberculosis was 35 years, and overall 54% of cases occurred in males (19).

Trends in tuberculosis incidence in high burden areas tend to mirror trends in HIV infection prevalence. The same study showed higher tuberculosis rates for females in the 15-24 years age group and higher tuberculosis rates for men in the 45-64 years age group. The prevalence of HIV infection was also higher in females age 15-24 when compared to males and higher in males in the 45-64 year age group when compared to females (19). Overall, this study showed a 9% decline in overall tuberculosis incidence. It is hypothesized that with increased eligibility to anti-retroviral therapy (ART) the rate of tuberculosis could decrease even more (20).

Despite decreases in incidence in South Africa, many challenges remain in the elimination and control of TB. In many ways the fight against the HIV epidemic and the TB epidemic are intertwined. Tuberculosis microbiology testing is centralized in the South Africa public sector through the National Health Laboratory Service (19). However, discordance in laboratory data compared to reported cases due to incomplete electronic records and loss to follow up continues to be a problem in addition to failure to initiate treatment in some cases (19, 21). The epidemiology of tuberculosis in high incidence areas depends much more on transmission than in low burden areas. This in

turn affects how latent tuberculosis infections are handled and treated in these areas and brings up questions regarding the most effective LTBI treatment options.

Latent Tuberculosis in South Africa and Other High Burden Countries

While tuberculosis infections in low incidence settings tend to focus on the risk of reactivation, reinfection is a much bigger threat in high incidence areas due to the high level of ongoing transmission. Therefore, LTBI is handled differently in these areas. High levels of HIV infection in high tuberculosis incidence areas also play a large role in control efforts. In general, because of the high transmission rates and the likelihood of reinfection, treatment for LTBI with isoniazid is not considered as beneficial as in low incidence countries (22).

It has been hypothesized that community-wide interventions, such as mass screenings to rule out active tuberculosis disease and then starting isoniazid preventative therapy could reduce tuberculosis burden in high incidence areas (23). A cluster randomized trial to measure the overall and direct effects of 9-months daily isoniazid therapy on a workforce of miners in South Africa, 89% of which had a latent tuberculosis infection, found that there was no significant effect on tuberculosis control in South African gold mines through a mass screening and treatment intervention. This finding occurred even with successful use of isoniazid therapy among the miners (23). Control of LTBI in high incidence areas must focus on directly interrupting transmission. Multiple studies show that the effect of preventative therapy in high incidence countries is lost quickly after the discontinuation of treatment, and treatment is not as durable in HIV-infected individuals (22, 23).

In some instances, continuous isoniazid preventative therapy has been suggested in high risk individuals, although it is not widely implemented (23). South Africa recommends a tuberculin skin test prior to starting preventative treatment. However, 86.7% of high incidence countries that provide preventative treatment do so without also testing for HIV infections despite the high prevalence (18). South Africa typically recommends 6-36 months of isoniazid treatment and is one of the few high burden countries with defined indicators for tuberculosis screening and preventative treatment in children younger than 5 years of age with a household contact (18). Because transmission and reinfection are a much larger concern for the tuberculosis epidemic in high incidence areas, LTBI is handled very differently than in low incidence areas. It is important to understand the effectiveness of LTBI treatment regimens in these settings, as it may differ from low incidence settings. However, the treatment of latent infections remains an important step in breaking the cycle of transmission of tuberculosis in all areas.

Importance of Treating LTBI and Difficulties

The rapid identification and treatment of latent tuberculosis infections is critical in stopping the global epidemic of tuberculosis, especially in low incidence areas. The treatment of latent tuberculosis infections carries an important secondary benefit over time of preventing primary cases from occurring in the first place (6). However, there are still many challenges in the diagnosis and treatment of latent tuberculosis infections, as well as in differentiating between latent infections and active disease. Uncertainty regarding reactivation risk also results in LTBI posing a unique public health problem.

Diagnosing LTBI

There is currently no direct way to test for a latent tuberculosis infection. Current methods rely on a measurement of the host immune response as a surrogate for the presence of viable bacteria (24). For over a century, the only method of testing for latent infection was the tuberculin skin test (TST). This test involves injecting a purified protein derivative of Mtb-secreted proteins intradermally into the forearm. This injection site is then monitored and examined after 48-72 hours for evidence of a hypersensitivity reaction in the form of an induration (25). A major issue with using a TST to diagnose LTBI is the low specificity of the test. This test commonly causes false positive results in individuals who have received the Bacillus Calmette-Guerin (BCG) vaccine for protection against active tuberculosis disease, as well as in those who have been previously exposed to non-tuberculosis mycobacteria (25). These false positives are due to the overlapping antigens contained in Mycobacterium tuberculosis, the BCG vaccine, and other non-tuberculous mycobacteria.

The introduction of interferon-γ assays for cells in vitro (IGRA) has improved the ability to more accurately diagnosis LTBI. These tests use two purified antigens specific to *Mtb* (and not found in BCG or non-tuberculous mycobacteria: CFP-10, ESAT-6) to simulate peripheral-blood lymphocytes to produce interferon-γ, the levels of which can then be measured (24). Currently the United States uses two of these tests along with the TST, called QuantiFERON-TB Gold and T-SPOT.TB (24). IGRA tests are generally 80-90% sensitive and 56-83% specific, compared to the sensitivity and specificity of TST at 90-100% and 29-39%, respectively (24). IGRA tests do not require a return visit to read results like the TST, and they also do not need to be performed by trained medical personnel. However, IGRA tests require a blood sample be taken and therefore are

slightly more invasive. Finally, IGRA tests are not cross-reactive with the BCG vaccine and can avoid the "booster" response commonly seen with the TST (24).

Determining Reactivation Risk and Initiating Treatment

After a latent tuberculosis infection has been identified through either a TST or IGRA, a major difficulty is then determining the overall reactivation risk of the individual, which in turn affects whether the individual should initiate LTBI treatment. Given that such a large proportion of the world is latently infected with *Mtb*, it can also be difficult to determine the most cost-effective way to screen individuals. A very small percentage of individuals with LTBI will ever go on to develop active TB, also making it difficult to determine the most cost-effective ways to treat latent infections once discovered. Some experts suggest limiting screening only to high risk groups: contacts of active TB cases, HIV-infected individuals, individuals born in a high risk country, injection drug users, and patients on immunosuppressive medications (24). Others suggest that IGRA should be used to confirm a positive TST result if LTBI is suspected, as well as for hard to reach populations because the result is generally available within 24 hours and does not require a return visit (25).

To summarize, reactivation of a latent tuberculosis infection to active disease occurs when Mtb bacteria from old and scarred granulomatous lesions are reactivated into an active and virulent state (26). It is through this process that the majority of active TB cases in low incidence areas originate. However, given that there are many uncertainties in diagnosing and evaluating reactivation risk, it is difficult to determine the most cost-effective method for finding and treating cases of LTBI to stop the TB epidemic. In high burden countries, the risk of transmission and reinfection is a major threat to the elimination of tuberculosis disease, as a vast majority of individuals are latently infected with *Mtb*. Despite difficulties, proper identification, diagnosis, and

treatment of LTBI is a crucial aspect in breaking the transmission cycle of tuberculosis disease and elimination of the disease.

Treating Latent Tuberculosis Infections

Rationale and Examples of Treatment Regimens

A major barrier to the treatment of latent tuberculosis infections are the long and intensive treatment times and, in some cases, adverse responses to medications that occur in otherwise healthy individuals. Because individuals who are being treated for latent tuberculosis infections are not actively showing symptoms of disease, the risk to benefit ratio for treatment is different than it is for active TB and must be given further consideration. Numerous treatment regimens have been tested and implemented, some of which have been discontinued for safety reasons.

The treatment regimens that provide individuals with the safest and most effective outcome have evolved over time. In the early 2000's the Centers for Disease Control and Prevention (CDC) recommended treatment regimens of 6-9 months of daily isoniazid, 4 months of daily rifampin, or 2 months of daily rifampin and pyrazinamide (27). Although 2 months of rifampin and pyrazinamide had the advantage of being a much shorter regimen and was well tolerated in HIV-infected individuals, there was little experience in HIV-negative individuals. A multicenter, open label clinical trial comparing 2 months of daily rifampin and pyrazinamide to 6 months of daily isoniazid therapy in HIV negative adults found that in patients who had liver enzyme follow-up data, 26% of patients receiving the rifampin/pyrazinamide arm developed hepatotoxicity compared to 16% in the isoniazid only arm (27). It was also found that individuals in the

rifampin/pyrazinamide arm were approximately 5 times more likely to discontinue treatment due to hepatotoxicity compared to the isoniazid only arm (OR=5.19) (27).

9H Therapy Versus 3HP Therapy

Recently, regimens of 9 months of daily isoniazid therapy (9H) and three months of weekly rifapentine plus isoniazid therapy (3HP) emerged as some of the main options for treating LTBI, especially in the United States. Prior to the implementation of 3HP therapy, isoniazid therapy by self-administration had been the standard of care for over 50 years (28). Using a combination of rifapentine and isoniazid once weekly has shown better acceptance and adherence in the treatment of latent tuberculosis infections.

In the PREVENT TB trial comparing the effectiveness of 9H therapy and 3HP therapy, it was found that treatment for LTBI with 3HP therapy was noninferior to 9H therapy, the current standard of care (29). A major benefit of 3HP therapy is that it requires fewer treatment doses and a shorter overall duration of therapy, which may improve adherence. This was the case in the PREVENT TB trial, as 82.1% of participants completed treatment in the 3HP arm compared to 69.0% in the isoniazid-only arm (29). However, this same study found that individuals taking 3HP therapy were more likely to discontinue treatment due to any adverse event compared to those taking isoniazid only daily (4.9% vs. 3.7%). Adverse events that were deemed to be related to study drugs were also more common in the 3HP arm (8.2% vs. 5.5% for the 9H arm) (29). However, the rates of Grades 3, 4, and 5 toxic effects did not appear to differ across therapies (29).

Reasons for Not Completing Treatment for LTBI

A major concern in the treatment of LTBI is noncompletion. It is critically important that individuals who begin therapy for a latent tuberculosis infection complete that regimen; however, for a variety of reasons this is not always the case. Rates of

completion for each regimen are also used to evaluate the effectiveness of a treatment regimen. A post-hoc analysis of the PREVENT TB trial, which aimed to evaluate some of the factors leading to noncompletion among participants taking either a regimen of 3HP by direct observed therapy or self-administered 9H therapy for LTBI, found that 22.6% of individuals did not complete treatment during the trial (30). Of the 1,406 individuals who did not complete treatment, 317 discontinued due to an adverse event and the other 1,089 discontinued due to other reasons. Although the proportion who discontinued due to an adverse event was similar in the 3HP group compared to the 9H group (6.4% and 5.9%, respectively), the proportion who discontinued for other reasons was much higher in the 9H group at 24.5% compared to the 3HP group (12.7%) (30). This was likely due to the much longer treatment times for the 9H group compared to the 3HP group.

The study found that risk factors for non-completion due to an adverse event included being non-Hispanic while on 3HP treatment, having cirrhosis while on 9H treatment, being male and consuming alcohol, and any use of concomitant medications (30). The risk factors for noncompletion due to other reasons included receiving 9H therapy, missing at least one early visit, being male and on 9H treatment, being male with a history of incarceration, alcohol abuse, ever using intravenous drugs, being of a younger age while on 9H treatment, and smoking (30). This study defined completion as taking at least 11 of 12 doses of study medication in 10-16 weeks for 3HP and taking at least 240 of 270 doses of study medication in 35-52 weeks for 9H therapy. If discontinuations occur in LTBI treatment, the evidence shows that they tend to happen early in treatment. An early missed visit is one of the best indicators for whether an individual will go on to complete treatment for LTBI (30). It is critical for individuals who initiate treatment for LTBI complete their regimens. Evaluating the reasons for noncompletion as well as the risk factors for discontinuation are critical as it can help to identify factors in persons who may need tailored interventions (30). As more latent

infections are treated, this reduces the number of new TB cases that occur due to reactivation. This, in turn, reduces transmission and new cycles of latent TB infection and secondary active TB cases.

Description and Support for 3HP Therapy

Once it was determined that 3HP therapy was non-inferior to 9H therapy in treating LTBI, there were important gaps in knowledge that needed to be addressed. These gaps in knowledge included how successful the regimen would be in diverse programmatic settings and the cost effectiveness of the regimen given the requirement for direct observed therapy. One major concern was that although 3HP was incredibly successful in clinical trials, it may not be as successful in practical program settings due to the population diversities in different program settings and the high levels of oversight involved in clinical trials. To address this, an observational cohort of 3,288 LTBI patients receiving 3HP therapy through 16 different U.S programs by DOT was followed to assess treatment completion, adverse drug reactions, and factors associated with treatment discontinuation. Clinics, health departments, student health centers, correctional facilities, and homeless shelters were all included in this study. It was found that 87.2% of the cohort completed treatment, which was a similar result as in clinical trials (28). More specifically, 94.5% of children aged 2-17 years completed treatment. The lowest risk of discontinuation was among TB contacts and students, and the highest risk was among those who were incarcerated, homeless, or older than 65 years (28). Treatment completion was also higher among foreign-born individuals compared to U.S born individuals (90.3% vs. 85.2%) (28).

Another question regarding the implementation of 3HP therapy is the cost effectiveness of the regimen, especially given the need for direct observed therapy (DOT) and the high cost of rifapentine. A major barrier to widespread implementation of 3HP

therapy is the need for direct observed therapy (DOT), where a trained health care worker must actively watch an individual take each dose of treatment medication. Requiring the presence of a health care worker to implement DOT is labor intensive, as well as time consuming and expensive for public health departments which may be limited in funds. A computation model evaluating incremental costs per active TB case prevented per quality adjusted life year (QALY) gained by 3HP treatment compared to 9H found that over 20 years 3HP would result in 5.2 fewer cases of TB and 25 fewer lost QALYS per 1,000 individuals treated (31). The model concludes that 3HP treatment is a cost effective alternative to 9H treatment if the cost of rifapentine decreases, if the effectiveness of the regimen could be maintained without the use of DOT, and if treatment was limited to those with a high risk of disease progression (31). Typically, the costs of LTBI treatment are borne by the TB control programs in the public health sector. Although the upfront costs of 3HP are higher than 9H, 3HP eventually recovers some of these costs by preventing more cases of active TB than 9H (31). Overall, a major question that arose from this was whether the DOT requirement for 3HP could be eliminated or relaxed with levels of adherence and safety remaining stable, as these could significantly improve the cost-effectiveness of 3HP therapy and lead to wider implementation.

The purpose of the Tuberculosis Trials Consortium (TBTC) Study 33 was to evaluate 3HP therapy via self-administration vs. directly observed therapy, as the widespread implementation of 3HP had been limited because DOT was often unacceptable to patients, expensive for TB programs, and unavailable through primary care providers (32). This study evaluated treatment completion for 3HP among 3 arms: a direct observed therapy group, a self-administered group, and a self-administered group with text message reminders. The trial included clinical sites from the United States, Spain, Hong Kong, and South Africa. Among all sites, 87.2% completed treatment in the DOT group, 74% completed treatment in the self-administered group, and 76.4%

completed treatment in the self-administered plus text message reminders group, with neither SAT group meeting the non-inferiority criteria for the trial (32). However, when the analysis was limited to the U.S, 85.4% completed treatment in the DOT group, 77.9% completed treatment in the SAT group, and 76.2% completed treatment in the SAT plus text message reminders group, meeting the noninferiority criteria (32). Factors for noncompletion included being enrolled in South Africa, being a current smoker, and being a female within the SAT group (32). Regarding safety, there were a total of 208 adverse events in 174 (17.4%) participants. Seventy-eight (7.8%) of participants had an adverse event that was deemed to be drug related, 5 of which were serious. Overall, 45 (4.5%) participants discontinued due to an adverse event (32). As seen previously, the median dose for an adverse drug reaction was the third dose, and 43 (4.3%) participants had what was described as a "systemic drug reaction" (32). Overall, when South Africa was excluded for the analysis for this study, it was found that completion in the self-administered group was actually better for 3HP than what had been seen in previous studies using both 9H therapy and 4 months of daily rifampin (32).

In 2011, CDC declared that 3HP therapy was as safe and effective as other recommended LTBI regimens and achieves substantially higher completion rates (33). Subsequent studies showed that in individuals who were HIV positive and tuberculin skin test positive or close contacts of TB cases, 3HP treatment was as effective and safe for LTBI treatment as 9H. It was also better tolerated than 9H if CD4 counts were still higher than 500 and no antiretroviral therapy had been started (34). Moreover, 3HP treatment was safe and effective in children ages 2-17, further expanding the possible implementation of 3HP (35).

The CDC recommendations for 3HP treatment were updated in 2018 to include recommendations for use of 3HP in children aged 2-17, HIV infected individuals

(including individuals with AIDS taking anti-retroviral therapies that had acceptable drug-drug interactions with rifapentine) by direct observed therapy or self-administered therapy in individuals older than 2 (36). Currently, some experts still prefer DOT in children aged 2-5 due to the higher risk of disease progression. The decision to implement direct observed therapy or to allow self-administered therapy is based on local practice, individual patient attributes and preferences, and other considerations (36).

Three months of weekly rifapentine plus isoniazid has proven to be a cost-effective and safe treatment for LTBI. The shorter treatment length leads to higher rates of completion and the prevention of more cases of active tuberculosis disease. However, more research is ongoing on the safety of this regimen to further understand the symptoms that may be caused by treatment with rifapentine and isoniazid. The poorly defined "hypersensitivity" reaction seen in some patients manifested as a flu-like illness is of interest to researchers.

Symptoms and Drug-Related Adverse Events During LTBI Treatment

Known Reactions and Safety Concerns for Treatment with Isoniazid

A widely documented adverse outcome associated with isoniazid use is hepatoxicity. Isoniazid is a first line treatment for nearly all forms of tuberculosis disease due to its early bactericidal activity against rapidly dividing *Mtb* cells (37). According to the American Thoracic Society, common adverse events that have been documented with isoniazid use include aminotransferase elevations up to five times the normal limit in 10-20% of persons receiving isoniazid alone for LTBI infections. Clinical hepatitis is also a possibility, although this risk generally increases with increasing age (37). Additionally,

there is a documented risk of peripheral neurotoxicity that may be increased with conditions associated with neuropathy such as nutritional deficiencies, diabetes, HIV infection, and alcoholism. Hypersensitivity reactions to isoniazid presenting as fever, rash, and hemolytic anemia may occur, but this is very rare (37).

Hepatotoxicity to isoniazid during 9H treatment for LTBI is a reason why researchers began to look towards shorter regimens with additional medications, such as 3HP, which combines isoniazid with rifapentine. In a secondary analysis of hepatotoxicity in the PREVENT TB trial, it was found that 3HP treatment was less hepatotoxic than 9H treatment for LTBI (38). In this study, hepatotoxicity was categorized as either aspartate aminotransferase (AST) levels greater than 3 times the upper limit of normal (ULN) with symptoms such as nausea, vomiting, jaundice, and fatigue, or AST levels greater than 5 times time the upper limit of normal without symptoms. Overall, it was found that 1.8% of individuals receiving 9H treatment developed hepatotoxicity compared to 0.4% of individuals in the 3HP by direct observed therapy group. Treatment limiting hepatotoxicity also developed four times more frequently in the 9H arm compared to 3HP. Documented risk factors for developing hepatoxicity in all arms included being older, having elevated transaminases, having underlying liver disease, consuming alcohol, malnutrition, and being pregnant or in the immediate post-partum period (38). Those who developed treatment limiting hepatotoxicity tended to be older, female, and of non-Hispanic white race (38).

Overall, evidence suggests that 3HP treatment may be preferred in people who are of a higher risk of developing hepatotoxicity. This study suggests that hepatitis and liver function should be a factor in developing a treatment plan and an adverse clinical monitoring plan should be put into place (38). This evidence of lower rates of

hepatotoxicity, along with shorter treatment times, is a major cause for support of 3HP treatment over 9H treatment in many cases.

Safety Concerns with Rifamycin Class Drugs and Origins of the "Flu-Like" Syndrome

Rifamycins have been used to treat tuberculosis infections for many years, including drugs such as rifampin, rifabutin, and rifapentine. One member of this family, rifampin, was introduced as an anti-tuberculosis agent in 1967 (39). In a series of 20,667 patients treated with rifampin very few developed any adverse reactions to the drug. Some of the reactions that were seen included acute renal failure, rash, fever, flu-like syndrome, and anaphylactic reactions such as hypotension, angioedema, bronchospasm, and urticaria occurring within minutes (39). Of note, of the individuals who did develop adverse effects in this study, 83% had previously been treated with the drug with no reaction, bringing into question whether the reactions were allergic in nature (39).

Rifampin has long been associated with a "flu-like" illness with intermittent doses, although this syndrome is not well understood. A study of 330 patients taking rifampin and ethambutol either once weekly, twice weekly, or daily found that there was a direct association between adverse events and the interval between doses, with those taking the medications once weekly having the highest levels of adverse events and discontinuations (40). These reactions included cutaneous reactions, abdominal reactions, respiratory reactions, and a "flu-like" syndrome that occurred in 40 patients (40).

The flu-like syndrome associated with rifampin consisting of fever, chills, headache, dizziness, bone pain, malaise, cutaneous reactions (such as flushing, itching), and gastrointestinal symptoms (such as loss of appetite, nausea, mild abdominal pain, and occasional diarrhea or vomiting) has been seen in multiple studies and case reports

involving intermittent rifampicin use (41-46). It was initially associated with a higher risk in women and older individuals, although rifampin-dependent antibodies have been shown to be the same across sex and are found in most cases (42, 47). Intolerance to anti-tuberculosis drugs is significantly associated with failure to complete treatment (48). Therefore, regimens that avoid unnecessary adverse events are crucial in the treatment of LTBI. Overall, concerns of this flu-like syndrome seen with the use of high-dose, intermittent rifampin therapy have limited its use (49).

Although regimens that contain rifapentine have been shown to be safer overall for LTBI than many other regimens, such as 9H, some safety concerns remain. Rifapentine may shorten treatment time when substituted for rifampin, which is a very important aspect of LTBI treatment (50). Rifapentine also has a longer half-life and lower MIC against *Mtb* compared to rifampin (51). The PREVENT TB trial showed that 3HP therapy was as safe and effective as 9H therapy and had the advantage of being a much shorter regimen. However, there were questions surrounding whether the safety of the regimen would remain in diverse program settings outside of clinical trials, where there may be less overall oversight.

In the analysis of the safety of 3HP by DOT in program settings, it was found that 35.7% of the cohort experienced an adverse drug reaction, 76% of whom went on to complete treatment. On average, adverse drug reactions occurred after about 3 doses of 3HP therapy. The most common reported symptoms included nausea, fatigue, sore muscles, headache, fever/chills, dizziness, and abdominal pain. Only 0.8% of the cohort was hospitalized and there were no deaths or long-term sequala while on 3HP therapy in program settings (28). Of note was that 21% of individuals who reported an adverse drug reaction discontinued treatment, most commonly citing nausea, fever/chills, fatigue, sore muscles, rash or hives, dizziness, and headache (28). Overall, 3HP with DOT

treatment appeared to be effective in both clinical trial settings and practical program settings based on this study (28).

Drug Hypersensitivity Reactions in Treatment for LTBI

The "flu-like" syndrome seen in intermittent rifampin use is sometimes referred to as a hypersensitivity reaction, although it is poorly defined and not well understood. Prior to the PREVENT TB trial comparing the safety and effectiveness of 3HP by DOT to self-administered 9H therapy, the flu-like syndrome had not been reported in isoniazid and rifapentine used as part of a regimen for active tuberculosis. However, early in the trial there were reports of possible drug hypersensitivity and flu-like syndrome (52). Although there have been reports of isoniazid related flu-like syndrome consisting of pruritic rash, malaise, headache, fever, red eyes, leukocytosis, and hypotension, cases of this syndrome are very rare.

In a secondary analysis of the PREVENT TB trial involving these possible hypersensitivity reactions, researchers sought to identify and define clinically significant systemic drug reactions (SDR) and identify risk factors for the patients who were not able complete treatment. Isolated hepatotoxicity, isolated rash, adverse events with known non-drug causes, and adverse events of grade 1 severity were excluded from that analysis. Within the PREVENT TB trial, a systemic drug reaction was ultimately defined to be either hypotension (systolic blood pressure below 90 mmHg), urticaria (hives), angioedema, acute bronchospasm, or conjunctivitis; or greater than four of the following symptoms concurrently, more than one of which had to be grade 2 or higher: weakness, fatigue, nausea, vomiting, headache, fever, aches, sweats, dizziness, shortness of breath, flushing, or chills (52). SDRs were further classified as cutaneous, flu-like, gastrointestinal, respiratory, or not defined.

In the PREVENT TB trial, 1,520 of 7,552 (20%) participants reported adverse events; the adverse events in 526 (7%) participants were attributable to study drugs. Of the 526 adverse events attributable to study drugs, 153 (29%) were systemic drug reactions. Overall, 3.5% of the 3HP arm and 0.4% of the 9H arm experienced these reactions (52). There were several differences in the severity and presentation of SDR between the two study arms. Of the 14 systemic drug reactions that were considered to be severe, 13 occurred in the 3HP arm. Additionally, in the 3HP arm 17% were classified as cutaneous and 63% were flu-like. In the 9H arm, 60% were cutaneous and 13% were flu-like. Within the 3HP arm, none of the individuals who experienced severe SDR were able to fully rechallenge or finish treatment according to the study protocol, however, there were no deaths or permanent sequela in these individuals (52).

A multivariate analysis showed that factors independently associated with a higher risk of SDR were receiving 3HP, white race, female sex, age greater than 35 years, and lower BMI. The median time to onset of these reactions were after 3 once-weekly doses for 3HP and 16 daily doses for 9H. Most individuals developed the reaction within 4 hours of taking the dose and resolved within 24 hours. Common symptoms included fatigue, headache, nausea, weakness, chills, and myalgia (52).

The PREVENT TB trial was the first to report possible hypersensitivity reactions in 3HP treatment for LTBI, although the definition for this syndrome was not developed until after the study began. These hypersensitivity reactions were a definite treatment limiting factor, especially within the 3HP arm. Based on these results, TBTC Study 33 was designed to prospectively collect data on the signs and symptoms participants had experienced since the last monthly visit. Data on many symptoms of particular interest in the PREVENT TB trial were prospectively collected in Study 33, including symptoms associated with the hypersensitivity reactions in the PREVENT TB trial such as nausea,

vomiting, fatigue, weakness, jaundice, rash, bruising, and peripheral neuropathy. The possible hypersensitivity syndrome seen in the PREVENT TB trial was also seen in TBTC Study 33 with 3HP treatment, although the risk factors are still unknown (32).

Conclusion

Treatment of latent tuberculosis infections is important in reducing the overall number of active tuberculosis cases. Safe and effective treatment regimens are a crucial part of breaking the overall transmission cycle of the tuberculosis epidemic. In particular, 3HP provides shorter treatment times and less overall doses which are factors associated with better treatment completion rates. However, important gaps in knowledge remain regarding the signs and symptoms seen in individuals taking 3HP treatment.

Due to the many remaining questions around the possible hypersensitivity reactions in 3HP treatment, more research is needed to better understand the patterns behind the signs and symptoms associated with 3HP treatment for LTBI as well as factors and symptoms associated with possible hypersensitivity reactions. Identifying possible sociodemographic factors and treatment administration approaches associated with hypersensitivity reactions can help guide physicians and patients on the most appropriate treatment course for LTBI. The ability to identify patterns in symptoms development and understand the corresponding risk factors is an important aspect of determining how to avoid these adverse reactions and increase the overall completion rates for LTBI treatment. Higher rates of treatment completion for LTBI therapy can drastically reduce the number of reactivated cases of active tuberculosis disease, which are the main source of tuberculosis cases in low incidence areas such as the United States.

CHAPTER 2: MANUSCRIPT

Incidence and Prediction of Symptoms and Drug Hypersensitivity Reactions in Persons Receiving Weekly Rifapentine Plus Isoniazid (3HP) for Treatment of Latent Tuberculosis Infection

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Introduction

Tuberculosis disease is the leading cause of death from a single infectious agent worldwide (1). The World Health Organization estimates that approximately one-quarter of the world is latently infected with *Mycobacterium tuberculosis*, the causative agent of tuberculosis disease, with 5-10% of individuals with healthy immune systems expected to develop active tuberculosis disease (2, 9). The management of latent tuberculosis infections (LTBI), especially in low incidence settings such as the United States, is critical in stopping the overall tuberculosis epidemic (7). A vast majority of tuberculosis cases in these areas are caused by the reactivation of LTBI rather than direct transmission of the pathogen (3, 4, 15). Proper identification and treatment of LTBI ensures a critical secondary benefit over time by preventing primary cases from occurring (6).

The Centers for Disease Control and Prevention (CDC) has added a regimen of three months once-weekly isoniazid and rifapentine (3HP) to the treatment recommendations for latent tuberculosis infection, via self-administered or direct observed therapy (36). This regimen is recommended in a variety of populations,

including adults, children aged 2-17 years, and HIV infected individuals (34, 36). 3HP was previously shown to be as tolerable, effective, and less hepatotoxic as 9 months of daily self-administered isoniazid therapy (9H), another commonly prescribed LTBI regimen that had previously been the standard of care. However, questions remain regarding the signs, symptoms, and possible hypersensitivity reactions seen in patients on 3HP therapy (29, 52).

Rifamycins, the class of drugs from which rifapentine is derived, have long been associated with a flu-like illness when used intermittently in high doses for active tuberculosis, particularly the drug rifampin. This syndrome is poorly understood and consists of symptoms such as fever, chills, headache, dizziness, bone pain, malaise, cutaneous reactions, and gastrointestinal symptoms (41-48). The PREVENT TB clinical trial compared the effectiveness of 3HP therapy to 9H therapy and was the first to report possible hypersensitivity reactions in 3HP treatment for LTBI. Of note, due to absence of a standard definition of hypersensitivity, the PREVENT TB researchers created a definition of hypersensitivity after the first cases were seen (52). This possible hypersensitivity reaction was a treatment limiting factor that occurred in 3.5% of the 3HP arm that did not complete treatment. (52). As a result, TBTC Study 33 was designed to prospectively collect data on a variety of signs symptoms seen in the PREVENT TB trial, while comparing treatment completion of 3HP therapy by direct-observed therapy and self-administered therapy (32).

Though hypersensitivity can be an important treatment limiting factor, the presentation of signs and symptoms during 3HP LTBI treatment and risk factors for this hypersensitivity syndrome seen in patients on this regimen are poorly understood (52). 3HP treatment provides shorter treatment time and less overall doses which leads better treatment completion rates. With the regimen now recommended in a wide variety of

populations and settings, understanding risk factors for adverse events is critical in increasing treatment completion and breaking the overall transmission cycle of tuberculosis disease.

We sought to better understand the patterns behind signs and symptoms seen in patients on 3HP therapy, identify possible hypersensitivity reactions, and understand the sociodemographic risk factors associated with hypersensitivity reactions in patients on 3HP treatment.

Methods

Study Population and Setting

TBTC Study 33 (the iAdhere study) was an open label, phase 4 randomized clinical trial conducted at study sites in the United States, Spain, Hong Kong, and South Africa. The objective was to evaluate the treatment completion rates of LTBI treatment with three months of weekly rifapentine plus isoniazid (3HP) using three different treatment strategies: directly observed therapy, self-administered therapy, and self-administered therapy with text message reminders. The study enrolled 1002 adults diagnosed with LTBI and recommended for treatment between September 2012 and April 2014. Adult males and non-pregnant, non-breastfeeding women were eligible for the trial. The study excluded known contacts of INH or rifampin-resistant TB index cases, and individuals with: prior intolerance to isoniazid or any rifamycin, prior treatment for active or latent TB lasting more than one week, and a baseline serum alanine transferase level more than 5 times the normal limit. HIV positive patients who were on antiretroviral therapy or planning to start within four months of enrollment were not eligible due to potential drug-drug interactions with rifapentine. All participants enrolled in Study 33 were included in this secondary analysis.

Data Source and Study Variables

Participants in Study 33 had signs and symptoms assessed at baseline (up to 14 days prior to starting treatment), 1, 2, and 3 months after treatment start, at month 4 (if prescribed 12-week treatment had not yet been completed within 3 months), and at a delayed toxicity evaluation visit ≥ 14 days after completing or discontinuing study treatment. Signs and symptoms were also evaluated on unscheduled visits if the

participant reported any adverse event described in the study protocol. The symptoms were reported as being present or absent at any point since the prior study visit. The study assessed 45 signs and symptoms from participants using a structured signs and symptoms checklist. The symptom groups of interest included pain (e.g. muscle, joint, headache), skin (e.g. rash, itching), abdominal (e.g. nausea, vomiting), respiratory (e.g. cough, chest pain), and systemic (e.g. dizziness, fatigue, loss of appetite). All events were graded according to the U.S National Cancer Institute Common Toxicity Criteria, version 2.0.

Data Analysis

All analyses were performed in SAS (version 9.4, SAS Institute, NC). The primary outcomes of interest were the development of symptoms while on 3HP treatment and the development of possible hypersensitivity reactions. Descriptive statistics of sociodemographic factors were analyzed at baseline. To analyze the progression of signs and symptoms, patterns of progression of each were generated for every participant at baseline and the month 1, month 2, month 3, and month 4 visit. The pattern was based on the presence or absence of the symptom of any grade and accounted for participants who had discontinued treatment but continued study visits for follow up. Participants were considered "on treatment" if the symptoms were reported up to 30 days after the last dose to include participants who had late study visits. Frequencies of each pattern were calculated and categorized into subgroups of newly developed symptoms or pre-existing symptoms that resolved and then reoccurred on treatment. Sign and symptom "development" was considered to be either: development of a sign or symptoms at any timepoint that was not reported at baseline or the occurrence of a sign or symptom that had been reported at baseline but had previously resolved. The three most common

patterns for all symptoms that developed in at least 5% of the study population were also evaluated.

The classical definition of hypersensitivity from the PREVENT TB trial was used in this study with modifications based on available data to identify possible hypersensitivity reactions at any time point, excluding baseline and delayed toxicity visits. The outcome in this analysis was defined as either Category I hypersensitivity: any case of hypotension (systolic blood pressure <90 mm Hg), hives of grade 2 or higher, angioedema, wheezing/acute bronchospasm of grade 3 or higher, or conjunctivitis of grade 2 or higher OR Category II hypersensitivity: greater than 4 of the following occurring concurrently: weakness, fatigue, nausea, vomiting, headache, fever, aches (bone pain, muscle pain, or joint pain), sweats (excessive sweating or night sweats), dizziness, shortness of breath, flushing, or chills, greater than 1 of which had to be grade 2 or higher. Chi-square tests and Fischer's exact test (when expected cell counts were less than 5) were conducted to assess the relationship between baseline demographic characteristics and hypersensitivity reactions, and the corresponding two-by-two tables were used to obtain an unadjusted odds ratio. Multivariable logistic regression was then used to determine risk factors for development of hypersensitivity reactions in the study population. Factors that were significant at an alpha level of $P < 0.05$ in bivariate analyses and factors that were suspected to be clinically meaningful based on previous literature and studies were included in the original multivariate model. Backwards elimination was performed to obtain a final multivariate logistic regression model. The factors suspected to be associated with hypersensitivity *a priori* were gender, age, and race.

Ethical Considerations

This analysis was approved by the ethics committees of the CDC, all study sites and Emory University. All participants gave written informed consent.

Results

Sociodemographic Statistics

There were 2,176 adults screened for Study 33, and 1,002 were enrolled in three treatment arms: direct observed therapy (N=337), self-administered therapy (N=337), and self-administered therapy with text message reminders (N=328). Forty-eight percent of participants were female, and the median age at enrollment was 36 years. Fifty-two percent of participants were white (N=518), 25% were black or African-American (N=250), 20% were Asian (N=200), and 34 individuals were categorized as other race (N=34). Only 11 participants (1.1%) were confirmed to be HIV positive. 776 (76%) participants were confirmed to be HIV negative, however, 215 (22%) declined testing at enrollment and were of unknown HIV status (Table 1). Seventy-seven percent of participants were enrolled at study sites in the United States.

Adverse Events

As previously reported in Study 33, there were 208 reported adverse events in 174 (17%) participants in the study (32). Seventy-eight participants had adverse reactions and were deemed by the site physician to be either “definitely”, “probably”, or “possibly” attributed to study drugs (32). Serious adverse events were rare in Study 33. Only 22 (2.2%) participants had adverse events that were serious (death, any life-threatening experience, hospitalization or prolongation of hospitalization, persistently or severely disabling event, congenital anomaly or birth defect, overdose of study drugs, or grade 4 toxicity event), of which only five (0.5%) of which were considered “definitely”, “probably”, or “possibly” related to study drugs (32).

Symptom Progression and Patterns at Study Visits

The most common signs and symptoms that developed as described in the Methods while on treatment were headache (27%), fatigue (22%), nausea (20%), dizziness (14%), rhinorrhea (14%), muscular pain (13%), cough (12%), weakness (13%), abdominal pain (12%), numbness (11%), sneezing (11%), and joint pain (11%) (Table 2). With the exception of cough, subjective fever, and diarrhea, the most common progression pattern was development within the first month of treatment, followed by the symptom resolving and not reoccurring for the remainder of treatment (Table 3). The most commonly reported symptoms (headache, nausea, fatigue, and dizziness) were typically mild in nature with few participants reporting grade 2 or higher (Figure 1). Fever, chills, and dizziness all appeared to be treatment limiting factors, as each contained a common pattern of development during the first month of treatment followed by the discontinuation of treatment.

The proportion of individuals who reported at least one symptom of any grade increased from baseline to the month one evaluation, and then decreased throughout the remainder of the follow-up period. At baseline, 593/1002 (59%) reported at least one symptom of any grade. At the month one evaluation, 843/974 (87%) participants reported at least one symptom, followed by 753/896 (84%) at the second month evaluation, and 673/850 (79%) at month 3. Only 19 participants had a month four evaluation, 14 of which (74%) reported at least one symptom. 350/895 (39%) participants reported at least one symptom at their delayed toxicity evaluation. In general, symptoms appeared to be common in participants but few lasted greater than one month or led to treatment discontinuation. Table 2 shows that for most signs and symptoms, development occurs in the first month and then resolves and does not

reappear. A steady decline in the proportion of participants reporting at least one symptom supports this finding.

Possible Hypersensitivity Reactions

Fifty-six (5.6%) participants experienced possible Category I or Category II hypersensitivity reactions (as defined in the Methods). Thirteen (23%) participants with hypersensitivity qualified as Category I, 42 (75%) qualified as Category II, and 1 (1.8%) individual met both criteria at the same time point. Over half of the participants (n=31, 55%) that met the criteria for a possible hypersensitivity reaction did not complete treatment. Bivariate analyses showed a statistically significant relationship between female gender, use of concomitant medications 2 weeks prior to the study start, age between 45 and 54 years, country of enrollment, non-Hispanic ethnicity, and having a history of liver disease (Table 4). Multivariate logistic regression showed that age older than 45 years and use of concomitant medications two weeks prior to starting treatment (defined as taking any other medication during the period of two weeks before starting study treatment) were statistically significantly associated with a higher odds of hypersensitivity reactions (Table 5). Older individuals were approximately two times (aOR 2.02) as likely to experience a hypersensitivity reaction (95% CI: [1.1, 3.6]) and individuals who used concomitant medication two weeks prior to starting treatment were nearly 4 times (aOR 3.82) as likely to experience a hypersensitivity reaction (95% CI [1.7, 8.8]). There did not appear to be a difference in risk of hypersensitivity reactions between treatment arms ($p>0.47$).

Discussion

With 3HP treatment now recommended in a wide variety of populations and settings, important gaps in knowledge regarding the signs and symptom development among patients on treatment and possible hypersensitivity reactions remain. We found that that the most common signs and symptoms that developed in patients undergoing 3HP therapy in this population were headache (27%), fatigue (22%), nausea (20%), and dizziness (14%). The most common pattern of sign and symptom progression was development during the first month of treatment and then resolving for the remainder of treatment, indicating that if signs or symptoms develop they tend to be mild in nature, are short-lived, and do not affect treatment completion. We identified 56 individuals who had possible hypersensitivity reactions during 3HP treatment. Multivariate logistic regression showed that individuals older than 45 years and those who used concomitant medications two weeks prior to study start were at a higher risk for these reactions. These findings indicate that older individuals should be monitored closely for hypersensitivity reactions while on 3HP treatment, and more research is necessary to understand potential interactions between concomitant medications and incidence of hypersensitivity reactions.

This study and analysis have several advantages compared to previously published research. Previous studies of 3HP for LTBI have not prospectively collected data of signs and symptoms at multiple time points during treatment, and typically have been reported only when severe or associated with an adverse event. Our study prospectively screened participants for a wide variety of signs and symptoms to evaluate the development and progression of adverse events of any grade. We found that symptoms such as headache, fatigue, nausea, and dizziness occurred frequently in this population. These symptoms were common, but were rarely severe, with the majority

being grade 1. More infrequent signs and symptoms included petechia, hives, syncope, angioedema, hemoptysis, and jaundice, which all occurred in less than 1% of participants. We found that if signs and symptoms develop, these tend to develop within the first month of therapy and are mild in nature, as they do not typically affect treatment completion. Our results indicate that closer monitoring during the first month of treatment may be beneficial for patients taking 3HP treatment. It is important for both physicians and patients to be aware of the risks of these symptoms occurring and understand that they typically will resolve.

Only signs and symptoms collected at baseline and monthly follow-up visits were used to establish the patterns of development in this study. Signs and symptoms reported during unscheduled adverse event study visits and delayed toxicity study visits were not included in the symptom progression analysis as not all participants had adverse events or delayed toxicity visits, making patterns difficult to identify. Despite this limitation, we were able to able to accurately capture most signs and symptoms because symptoms reported at an unscheduled visit would also appear at the subsequent monthly visit in most cases.

We identified 56 participants that had possible hypersensitivity reactions during treatment in this population. We chose to use the “classical” definition of hypersensitivity used in previous studies for consistency and because TBTC Study 33 was designed to prospectively collect data on these symptoms. Some modifications to the original definition had to be made in this study. The PREVENT TB trial did not systematically collect and specify individual grades for hives, bronchospasm/wheezing, or conjunctivitis, as those symptoms were only reported if they were part of other reportable adverse events. We chose grades defined in the Methods as cutoffs because

these were the grades at which the symptom was considered to interfere with function, according to the Common Toxicity Criteria.

A limitation to this study is that our definition of hypersensitivity may be more sensitive than previous analyses and has the potential for some misclassification bias. All symptoms were self-reported and applied to the entire time-period between the date they were reported and the previous monthly study visit. Therefore, exact onset of signs and symptoms was not known. This could have resulted in some individuals being classified to have a hypersensitivity reaction, particularly a Category II reaction, when the symptoms were not actually occurring concurrently. We also did not consider PI attribution to study drugs, as this information was not available for all participants classified as having a hypersensitivity reaction by our definition. In addition, this study used patient self-report and pill counts data from the dose records to determine whether participants were on treatment.

Despite South Africa enrolling 83 (8.3%) of participants in Study 33, no hypersensitivity reactions were identified there. While the small sample size in the DOT arm (N=26) of that site may explain this finding, there were also no hypersensitivity reactions seen in the SAT arms (N=57). It is possible that medication non-adherence (demonstrated in MEMs data that recorded bottle opening times in the self-administered arms, despite high self-reported doses) may be an explanation for no hypersensitivity reactions. However, genetic factors resulting in differences in metabolism of drugs, local dietary customs affecting pharmacokinetics of drugs, or behavioral differences in reporting signs and symptoms may have also played a role. Rifapentine is best absorbed in the presence of high fat foods more common in a Western diet.

Using the classical definition of hypersensitivity, we found that older age and use of concomitant medications two weeks prior to starting treatment were statistically significantly associated with hypersensitivity reactions. This suggests that individuals older than 45 may benefit from closer monitoring while on 3HP treatment. Frequent contact between physicians and older individuals undergoing 3HP treatment is important, especially during the first month of treatment where development of signs and symptoms were more common. Little is known about the relationship between concomitant medications and hypersensitivity reactions. Physicians should be aware of any possible concomitant medications and educate patients of the risks. Future studies are warranted to further understand this relationship and to identify if there are any specific classes or types of medications that lead to a higher risk of adverse events in patients on 3HP therapy. These results are consistent with a previous analysis of hypersensitivity reactions (52), however, this study had a much smaller sample size and used a more sensitive definition of hypersensitivity. We identified a higher percentage of individuals having hypersensitivity reactions in our studied compared to PREVENT TB (5.6% vs. 3.5%). This was likely due to our more sensitive definition, and we did not limit our analysis to adverse events only in participants that discontinued treatment.

Our findings suggest that in most cases, if patients develop symptoms while on 3HP treatment these symptoms will tend to be mild and resolve after the first month of treatment. Hypersensitivity reactions occurred in approximately 5.6% of individuals in this population and many did not complete treatment. Physicians and patients should be aware of the common symptoms discussed in this study, as well as the possible risk factors for development of hypersensitivity reactions. While we used the classical hypersensitivity definition in this study, important questions remain. Future studies are warranted to understand possible clustering of symptoms and systemic drug reactions in patients who take 3HP treatment.

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Tables

Table 1. Demographic Characteristics of Participants at Baseline

Characteristic		*Overall (N=1002)*
Median Age (IQR)		36 (27-49)
Female (%)		482 (48)
Race (%)		
	White	518 (52)
	Black or African American	250 (25)
	Asian	200 (20)
	Other	34 (3.4)
Enrollment Country (%)		
	United States	774 (77)
	Spain	100 (10)
	South Africa	83 (8.3)
	Hong Kong	45 (4.5)
Born Outside Enrollment Country (%)		603 (60)
Completed High School (%)		640 (64)
Homeless Within Last Year (%)		51 (5.1)
Occupation (%)[1]		
	Healthcare worker	136 (14)
	Employed, other	472 (47)
	Unemployed seeking work	168 (17)
	Unemployed not seeking work	185 (19)
	Retired	36 (3.6)
Current Smoker (%)		250 (25)
	<10 cigarettes/day	165 (17)
	10-20 cigarettes/day	70 (7.0)
	>20 cigarettes/day	12 (1.2)
	Don't know	3 (0.3)
	Smoked Longer Than 1 Year	241 (25)
Drug Use Within Last Year (%)		53 (5.3)
	Injecting drug use	9 (0.9)
	Non-injecting drug use	50 (5.0)
Diabetes or High Blood Sugar (%)		84 (8.4)
	Type I	6 (0.6)
	Type II	74 (7.4)
	Unknown Status	4 (0.4)
Any Concomitant Medications 2 Weeks Prior to Study Start[2]		566 (56)
History of Alcohol Use (%)		531 (53)
History of Alcohol Abuse (CAGE Score>=2) (%)		70 (7.0)
History of Liver Disease[3] (%)		42 (4.2)
HIV Status		
	Positive (%)	11 (1.1)
	Negative (%)	776 (77)
	Declined Testing (%)	215 (22)

[1]Five participants did not report a primary occupation
[2]Information on concomitant medications not available for 2 participants
[3]Presence of either: hepatitis B virus infection, hepatitis C virus infection, hepatitis of unknown type, hepatitis due to alcohol use, or cirrhosis

Table 2. Reported Signs and Symptoms (Any Grade) At Study Visits After Treatment Start

Sign/Symptom	*Reported At Baseline (N, %)*	*Reported After Baseline[1] (N, %)*	*Reoccurred After Resolving from Baseline[2] (N, %)*
Headache	175 (17.5)	242/827 (29)	33/175 (19)
Fatigue	68 (6.8)	210/934 (22)	14/68 (21)
Nausea	21 (2.1)	200/981 (20)	3/21 (14)
Dizziness	55 (5.5)	135/947 (14)	8/55 (15)
Rhinorrhea	85 (8.5)	125/917 (14)	16/85 (19)
Muscular Pain	94 (9.4)	121/908 (13)	14/94 (15)
Cough	118 (11.8)	110/884 (12)	13/118 (11)
Weakness	36 (3.6)	121/966 (12)	7/36 (19)
Abdominal Pain	49 (4.9)	112/953 (12)	11/49 (22)
Numbness in extremities	67 (6.7)	103/935 (11)	10/67 (15)
Sneezing	72 (7.2)	99/930 (11)	16/72 (22)
Joint Pain	177 (17.7)	86/825 (10)	29/177 (16)
Dry Mouth	37 (3.7)	90/965 (9.3)	3/37 (8)
Insomnia	91 (9.1)	83/911 (9.1)	22/91 (24)
Localized itching	64 (6.4)	85/938 (9.1)	10/64 (16)
Anorexia	24 (2.4)	81/978 (8.3)	3/24 (13)
Vomiting	5 (0.5)	69/997 (6.9)	0
Subj Fever	14 (1.4)	69/988 (7.0)	1/14 (7)
Chills	15 (1.5)	67/987 (6.8)	1/15 (7)
Localized Rash	71 (7.1)	59/931 (6.3)	11/71 (15)
Diarrhea	22 (2.2)	61/980 (6.2)	0
Mood Changes	55 (5.5)	59/947 (6.2)	9/55 (16)
Bone Pain	43 (4.3)	45/959 (4.7)	3/43 (7.0)
Chest Pain	39 (3.9)	43/963 (4.5)	1/39 (2.6)
Night Sweats	31 (3.1)	43/971 (4.4)	3/31 (9.7)
Generalized itching	15 (1.5)	38/987 (3.9)	1/15 (7)
Unintended weight loss	12 (1.2)	35/990 (3.5)	0
Conjunctivitis	20 (2.0)	32/982 (3.3)	4/20 (20)
Subj Palpitations	16 (1.6)	30/986 (3.0)	3/16 (19)
SOB/Dyspnea	36 (3.6)	30/966 (3.1)	7/36 (17)
Flushing	20 (2.0)	29/982 (3.0)	2/20 (10)
Diaphoresis	12 (1.2)	22/990 (2.2)	2/12 (17)
Easy bruising	44 (4.4)	16/958 (1.7)	4/44 (9.1)
Generalized rash	12 (1.2)	15/990 (1.5)	0
Bronchospasm/Wheezing	14 (1.4)	12/988 (1.2)	2/14 (14)
Petechiae	18 (1.8)	9/984 (0.9)	2/18 (11)
Hives	3 (0.3)	7/999 (0.1)	0
Syncope	5 (0.5)	5/997 (0.5)	0
Angioedema	3 (0.3)	1/999 (0.1)	0
Hemoptysis	1 (0.1)	1/1001 (0.1)	0
Jaundice	1 (0.1)	0	0

[1]Individuals who reported the sign/symptom at any monthly visit, if not reported at baseline
[2]Individuals who reported having the sign/symptom at baseline, then resolving, followed by the sign/symptom being reported again at any study visit after resolving

Table 3. Most Common Sign and Symptom Progression Patterns Reported at Study Visits After Treatment Start

Sign/Symptom	*Most Common (N)*	*2nd Most Common (N)*	*3rd Most Common (N)*
Headache	**1R** (80)	**3R** (30)	**2R** (28)
Fatigue	**1R** (48)	**2R** (34)	**3R** (33)
Nausea	**1R** (58)	**1D** (28)	**2R** (27)
Dizziness	**1R** (55)	**1D** (22)	**2R** (18)
Rhinorrhea	**1R** (34)	**2R** (31)	**3R** (28)
Muscular Pain	**1R** (39)	**2R** (23)	**3R** (21)
Cough	**2R** (29)	**1R** (28)	**3R** (20)
Weakness	**1R** (26)	**1D** (21)	**2R/3R** (19)
Abdominal Pain	**1R** (39)	**2R** (18)	**3R** (17)
Numbness in extremities	**1R** (27)	**3R** (18)	**2R** (16)
Sneezing	**1R** (27)	**2R** (27)	**3R** (18)
Joint Pain	**1R** (22)	**3R** (17)	**2R** (11)
Dry Mouth	**1R** (27)	**2R** (17)	**3R** (14)
Insomnia	**1R** (19)	**2R** (14)	**1D** (13)
Localized itching	**1R** (32)	**2R** (15)	**3R** (11)
Anorexia	**1R** (19)	**1D** (19)	**2R** (17)
Vomiting	**1R** (16)	**2R** (14)	**3R/1D** (13)
Subj Fever	**1D** (17)	**1R** (14)	**2R/3R** (13)
Chills	**1R** (20)	**1D** (14)	**3R** (10)
Localized Rash	**1R** (15)	**3R** (12)	**2R** (9)
Diarrhea	**2R** (17)	**1R** (14)	**3R** (11)
Mood Changes	**1R** (14)	**1D** (10)	**2R** (9)

1R: First reported at month **1**, **R**esolved for rest of follow-up period
2R: First reported at month **2**, **R**esolved for rest of follow-up period
3R: First reported at month **3**, **R**esolved for rest of follow-up period
1D: First reported at month **1**, **D**iscontinued treatment

Table 4. Unadjusted Associations Between Hypersensitivity Reactions and Demographic Characteristics

Variable		*Hypersensitivity (%)*	*No Hypersensitivity*	*p-value*[1]	*OR*	*Lower 95%*	*Upper 95%*
Gender	Male	19 (3.7)	501		ref	ref	ref
	Female	37 (7.7)	445	0.006	2.19	1.24	3.87
Race	Overall			0.012			
	White	41 (7.9)	477		ref	ref	ref
	Black or African American	8 (3.2)	242	0.012	0.38	0.18	0.83
	Asian	6 (3.0)	194	0.017	0.36	0.15	0.86
	Other	1 (2.9)	33	**0.502**	0.35	0.05	2.64
Age	Overall			0.002			
	25-34	10 (3.8)	256		ref	ref	ref
	18-24	7 (3.9)	174	0.953	1.03	0.38	2.76
	35-44	7 (3.2)	215	0.716	0.83	0.31	2.23
	45-54	22 (11)	170	0.001	3.31	1.53	7.17
	55-64	7 (6.3)	104	0.277	1.72	0.64	4.65
	>=65	3 (10)	27	**0.134**	2.84	0.74	10.97
Country of Enrollment	Overall			**0.046**			
	United States	50 (6.5)	724		ref	ref	ref
	Spain	4 (4.0)	96	0.336	0.60	0.21	1.71
	South Africa	0 (0)	83	**0.011**	N/A		
	Hong Kong	2 (4.4)	43	**1.000**	0.67	0.16	2.86
Born Outside Country of Enrollment	Yes	35 (5.8)	568		ref	ref	ref
	No	21 (5.3)	378	0.715	0.90	0.52	1.57
Education	Completed HS	33 (5.2)	607		ref	ref	ref
	Did not Complete HS	23 (6.4)	339	0.428	1.25	0.72	2.16
Homeless within last year	No	51 (5.4)	900		ref	ref	ref
	Yes	5 (9.8)	46	**0.199**	1.92	0.73	5.04
Occupation	Overall			0.526			
	Employed, non-HCW	28 (5.9)	444		ref	ref	ref
	Health Care Worker	4 (2.9)	132	0.169	0.48	0.17	1.39
	Unemployed, not seeking work	13 (5.9)	208	0.979	0.99	0.50	1.95
	Unemployed, seeking work	11 (6.5)	157	0.775	1.11	0.54	2.28
Smoking Status	Does Not smoke	45 (6.0)	707		ref	ref	ref
	Smokes	11 (4.4)	239	0.345	0.72	0.37	1.42
Drug Use in Last Year	No	52 (5.5)	897		ref	ref	ref
	Yes	4 (7.5)	49	**0.532**	1.41	0.49	4.05
	No	48 (5.2)	868		ref	ref	ref

Diabetes or high blood sugar	Yes	8 (9.5)	76	**0.130**	1.90	0.87	4.17
Concomitant medications[2]	No	7 (1.6)	423		ref	ref	ref
	Yes	49 (8.7)	517	<0.001	5.73	2.57	12.78
History of alcohol abuse	CAGE <2	54 (5.8)	878		ref	ref	ref
	CAGE >=2	2 (2.9)	68	**0.422**	0.48	0.11	2.00
History of Liver Disease	No	51 (5.4)	901		ref	ref	ref
	Yes	5 (12)	37	**0.081**	2.39	0.90	6.33
HIV Status	HIV negative	43 (5.5)	733		ref	ref	ref
	HIV positive	1 (9.1)	10	**0.471**	1.70	0.21	13.62
Hispanic Ethnicity	Hispanic ethnicity	30 (7.6)	363		ref	ref	ref
	Non-Hispanic ethnicity	26 (4.3)	583	0.024	0.54	0.31	0.93
Treatment Arm	Overall			0.518			
	DOT	15 (4.5)	322		ref	ref	ref
	SAT	20 (5.9)	317	0.385	1.35	0.68	2.69
	SAT with reminders	21 (6.4)	307	0.266	1.47	0.74	2.90

[1]p-values obtained from Chi-Square Test. Use of Fischer's exact test indicated in bold
[2]Use of any concomitant medications 2 weeks prior to study start

Table 5. Adjusted Odds Ratios for Hypersensitivity Reactions in a Multivariate Logistic Regression Model

	Unadjusted Bivariate Analysis				*Multivariate Logistic Regression*			
Variable	*OR*	*95% CI*		*p-value*	*aOR*	*95% CI*		*p-value*
Female	**2.19**	**1.24**	**3.87**	**0.006**	1.63	0.91	2.94	0.104
White Race	**2.69**	**1.47**	**4.92**	**0.001**	1.84	0.98	3.43	0.057
Age >=45	**2.86**	**1.65**	**4.94**	**<.0001**	**2.02**	**1.14**	**3.56**	**0.015**
Concomitant Medications	**5.73**	**2.57**	**12.78**	**<.0001**	**3.82**	**1.66**	**8.81**	**0.002**
SAT Treatment Arm	1.35	0.68	2.69	0.385	1.37	0.68	2.75	0.661
SAT with Reminders Treatment Arm	1.47	0.74	2.90	0.266	1.44	0.72	2.89	0.478

Figures

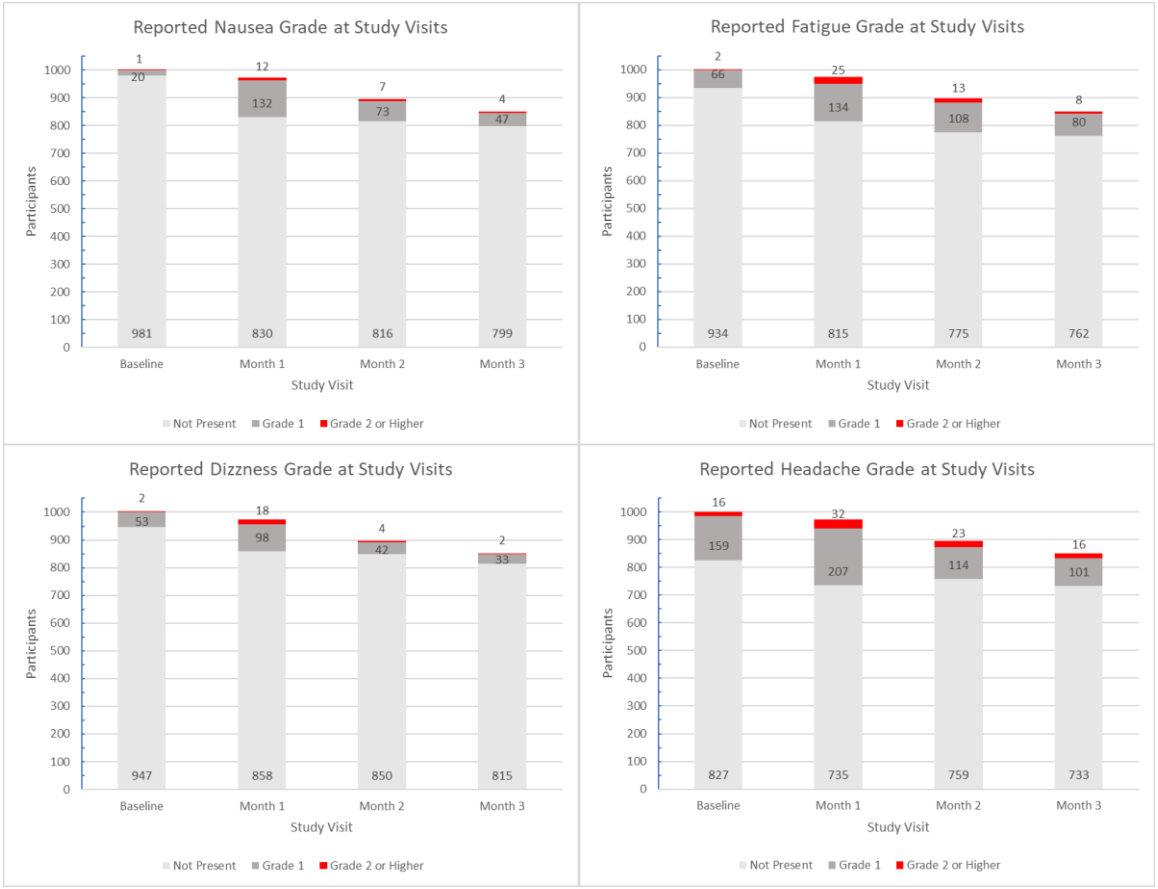

Figure 1. Reported grade of most commonly reported symptoms at each study visit.

CHAPTER III: PUBLIC HEALTH IMPLICATIONS

Approximately 87% of all cases of tuberculosis in the United States are caused by the reactivation of a latent tuberculosis infection, rather than direct person-to-person transmission (32). It is critical that individuals who undergo treatment for latent tuberculosis infection can complete safe and effective regimens in order to break an important part of the overall tuberculosis transmission cycle. Three months of rifapentine plus isoniazid therapy (3HP) is now recommended in a wide variety of settings and populations and has been proven to be at least as safe and effective as the previous standard of care regimen, 9 months of daily isoniazid therapy. However, certain gaps in knowledge remain regarding the development of signs and symptoms and incidence of hypersensitivity reactions on this regimen. This study sought to close some of these gaps and provide a description of symptom progression and factors associated with the development of hypersensitivity reactions.

Our study identified 56 individuals out of 1002 participants that had possible hypersensitivity reactions (5.6%). This confirms that the hypersensitivity reaction identified in PREVENT TB was also seen in this population and not uncommon. Hypersensitivity was a treatment limiting factor in this population, as over half of the suspected cases did not complete treatment. Our study found a greater percentage of the population having hypersensitivity reactions (5.6% in this study vs. 3.5% in PREVENT TB); however, our study prospectively screened participants for symptoms, rather than relying on patient reports of an adverse event which likely detected signs and symptoms more commonly and particularly less severe.

Factors that were associated with hypersensitivity reactions in this population included older age and use of concomitant medications two weeks prior to starting treatment. Based on these findings, individuals older than 45 and those who use

concomitant medications should be monitored closely, especially within the first month of treatment. For example, increased communication between healthcare providers and patients, such as the addition of a two-week phone call or email follow-up during the first month of treatment could be considered. In addition, programs could consider developing educational materials such as pamphlets for healthcare providers and patients on timing of signs and symptoms, symptoms associated with possible hypersensitivity reactions, and populations at risk for hypersensitivity reactions. Future studies should focus on further characterizing the relationship between concomitant medications and their effect on possible hypersensitivity reactions, including any biologic or pharmacokinetic mechanisms behind the association. The results of this study may be used to guide treatment regimen decisions by healthcare providers and their patients. In summary, our findings suggest that 3HP is safe and tolerable in all populations, however, older individuals are at a higher risk of developing hypersensitivity reactions while on this regimen. These individuals should continue to receive 3HP treatment if recommended by a healthcare provider, but could benefit from closer monitoring.

Although the hypersensitivity reaction identified in PREVENT TB was also seen in this population, there are still important gaps in knowledge surrounding the causes and definition of this syndrome. Previous studies on the flu-like syndrome seen with intermittent rifampin use suggested that the syndrome may not be autoimmune in nature, but the exact cause is not known. This studied identified sociodemographic factors that were associated with greater odds of developing hypersensitivity. Future studies should expand on these findings and investigate potential biologic causes behind the reaction. Additionally, future studies should further investigate the clustering of symptoms seen in participants with adverse reactions to 3HP further to refine the current definition of hypersensitivity.

We describe in this study the common symptoms developed in patients on 3HP therapy as well as the patterns of progression. We also describe possible hypersensitivity reactions and several potential sociodemographic risk factors. This study answers some of the important questions regarding the safety and tolerability of 3HP treatment and establishes that the hypersensitivity reactions seen in the PREVENT TB trial were not isolated. The findings from this study provide important knowledge in the treatment of latent tuberculosis infections and add to the growing body of knowledge on the safety and tolerability of LTBI treatment regimens.