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Factors Associated With Non-completion of Latent TB Infection Treatment in the Homeless Population Enrolled in the PREVENT TB Trial

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APPROVAL PAGE

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ABSTRACT

Introduction: Tuberculosis (TB) is one of the most common infectious diseases worldwide. One third of the world's population is infected with TB. *Mycobacterium tuberculosis*, the bacterium that causes TB, can infect the body and remain inactive (latent infection), or the infection can progress and cause the disease. Certain populations are at a particular risk to develop TB; these groups include persons infected with HIV, homeless persons, incarcerated individuals, and those who live in areas where TB is endemic, such as Southeast Asia. The standard treatment regimen to prevent progression to TB is the nine months of self-administered isoniazid (300 mg) (also known as the 9H regimen) for the treatment of latent TB infection (LTBI). However, a short regimen of 12 weekly doses of isoniazid (900 mg) plus rifapentine (900 mg), (also known as the 3HP regimen) has been recently shown to be as effective as the standard regimen with higher treatment completion rates by the PREVENT TB trial.

The objective of this analysis is to evaluate factors associated with non-completion of LTBI treatment among homeless participants enrolled in the PREVENT TB trial.

Methods: The study population consisted of 6, 232 participants enrolled in the PREVENT TB trial after excluding participants enrolled in non-North American sites, pregnant women, and children. Non-completion of treatment was defined as receipt of: <11 of 12 doses within 10-16 weeks for 3HP or <240 of 270 doses within 35-52 weeks for 9H. Missing an early visit was defined as missing ≥1 of the first 3 observed doses in the 3HP regimen followed by receiving an observed dose during the treatment period; or missing ≥1 of the first 3 monthly visits in the 9H regimen, followed by a monthly visit at any time during treatment. Chi-square test, univariate and multivariate logistic regression analyses were conducted to evaluate demographic, clinical, social, and behavioral factors associated with non-completion of LTBI treatment in the homeless population by using SAS® version 9.3 (Cary, North Carolina).

Results: The cohort for analysis included 6,232 participants (3HP = 3,230 and 9H=3,002), of which 505 were homeless (8.1%). Most homeless participants were male (86.7%), born in the U.S. (87.1%), and African descendants (53.1%). The median age was 46 compared with 36 in the non-homeless group. Other characteristics associated with homelessness were unemployment, smoking, alcohol consumption, and use of concomitant medications. Homeless participants in both treatment regimens were more likely to be of African descent ($p<0.001$) and have a BMI classifying them as overweight ($p<0.001$). In the multivariate analysis, factors found to be statistically associated with LTBI treatment non-completion among homeless were: missing an early clinic visit compared to those who did not miss a clinic visit (OR: 4.57; 95%CI: 2.46, 8.49: $p<0.0001$), receiving the 9H regimen (OR: 2.11; 95%CI: 1.40, 3.18; $p=0.0003$), born in non-US compared to those who were born in US (OR: 1.96; 95% CI: 1.1, 3.48; $p=0.0220$), and history of incarceration (OR: 1.69; 95%CI: 1.11, 2.57: $p=0.0148$).

Conclusion: Homeless persons present many challenges in treatment for any disease, particularly one that requires lengthy treatment and follow-up such as tuberculosis, as well as prophylactic treatment for LTBI. Appropriate interventions to improve completion of LTBI treatment such as coordination with social and educational programs,

as well as with homeless shelters, could increase adherence among the homeless population.

KEYWORDS: homeless, latent tuberculosis, non-completion of treatment

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1. INTRODUCTION

Tuberculosis (TB) is one of the most common infectious diseases worldwide. Although the rate of TB in the United States (U.S.) has declined significantly in recent years (2.96 cases per 100,000 persons) with a total of 9,421 cases in 2014, compared to 10.4 cases/ 100, 000 26,673 cases, at the peak of the historical resurgence in 1992 (CDC, http://www.cdc.gov/tb/statistics/reports/2014/pdfs/tb-surveillance-2014-report.pdf). TB still remains a public health problem in the U.S. Efforts to control tuberculosis are challenged by a variety of factors. TB therefore persists as a public health concern, though on a smaller scale than that of the rest of the world. Its looming global presence highlights the importance of controlling it in the U.S. (CDC, http://www.cdc.gov/tb/topic/globaltb/default.htm). TB is caused by a bacterium, *Mycobacterium tuberculosis*, that is spread from person to person via droplet aerosols. TB mainly affects the lungs, but it can present in other parts of the body, such as the kidneys and brain (CDC, http://www.cdc.gov/tb/publications/faqs/qa_introduction.htm#anchor_two). Despite the steady decline of TB in the U.S., there is a disproportionate burden of TB among racial and ethnic minorities (CDC, http://www.cdc.gov/tb/topic/globaltb/default.htm). Due to airborne spread, persons in close contact with persons with TB are thus at a high risk of acquiring TB. Once *M. tuberculosis* enters a person's body, it has the capacity to cause TB disease, unless the person's immune system suppresses the infection. There is an interplay of various factors that affects whether TB will develop into disease or it will remain latent. Persons with conditions that affect the immune system are at particular risk of developing TB when coming into contact with a known TB case. Such conditions

include: substance abuse, diabetes mellitus, silicosis, cancer of the head or neck, leukemia or Hodgkin's disease, severe kidney disease, low body weight, treatment for rheumatoid arthritis or Crohn's disease, and steroid or immunosuppressive treatments for organ transplants (CDC, http://www.cdc.gov/tb/publications/faqs/qa_introduction.htm#anchor_two). TB is a particular risk in HIV positive persons. HIV suppresses the immune system and increases the likelihood that latent TB will progress to active TB (CDC, http://www.cdc.gov/tb/publications/factseries/tbandhiv_eng.htm). These conditions, some more than others, are represented well in the U.S. The steady decline in TB in the U.S. should not diminish our efforts in eliminating TB.

TB is unique among the spectrum of infectious diseases. It is contagious in droplet form and preys upon underserved people as well as those who reside in crowded living conditions. Its treatment is lengthy. TB is a worldwide burden in countries that are underdeveloped. While treatment is available for TB, many challenges inhibit people from seeking and complying with treatment. Worldwide, many people with active TB disease do not have access to health care and reside in suboptimal living conditions fraught with poor ventilation and crowding.

Standard treatment regimens for active TB disease are lengthy (CDC, http://www.cdc.gov/tb/topic/treatment/default.htm#treatmentTBDisease). Six to nine months of antibiotics for treatment would be challenging for anyone to take, especially for someone who has adverse social factors such as homelessness and unemployment. Treatment regimens for latent TB are equally lengthy and demand compliance and consistency (CDC, http://www.cdc.gov/tb/topic/treatment/ltbi.htm). There is a risk for

dangerous health outcomes should patients decide to withdraw from treatment or not take the medicines appropriately. Perhaps these difficulties in treatment compliance have kept TB at the forefront of public health.

Homeless people face many challenges both socially and medically. Their disadvantaged status does not bode well for their general well-being, especially their health. They live in crowded conditions, have limited access to medical care, and are underserved, which make them ideal repositories for the TB bacillus. TB is not a disease that is managed easily and it is especially difficult for homeless persons to receive health care. Requiring homeless persons to complete treatment for LTBI and active TB is challenging.

2. LITERATURE REVIEW

Data and Statistics

One third of the world's population is infected with *M. tuberculosis*. In its asymptomatic form, it is called latent TB infection (LTBI). While alarming, this statistic does not suggest that one third of the world's population has active TB disease. One third of the population has been infected with the causative bacterium of TB but has not developed the disease and it will not transmit to others. The WHO also estimated that there were over 9 million new cases worldwide of TB in 2014 (WHO http://www.who.int/gho/tb/en/, 2015). The burden of TB is mostly in developing countries- 95% of all cases and deaths occur in developing countries.

TB was accountable for the deaths of 1.1 million persons non-infected with Human Immunodeficiency Virus (HIV) and 0.36 million persons infected with HIV

(WHO, http://www.who.int/gho/tb/en/, 2015). HIV is a particular risk factor for the development of TB. In fact, persons infected with HIV have a 26 to 28 fold risk of developing TB. In addition, TB is the leading cause of death among persons infected with HIV, causing 25 percent of all HIV-associated deaths. Not only is infection of *M. tuberculosis* a threat to develop the disease, but death from TB is a threat to persons infected with HIV due to their immunocompromised status (WHO, http://www.who.int/hiv/topics/tb/tbhiv_facts_2015/en/).

The Worldwide Geography of TB

The distribution of TB varies by region. The most recent statistics demonstrate that the regions with the greatest number of new TB cases for 2013 were in Southeast Asia and Western Pacific regions (WHO, http://apps.who.int/iris/bitstream/10665/191102/1/9789241565059_eng.pdf?ua=1). Yet Africa reported the greatest number of new cases per population, with 280 cases per 100, 000 for 2013 (WHO, http://apps.who.int/iris/bitstream/10665/191102/1/9789241565059_eng.pdf?ua=1). Although rates of TB still remain high in parts of the world where TB is endemic, such as Southeast Asia and the Western Pacific, part of the recent decline in TB rates can be attributed to the six point elimination strategy to reduce TB. The WHO has embraced the END TB strategy, which employs prevention and research in an effort to engage partners from multiple sectors of the community with the common goal of eliminating TB (WHO, http://apps.who.int/iris/bitstream/10665/191102/1/9789241565059_eng.pdf?ua=1). The goal of the END TB Strategy is to reduce deaths associated with TB as well as reduce TB incidence. Parts of the END TB Strategy include screening high-risk groups, treatment of

all patients with TB, management of TB in tandem with management of comorbidities, effective infection control, social support of those with TB in order to prevent discrimination from diagnosis, and integrating findings from the most recent research about TB as well as continuing to study TB treatments in order to ascertain the best treatment strategies for particular groups.

The Burden of TB in the United States

In the U.S., the majority of TB cases occur in persons who are foreign-born. In 2014, according to the CDC, 66% of the TB cases in the U.S. occurred among foreign-born persons. Thus, TB in the U.S. reflects in some ways the statistics of global TB. Therefore, most of the CDC's TB control activities focused in high-burden countries can help to reduce the incidence of TB in the US (CDC http://www.cdc.gov/tb/topic/globaltb/default.htm). In this effort, the CDC provides technical assistance and research projects to improve TB control in several countries of the world with a high TB burden such as Botswana, Cambodia, China, Guyana, Ethiopia, Haiti, India, Kenya, Lesotho, Mexico, Peru, Philippines, Russia, South Africa, Thailand, and Vietnam.

In the early 1900s, one of every seven people died of TB in the U.S. and Europe (CDC http://www.cdc.gov/tb/publications/faqs/qa_introduction.htm#anchor_two). After the discovery of antibiotics such as streptomycin around the 1940s, the incidence of new TB cases started to slowly decrease in the US (CDC http://www.cdc.gov/tb/publications/faqs/qa_introduction.htm#anchor_two). This led to a decrease in TB control activities around the nation. An important factor that contributed to an upswing of TB cases in the US was the emerging HIV epidemic in the early 1980s (*Core Curriculum on TB: What the Clinician Should Know*, 2011) and an influx of immigrants to the U.S. from countries where TB is endemic, such as Southeast Asia. This increase in TB cases supported the argument to increase funding for TB control and to focus on improving TB control activities. Fortunately,

with special attention, there has been a steady decline in TB in the U.S. since then and the incidence rate has gotten to the lowest in the history of the US. The CDC reports that 9, 421 cases of TB were reported in the US in 2014 (CDC http://www.cdc.gov/tb/statistics/default.htm). A lesson was presented, that in order to keep the disease contained, constant efforts are needed by TB programs and institutions. As programs contract, with tightening budgets, it remains to be seen whether the lesson was learned.

Children and TB

Pediatric TB is a public health problem of special interest since the finding of a new case indicates recent transmission, in most cases from a contagious adult with TB. 2013 estimates from the WHO indicate that children contributed more than 500,000 new cases and that 74, 000 children die from TB annually (WHO, http://www.who.int/tb/challenges/childtb_factsheet.pdf?ua=1) . Also in 2013, a total of 485 cases (5% of the total) were reported among children younger than 15 years of age in the U.S., while the proportion of pediatric TB could be as high as 20 % of the total cases of TB in high burden countries (CDC http://www.cdc.gov/tb/topic/populations/tbinchildren/default.htm). TB in children younger than 5 years of age is of clinical importance since life-threatening and the most severe forms of TB disease, such as disseminated TB and TB meningitis, develop at this age group.

Once infected with the *Mycobacterium tuberculosis*, children are more likely to develop active TB disease than adults. This process also tends to occur more quickly in children (CDC http://www.cdc.gov/tb/topic/populations/tbinchildren/default.htm). Symptoms of TB in children are similar to the symptoms of TB in adults.

The CDC has identified TB in children as a "hidden epidemic" in the world. Many underdeveloped countries do not have resources to adequately diagnose TB and thus the reporting of cases may be underestimated. Children also struggle to cough up the sputum that is needed to test for TB, making a TB diagnosis more difficult. The WHO estimates that 10 million children were orphaned by parental deaths from TB in 2010. Children are most often infected with TB by close contacts, such as family members (CDC http://www.cdc.gov/tb/topic/populations/tbinchildren/global.htm).

Pathogenesis of TB

TB is caused by the *M. tuberculosis*. It is spread from person to person via droplets from the person infected with *M. tuberculosis*. TB often affects the lungs, but can affect other parts of the body such as the bones, kidney and brain (CDC, http://www.cdc.gov/tb/topic/basics/default.htm, 2015). TB is highly infectious in nature because it is spread through airborne droplets from an infected person (*Tuberculosis: Pathogenesis, Protection, and Control*, 1994). In fact, infectious particles with *M. tuberculosis* are emitted when an infected person speaks, coughs, or sneezes. There are variables in transmission of TB, including the "amount and concentration of bacilli present in the source case, the duration of exposure, and the aerodynamics of the inhaled particles" (*Tuberculosis: Pathogenesis, Protection, and Control*, 1994). Cough is a common symptom of pulmonary TB (*Tuberculosis: Pathogenesis, Protection, and Control*, 1994). The cough may begin as nonproductive but progress to a cough that is productive in sputum. The signs and symptoms of TB vary with the site involved, but in general the systemic signs of infection include fatigue, weight loss, and low grade fever. Diagnostic criteria for TB include sputum culture to confirm the presence of *M.*

tuberculosis as well as chest x-ray. Induced sputum, as well as bronchoscopy, are methods of obtaining a specimen if the patient is unable to produce sputum.

Latent TB

In addition to active TB disease, latent TB is also a concern. Initial acquisition of the *M. tuberculosis* bacterium does not develop into active TB disease in most persons (Jasmer, 2002). A person's immunity often keeps the infection latent. However, latent TB can easily progress to active TB if left untreated. It is therefore important that latent TB infection be treated with the same attention as active TB. More than 80 percent of active TB cases in the U.S. stem from latent TB (Hartman-Adams, 2014). Co-infections that depress the immune system, or aging, may contribute to a flare up of the latent bacillus and develop into TB (*Tuberculosis: Pathogenesis, Protection, and Control*, 1994). These first two years after infection pose the greatest threat to the development of active TB (Geiter, 2000). Failing to seek treatment for latent TB infection poses a five percent risk of developing active TB in the first two years after infection. There is a ten percent risk of developing active TB disease in individuals with normal immune systems who carry latent TB infection (*Core Curriculum on Tuberculosis: What the Clinician Should Know*, 2011). Treatment of latent TB is one of the strategies employed to eliminate TB in the U.S. Identifying and treating persons with latent TB may perhaps be the best method to reduce TB rates in high risk groups such as homeless persons (Bamrah, 2013). Despite the importance of identifying cases of latent TB, they are not as carefully measured as active TB cases (McAdam, 2009). Latent TB does not have the attendant symptoms that active TB does, and is often asymptomatic, thus causing some patients to prevent seeking or complying with treatment (Horsburgh Jr., 2004). Even

when treatment of latent TB is prescribed, treatment completion rates are low (Horsburgh Jr., 2004). Lengthy regimens to treat LTBI as well as drug side effects are the main reasons for low treatment completion rates.

Groups at Risk for TB

Certain populations are especially at risk for TB. These groups include drug users, homeless persons, and HIV positive individuals, among others. TB is a particular threat among those populations who reside in crowded conditions (CDC, 2015). The WHO also lists the following groups of people as risk groups for TB: being an illicit drug user, being an immigrant from a country where TB is endemic, and those who have had recent contact with a person who has TB. These groups of people are often co-infected with HIV and latent TB infection (Lobato, 2005). HIV may depress the immune system and can cause that LTBI infection develop into active TB disease. Even if persons within these groups are identified, treatment compliance is problematic. Incarcerated persons are also a vulnerable population at risk for TB. The CDC cites several reasons that place inmates at risk of contracting TB: living conditions at correctional facilities such as overcrowding, close living quarters and inadequate ventilation, difficulty with follow up once a TB patient is released from prison, or when a TB patient is newly incarcerated, language barriers and barriers to health care, and HIV co-infection with TB. In the study by Lobato et al., a study of treatment completion and acceptability was conducted that enrolled jail inmates as well as homeless persons in five jails throughout the United States. In the recruitment phase of the study, nineteen percent declined treatment for LTBI. Overall, 561 1,211 participants completed treatment, resulting in a completion rate

of 46.3%. This study found most participants were male, black or Hispanic, were intravenous drug users, and were unemployed.

HIV and TB Co-Infection

HIV is a known risk factor for TB but little research has been conducted to elucidate the role that TB plays in the course of HIV. One African study sought to delve into this relationship. Eighty persons with HIV and in definite stages of TB (latent, no TB, and active TB) were included in this study. Persons with HIV had not yet begun antiretroviral therapy. Biomarker analysis as well as flow cytometric analysis were performed on the plasma of the subjects. Despite the small sample size, this study supported the idea that not only active TB patients had systemic inflammation but also that patients with latent TB infection had elevated T-cell activation (Sullivan, 2015). Therefore, latent TB poses a danger to persons with HIV by possibly accelerating the progression to AIDS and, therefore, earlier mortality.

The presentation of TB in persons with HIV may be unique and not readily identifiable (Pimpin, 2011). TB and HIV co-infection also presents the challenge of disease management of both. Drug interactions, an increase in the number of pills to be taken, as well as potentially exacerbated medication side effects/ toxicity are some of the challenges faced by patients co-infected with HIV and TB. A systematic review found that risk factors for HIV-TB co-infection were "homelessness, imprisonment, alcohol abuse, sharing syringes, and close contact with a TB case" (Pimpin, 2011). This study underlined the fact that risk factors for HIV and TB overlap. It also revealed that many studies did not routinely screen TB patients for HIV. More concerted efforts need to be undertaken to test TB patients for HIV. However, persons with TB may decline to be

tested for HIV, for various reasons. The CDC recommends that all patient with TB, including latent TB, be screened for HIV.

Treatment for TB

Treatment for active TB is mandatory to prevent transmission to the general public. Standard treatment regimens are lengthy and do not encourage compliance. Current standard treatment regimens for TB consist of a variety of drugs to be taken for 6 to 9 months (CDC, http://www.cdc.gov/tb/topic/treatment/default.htm#treatmentTBDisease). Four drugs are considered to be the main lines of defense: isoniazid, rifampin, pyrazinamide, and ethambutol. These months of treatment are split up into the initiation phase and followed by the continuation phase (Blumberg, 2005). The continuation phase is either 4 or 7 months (CDC, http://www.cdc.gov/tb/topic/treatment/default.htm#treatmentTBDisease). There are baseline as well as periodic clinic visits throughout the course of treatment to monitor response to therapy and to discover and address any adverse events or untoward symptoms that develop from treatment. Many treatment medications have side effects and adverse effects that can be dangerous or can inhibit treatment compliance. Such adverse effects include hepatotoxicity and thrombocytopenia (Jasmer, 2002). Any interruption or premature discontinuation of therapy may lead to drug resistant TB and continuation of TB disease in the individual (CDC, http://www.cdc.gov/tb/topic/drtb/default.htm, 2015). Directly observed therapy (DOT) has been an important part of treatment to encourage compliance. DOT means taking the prescribed medications in the presence of a healthcare provider. Implied in directly observed therapy is that participants understand the importance of complying with

treatment and showing up at assigned appointment times. Quarantines may be implemented for patients with active TB who do not wish to begin treatment. Quarantines are important to protect the health of the general public, as TB can be easily transmitted.

Multi-Drug Resistant Tuberculosis (MDRTB)

MDRTB is TB that is resistant at least to isoniazid and rifampicin, the two drugs that are the main line of defense against TB. In 2013, 480,000 people worldwide developed MDRTB (WHO, http://apps.who.int/iris/bitstream/10665/191102/1/9789241565059_eng.pdf?ua=1). Inappropriate use of anti-TB drugs and treatment interruption can lead to MDRTB. MDRTB also can be acquired by airborne transmission from persons with MDRTB. Once TB has progressed to MDRTB, treatment options include additional anti-TB agents that may be less effective, may not be readily available, are expensive, and can cause multiple side effects (CDC, http://www.cdc.gov/tb/topic/drtb/default.htm).

PREVENT TB Trial

The PREVENT TB Trial, of the TB Trials Consortium (TBTC) was a randomized, open label phase 3 clinical trial that tested a shorter treatment regimen for latent TB infection (LTBI). This trial was conducted in the U.S., Canada, Brazil, and Spain and evaluated the standard treatment regimen of daily self-administered isoniazid (300 mg) for nine months (9H) against the shorter treatment regimen of once –weekly rifapentine (900 mg) and isoniazid (900 mg) for three months given under DOT (3HP). After all participants in the study were followed over 33 months, the trial showed that the short regimen was as effective as the standard regimen to treat LTBI (Sterling, 2011).

Treatment compliance was better in the shorter treatment regimen and thus supported the efficacy of a shorter treatment regimen for latent TB infection. Yet participants assigned to the combination therapy regimen were "more likely to have permanent drug discontinuation owing to an adverse event' (Sterling, 2011). Some of these events were later identified as Systemic Drug Reactions, most of which presented as a flu-like syndrome. Groups at increased risk to develop this type of reaction were of white race, female sex, increased age, and lower BMI. Most of the reactions were mild and resolved within 24 hours (Sterling et al., 2015). One of the main adverse events in the standard treatment regimen group was hepatotoxicity.

Homeless Persons and Tuberculosis

Homeless people have various factors that cause instability in their lives and, thus, prevent treatment compliance. Homeless people possess characteristics that, individually, place them at a higher risk of TB infection. Two main groups of persons encouraged to be tested for latent TB infection include persons recently in contact with known TB cases and those at risk of progression to active TB disease due to factors such as depressed immune systems and being a native from a country where TB is burdensome (Blumberg, 2005). Homeless persons fall into both of these categories. Homeless persons lead itinerant lives, often moving in and out of homeless shelters where they are in close proximity to people with marginal health, at best. Homeless persons often have comorbidities, such as HIV, which fosters the acquisition of TB (Bamrah, 2013). Many often use alcohol and/or illicit drugs that impair their judgement (Bamrah, 2013). In addition, many are often plagued with legal troubles and are in and out of jail. Many homeless persons have no access to medical care (Bamrah, 2013). Yet even access to

medical care may not encourage homeless persons to seek treatment for latent TB. A study in Canada touched on some barriers that homeless persons face despite living in a country that has universal health coverage. Homeless persons may not be aware that they are at risk for TB and have had bad experiences within the health care system that prevent them from seeking care (Malejczyk, 2014). Mental illness is present in a number of homeless individuals (Shelton et al., 2009). Homeless participants often are malnourished and often go hungry (Baggett et al., 2010). Amidst these troubles, homeless people face many challenges in beginning and complying with treatment for TB. There may be a biological foundation that also predisposes homeless persons to TB; TB genotyping data posits that homelessness increases the transmission of TB (Malejczyk, 2014). As the instability of the economy continues, paired with the increase in immigrants to the U.S. from countries where TB is endemic, TB is a risk for the population at large. Considering the above factors, and considering how unstable their lives are, a shorter treatment is more advantageous for homeless people, as it will be easier for them to follow.

It is especially important for homeless persons to be treated for latent TB considering the substantial financial burden that could result from lengthy, preventable hospitalizations attributable to TB (Marks, 2000). Since latent TB is largely asymptomatic, homeless persons are largely unaware that they carry latent TB and may not seek treatment until they have active symptoms. Thus, any manifestation of TB has then likely progressed to an advanced, active form, complications may have arisen that require lengthy hospitalizations, and transmission to others is likely to have occurred. In a cohort study, more homeless persons than non-homeless persons were incarcerated at the time of their diagnosis of TB (Marks, 2000). This study also found that, when compared

to their hospitalized non-homeless counterparts, hospitalized homeless persons were more likely to have HIV, be substance abusers, and inject drugs. Homeless TB patients also had a higher rate of hospitalization and a longer median length of stay. Treatment compliance was higher among hospitalized TB patients than for non-hospitalized patients.

It is difficult to get a true measure of the number of homeless persons in America and, in turn, an accurate rate of TB among homeless persons (Haddad, 2005). Many are not accounted for or are in and out of jail. Others lapse into periods of homelessness (Bamrah, 2013). The 2013 Bamrah et al. article found that homeless people had a tenfold increase in TB compared with the general population (36 to 47 out of 100000 homeless individuals versus 3.6 out of 100000 people in the general population for 2006-2010). This number is noteworthy, considering that homeless individuals comprise less than ten percent of the population in the U.S.

Objective

The objective of this analysis is to evaluate factors associated with non-completion of treatment among homeless participants enrolled in the PREVENT TB trial. A better assessment of these factors may help to direct prevention strategies in the homeless population to increase completion of LTBI treatment.

3. METHODS AND PROCEDURES

These analyses examine data collected from the PREVENT TB trial of the TB Trials Consortium (TBTC), Centers for Disease Control and Prevention, Division of TB Elimination. The PREVENT TB Trial, "A Study of the Effectiveness and Tolerability of

Weekly Rifapentine/Isoniazid for Three Months Versus Daily Isoniazid for Nine Months for the Treatment of Latent TB Infection", used two treatment regimens: 3HP: directly observed administration of isoniazid and rifapentine given weekly for twelve weeks and 9H, a daily self-administered dose of isoniazid taken for nine months. 9H is the standard and most common treatment regimen of LTBI. A total of 8, 053 participants were enrolled in the study. Participants evaluated were infected with *M. tuberculosis* or were at high risk of developing TB. They all had the latent TB. Participants were deemed to have latent TB in any of the following four scenarios: a recent conversion to a positive tuberculin skin test, HIV positive status with a positive tuberculin skin test, close contact with a culture confirmed TB patient, or a positive tuberculin skin test with an accompanying chest radiograph that shows fibrosis. After excluding non-North American sites, pregnant women, persons less than 18 years of age, and ineligible persons, the combined cohort consisted of 6, 232 individuals (Figure 1). Only sites within the U.S. and Canada were examined in this analysis for relative homogeneity of health practices in the north-American region.

Subjects were assigned to study groups according to simple unrestricted randomization. In group settings (such as households or homeless shelters), subjects could be placed on the same regimen as the first person in the group (cluster). That way, everyone in the cluster received the same treatment, as they were within contact of one another and are comparable amongst themselves. In this way, only the first person in the cluster was randomized in the study but everyone within the cluster received treatment. Randomization was stratified by HIV status and enrolling site. Throughout the course of the study, participants had a series of clinical evaluations. Participants in the 3HP DOT

treatment regimen had clinical evaluations at weeks 4, 8, and 12. Participants in the 9H treatment regimen underwent monthly clinical evaluations. Each clinical evaluation assessed such items as weight, adverse reactions, new diagnoses or hospitalizations, use of concomitant medications, and methadone withdrawal. Adverse events were recorded if their onset was at any time during the study, as well as up to 60 days after administration of the last study dose. For the 3HP regimen, adherence was measured by therapy records for the study drugs. For the 9H regimen, adherence was measured by pill count and self-report.

Factors associated with non-completion were categorized as demographic (including age, sex, race, ethnicity, country of origin, unemployment, homeless, history of incarceration, need for an interpreter), clinical (body mass index, HIV status, concomitant medication use, indication for LTBI treatment, cirrhosis, methadone treatment), social (alcohol consumption, smoking status, intravenous drug use), or behavioral (missed visits, treatment regimen, or enrollment site).

The classification of not completing treatment was as follows: in the 3HP regimen, missing at least one study drug dose within 10 to 16 weeks; in the 9H treatment regimen, missing thirty doses within 35 to 53 weeks. In addition to not completing treatment, missing clinic visits were also tracked. Missing an early visit was defined for the two treatment regimens as follows: missing 1 or more than 1 of the first 3 observed doses in the 3HP-DOT regimen followed by receiving an observed dose during the course of the treatment period; in the 9H-SAT regimen missing 1 or more than one of the first 3 monthly visits, followed by a monthly visit at any time during the treatment period.

Alcohol abuse was classified as a score of at least 2 on the CAGE questionnaire. Participants were asked if they currently smoked at the time of enrollment.

All participants provided written informed consent. The study protocol was reviewed and approved by the institutional review boards at the Centers for Disease Control and Prevention and at each of the participating clinical sites.

Non-completion of treatment (NCT) proportions were calculated for all potential factors evaluated. Age was categorized as above or below the median age of the study population (38 years). Odds ratios (ORs), 95% confidence intervals (CIs), and *P* values were calculated for potential risk factors for NCT. All factors with a p-value ≤ 0.2, as well as those that were near significant, in the univariate analysis were included in the multivariate model, in addition to age and sex. We performed backward elimination to select statistically significant factors with p-value < 0.05. Univariate and multivariate analyses were conducted among various factors outlined above using SAS® version 9.3 (SAS Institute, Inc., Cary, North Carolina).

4. RESULTS

The combined cohort for analysis included 6,232 participants (3HP = 3,230 and 9H=3,002) (Figure 1), of which 505 were homeless (8.1%, 3HP = 289, 9H = 216). Most homeless participants were male (86.7%), born in the U.S. (87.1%), and of African descent (53.1%). The median age was 46 compared with 36 in the non-homeless group. Other characteristics associated with homelessness were unemployment, smoking, alcohol consumption, and use of concomitant medications. Additional demographic characteristics can be found in Table 1.

Comparison of demographic factors among homeless participants, stratified by treatment regimen are shown in Table 2. Most of the factors evaluated in this table shown to be non-significant. Thus, the distribution of factors among the homeless participants was similar in both treatment regimens. The table also shows that most homeless participants in both treatment regimens were more likely to be of African descent (124/216, 57.41% for the 9H regimen and 144/289, 49.83% for the 3HP regimen) and have a BMI classifying them as overweight (87/216, 40.28% for the 9H regimen versus 112/289, 38.75% for the 3HP regimen).

Table 3 shows treatment completion among all of the studied participants, stratified by treatment arm and homelessness. Homeless participants assigned to the 3HP regimen, were more likely to complete LTBI treatment (227/289, 79%, $p<0.001$) than homeless participants assigned to the 9H regimen (132/216, 61%, $p<0.001$).

Tables 4A and 4B show the reasons for non-completion of treatment by treatment regimen. In the 9H regimen, the most frequent factor was being lost for more than 3 months (40%), followed by the category classified as 'other' (26%) and drug toxicities (12%). In the 3HP regimen, the most frequent reason for not completing treatment among homeless persons was the 'other' reason (27%), followed by drug toxicities and being lost for more than 3 months (20%).

Tables 4C and 4D present classification of the "other" reasons presented in Tables 4 A and 4B. For the 9H regimen, incarceration and loss of a participant accounted for the other reason. This was also the case with the "other" reason in the 3HP regimen. Even

after classification of the "other" variable, there were still unknown/ missing reasons within the "other" variable for non-completion of treatment.

Results from a univariate analysis within the homeless population are presented in Table 5. Participants assigned to the 9H regimen, were more likely not to complete treatment compared to participants assigned to receive the 3HP regimen (OR: 2.1; 95%CI: 1.4, 3.18; p<0.001). Other factors associated with non-completion of treatment were contact of a TB case as a reason to receive LTBI treatment (OR: 1.64; 95%CI: 1.04, 2.58; p=0.03) and missing an early clinic visit (OR: 5.3; 95%CI: 2.71, 10.4; p<0.0001). Some factors were almost significant, such as ethnicity (OR 1.70, 95% CI: 0.96 – 3.01, p=0.072), birthplace (OR 1.65, 95% CI 0.96 – 2.83, p= 0.07) , and history of incarceration (OR 1.635, 95% CI 0.97 – 2.12, p = 0.07).

Multivariate analysis is displayed in Table 6. The multivariate model assesses the association of certain factors with the outcome of non-completion of LTBI treatment while controlling for other factors. Factors found to be statistically associated with treatment non-completion among homeless were: the 9H regimen (OR: 2.11; 95%CI: 1.40, 3.18; p=0.0003), born in non-US compared to those who were born in US countries (OR: 1.96; 95%CI: 1.1, 3.48; p=0.0220), history of incarceration (OR: 1.69 ; 95%CI: 1.11, 2.57: p=0.0148), and missing an early clinic visit compared to those who did not missed a clinic visit (OR: 4.57; 95% CI: 2.46, 8.49: p<0.0001). Similar results were obtained when the same analysis was applied to the population selected by the first participant enrolled in a cluster. (Table S5).

Table 7 presents the homeless participants stratified by regimen and site. Sites located in Texas and Washington State had the highest proportion of enrollment of homeless participants. Table 8 shows the sizes of the different clusters enrolled, stratified by homeless status. The largest cluster was the one with 31 participants (29 in the 3HP and 2 in the 9H regimen).

Table 9 shows the size of clusters among only the homeless population, stratified by treatment regimen. The largest cluster was the one with 29 participants enrolled, all in the 3HP regimen.

Table S1 presents characteristics of the first participant enrolled in a cluster, stratified by homeless status. Homeless participants were more likely to be male (84.9%), born in the U.S. (87.3%), being African descent (58.3%) and be of non-Hispanic origin (89%). The median age in the homeless population was 46 compared to 37 in the non-homeless population ($p<0.001$). They were also more likely to be unemployed, being a current smoker and report alcohol consumption at the time of enrollment ($p<0.001$).

Table S2 details the characteristics of the clustered homeless participants, stratified by treatment regimen. Most of the factors evaluated were equally distributed between both regimens indicating that the effects of randomization were still present after some exclusions were done to define the study population of this study.

Table S3 shows the univariate analyses among the clustered homeless participants. The most significant factor was missed an early clinic visit associated with non-completion of treatment (OR: 5.3; 95%CI: 2.71, 10.4; $p<0.001$). Other factors

associated with non-completion of treatment were being Hispanic (OR: 2.1; 95%CI: 1.13, 3.98; p=0.02), born in a non-US country (OR: 2.1; 95%CI: 1.14, 3.70; p=0.02), contact of a TB case as the reason to receive LTBI treatment (OR: 1.64; 95% CI: 1.04, 2.58; p=0.03), and missed an early clinic visit (OR: 5.3; 95%CI: 2.71, 10.4; p<0.001),

Table S4 shows the multivariate analyses for non-completion of treatment among the first participant enrolled in the cluster. Among the clustered homeless participants, the most significant factor associated with non-completion of treatment was missed early clinic visit (OR: 5.2; 95%CI: 2.55, 10.46; p<0.001), followed by born in the US compared to those born in non-U.S. countries (OR: 2.81; 95%CI: 1.48, 5.35; p=0.0016), receiving 3HP compared to 9H regimen (OR: 2.2; 95%CI: 1.41, 3.53; p=0.0006), and history of incarceration (OR: 2.1; 95%CI: 1.28, 3.32; p=0.0029).

5. DISCUSSION

The most significant factor in the multivariate analysis for non-completion of treatment in the homeless population was missing an early clinic visit (OR: 4.57, 95% CI: 2.46- 8.49; p<0.0001) after controlling for other factors. This result is consistent when the analysis was limited to the first participant enrolled in a cluster. This finding follows logic, as it questions the compliance of the participants. Monitoring missed clinic visits is important to ensure that treatment is being followed as prescribed and to monitor for any potential adverse events. The shorter 3HP regimen was also associated with better treatment compliance (OR: 2.1; 95% CI: 1.42- 3.18; p=0.0003). Thus, homeless participants in the 9H regimen were 2.13 times more likely not to complete treatment compared to 3HP. The 3HP regimen is more advantageous than 9H for homeless persons,

as it requires less of a time commitment from them. Incarceration also plays a role in determining treatment compliance. A homeless person with history of incarceration may have other social factors that may prevent him or her from complying with treatment. In addition, there is the possibility that a homeless person with history of incarceration may interrupt treatment due to a new incarceration. The interruption in treatment is problematic on many levels. Although alcohol use was not significantly associated with non-completion of treatment in the univariate analysis, alcohol use may impair the judgment of a person and also may contribute to hepatotoxicity with treatment medications.

Nuzzo et al. found that LTBI treatment completion was highest among refugees (296/333, 89%) and also found some evidence that treatment completion was higher among those persons who received a shorter treatment regimen. However, this finding was not statistically significant in this analysis after adjusting for other factors.

Our study found that many homeless persons either used or abused alcohol (use: 223/501=44.2%, abuse:181/501=35.8%). A report on homelessness (Haddad, 2005) found that excessive alcohol use was greater among homeless than non-homeless persons. This is concerning, considering that the drugs used in this study may cause hepatotoxicity. Hepatotoxicity is exacerbated by alcohol use, especially by alcohol abuse. This report also found that more non-homeless persons (84%) completed TB treatment compared to homeless persons (77%) which may be a factor for increasing the transmission of *M. tuberculosis* in this population.

The findings in these analyses are supported by a similar study that examined both treatment initiation and continuation of LTBI treatment. This study found that most participants were foreign-born and a racial/ethnic minority and those more likely to initiate treatment had a history of incarceration (Goswami, 2012). The study also showed that treatment completion was more likely to occur among non-smokers. This study noted that initiating, rather than completing, LTBI treatment was more challenging.

The burden of TB among males, particularly homeless males, is supported by a cross-sectional Korean study (Lee, 2013). Out of the 313 homeless participants, 309 of them were male. This study also supported the fact that homeless persons carry a disproportionate burden of TB when compared to the general population.

As our study favors combination therapy for the treatment of LTBI in the homeless population, the administration of the combination therapy under directly observed therapy may increase compliance. Increasing LTBI treatment completion in persons at risk of developing TB is an important component of TB control/elimination strategy.

Limitations

One limitation of the study was not examining the effect of certain comorbidities such as diabetes on examining treatment completion. Studies are emerging that show the link between Type II diabetes and TB (Martínez-Aguilar et al., 2015); (Restrepo & Schlesinger, 2014). This is noteworthy, as most participants in this study had a BMI categorizing them as overweight and most homeless participants were Africa-American.

Type II diabetes is a particular burden among those with a high BMI as well as African-Americans, so its distribution among participants in this study would have been compelling to explore.

Injection drug use as well as methadone use were self-reported. Due to the sensitive nature of these questions, participants may not have been forthcoming with this information. This may have resulted in misclassification bias.

Another limitation is that the study assumed that those who were assigned to the 9H regimen took their doses as prescribed without being under the direct observation of a clinician. The counting of 9H doses relied on the participant's report. DOT completion reporting is likely to be more reliable. Self-reported completion might overestimate actual completion, causing the treatment completion differences between treatment regimens reported in this study to be conservative underestimates.

Among both the homeless and non-homeless participants, quite a number of them have an unknown HIV status (159/505, 31.49% among homeless participants versus 2839/5727, 49.57% among non-homeless participants). Many characteristics of homeless persons that place them at risk for TB are also risk factors for HIV. Therefore, it would be beneficial to obtain an HIV test on these participants and initiate anti-retroviral therapy, if they are HIV positive. HIV status is especially important considering it is a known risk factor for TB. In one study, forty percent of incident TB cases were seropositive for HIV (Moss, 2000).

Less than ten percent of the study participants enrolled in the PREVENT TB trial were homeless (6%), which may limit these analyses. However, the number of homeless persons in the study are comparable with estimates of homeless persons in the United States of 842,000 people, or one percent of the population. (National Coalition for the Homeless, http://www.nationalhomeless.org/factsheets/How_Many.html).

6. CONCLUSION

Early, effective treatment for LTBI among high risk groups such as homeless persons is challenging but in the best interest of the general public. Better prevention strategies and coordination among different sectors of public health need to be implemented in order to ensure compliance of treatment. Unique approaches need to be implemented towards homeless persons so they understand the gravity of being treated for latent TB. The PREVENT TB trial, as well as other studies, have supported better compliance rates with shorter LTBI treatment regimens. Therefore, every effort should be made to offer shorter treatment regimens to homeless persons and those persons in whom compliance may be challenging. A more seamless treatment regimen should also be available for homeless persons with history of incarceration. Homelessness as well as incarceration have high recidivism rates so follow-up is important in those persons who vacillate between the two states. Homeless and incarcerated individuals live on the fringes of society so it is a particular challenge for people to invest in them. Focused strategies that encourage treatment compliance will surely make the elimination of TB more of a possibility.

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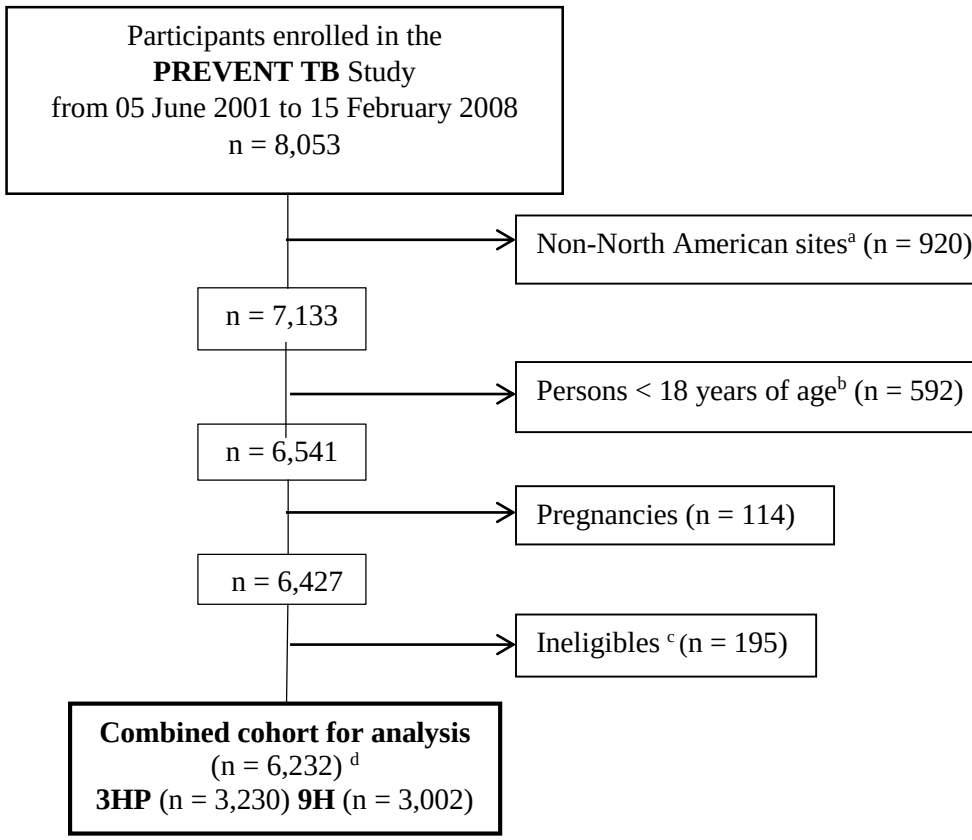
Figure 1. Flow Chart of Participants Evaluated for Factors Associated with Non-completion of Latent TB Infection Treatment in Homeless Participants Enrolled in The PREVENT TB Study – North American Sites (from the Tuberculosis Trials Consortium)



Abbreviation: AE, adverse event

[a] This analysis includes enrolling sites from U.S. and Canada. Enrolling sites from Brazil and Spain were excluded.

[b] This analysis considers adults age 18 or older.

[c] PREVENT TB Study reasons for ineligibility: source case resistant isoniazid/rifampin (50%), source case culture negative (31%), other (19%). Exclusion criteria: **a)** current confirmed TB, **b)** suspected TB, **c)** TB resistant to isoniazid or rifampin in the source case, **d)** history of treatment for >14 consecutive days with a rifamycin or >30 consecutive days with isoniazid during the previous 2 years, **e)** documented history of completing adequate treatment for active TB or latent *M. TB* infection in a HIV-seronegative person, **f)** history of sensitivity/intolerance to isoniazid or rifamycins, **g)** serum aspartate aminotransferase (AST) >5 times the upper limit of normal (ULN) if AST was determined, **h)** pregnant or lactating females, **i)** persons currently receiving or planning to receive HIV-1 therapy within 90 days after enrollment, or **j)** weight < 10.0 kg.

[d] Reasons for LTBI treatment (not-mutually exclusive): contact of infectious TB case (n = 4,156), tuberculin skin test converter (n = 2,205), HIV positive (n = 140), and fibrosis (n = 181).

Table 1. **Demographics Characteristics Among Homeless and Non-Homeless Participants in the United States and Canadian Sites in the PREVENT TB Trial**

(N= 6232)

Factor	**Homeless n=505 (%)**	**Non-homeless n= 5727 (%)**	**p-value**
Sex			<0.001
Male	438 (86.73)	3056 (53.36)	
Female	67 (13.27)	2671 (46.64)	
Age-years			<0.001 [a]
Median	46	36	
Interquartile range	40, 52	27, 47	
Site[b]			<0.0001
Other sites	488 (96.63)	5398 (94.26)	
Site 70	17 (3.37)	329 (5.74)	
Birthplace in the U.S.			<0.001
Yes	440 (87.13)	2050 (35.80)	
No	65 (12.87)	3677 (64.20)	
Race			<0.001
African descendent	268 (53.07)	1361 (23.76)	
Asian	11 (2.18)	869 (15.17)	
White	186 (36.83)	3283 (57.32)	
Other [d]	40 (7.92)	214 (3.74)	
Ethnicity			<0.001
Hispanic	56 (11.09)	2546 (44.46)	
Non-Hispanic	449 (88.91)	3181 (55.54)	
BMI-numeric			0.5223 [a]
Median	27	27	
Interquartile range	(24,31)	(24,31)	
BMI Category			0.1701
<18.5	9 (1.78)	95 (1.66)	
18.5 – 24.9	146 (28.91)	1639 (28.62)	
25-29.9	199 (39.41)	2022 (35.31)	
>30	151 (29.90)	1971 (34.42)	
Education Category			<0.001
8th grade or less	44 (8.71)	1084 (18.93)	
8th grade to some college	432 (85.54)	3514 (61.36)	
College degree or greater	29 (5.74)	1129 (19.71)	
History of incarceration [e]			<0.001
Yes	194 (38.42)	199 (3.47)	
No	311 (61.58)	5528 (96.53)	
Unemployment			<0.001
Yes	331 (65.54)	444 (7.75)	
No	174 (34.46)	5283 (92.25)	
Latent TB contact			

Factor	Homeless n=505 (%)	Non-homeless n= 5727 (%)	p-value
Yes	348 (68.91)	3808 (66.49)	0.2689
No	157 (31.09)	1919 (33.51)	
Latent TB fibrosis			<0.001[c]
Yes	1 (0.20)	180 (3.14)	
No	504 (99.80)	5547 (96.86)	
Latent TB HIV positive			<0.001
Yes	33 (6.53)	107 (1.87)	
No	472 (93.47)	5620 (98.13)	
Latent TB TST converter			0.0024
Yes	210 (41.58)	1995 (34.83)	
No	295 (58.42)	3732 (65.17)	
HIV status			<0.001
Positive	36 (7.13)	112 (1.96)	
Negative	310 (61.39)	2776 (48.47)	
Unknown	159 (31.49)	2839 (49.57)	
Smoking at enrollment			<0.001
Yes	370 (73.27)	1540 (26.89)	
No	135(26.73)	4187 (73.11)	
Alcohol consumption [f]			<0.001[g]
use	223 (44.16)	2675 (46.71)	
abuse	181 (35.84)	302 (5.27)	
no	101(20)	2750 (48.02)	
Injection drug use			<0.001
Yes	111 (21.98)	156 (2.72)	
No	394 (78.02)	5571 (97.28)	
Methadone treatment			<0.001
Yes	25 (4.95)	112 (1.96)	
No	480 (95.05)	5615 (98.04)	
Use of concomitant medications			0.0002
Yes	288 (57.03)	2764 (48.26)	
No	217 (42.97)	2963 (51.74)	
Use of a translator			<0.001
Yes	25 (4.95)	1616 (28.22)	
No	480 (95.05)	4111 (71.78)	
Liver disease			<0.001
Yes	101 (20)	151 (2.64)	
No	404 (80)	5576 (97.36)	

Abbreviations: 3HP-DOT, 3 months of directly observed, once-weekly rifapentine (maximum dose, 900 mg)
plus isoniazid (maximum dose 300 mg); 9H-SAT, 9 months of daily self-administered isoniazid; LTBI: latent
TB infection. HIV: human immunodeficiency virus. BMI: body mass index. TST: tuberculin skin test.
[a] Median Two-Sample Test using the proc npar1way SAS procedure.
[b] The variable site was categorized arbitrarily taking site with the highest number (70) as the reference.

[c]Fisher's exact test
[d] Includes North American Indian and other participants in the United States and Canada.
[e] History of residing within a correctional institution for ≥ 1 month before enrollment.
[f] Use: affirmative response to a question asking whether the participant ever drank alcoholic beverages.
Abuse:
score of ≥2 on the CAGE questionnaire.
[g] Mantel-Haenszel Chi-Square

Table 2. Demographic Characteristics of Homeless Participants in the PREVENT TB Trial, Stratified by Treatment Regimen (N=505)

Factor	**Treatment Regimen 9H SAT n=216**	**Treatment Regimen 3HP DOT n=289**	**p-value**
Sex			0.1566
Male	182 (84.26)	256 (88.58)	
Female	34 (15.74)	33 (11.42)	
Age-years			0.5916[a]
Median	45	47	
Interquartile range	40,53	40,52	
Birthplace in the U.S.			0.1627
Yes	183 (84.72)	257 (88.93)	
No	33 (15.28)	32 (11.07)	
Race			<0.001[b]
African descendent	124 (57.41)	144 (49.83)	
Asian	7 (3.24)	4 (1.38)	
White	81 (37.50)	105 (36.33)	
Other[c]	4 (1.85)	36 (12.46)	
Ethnicity			0.3827
Hispanic	27 (12.50)	29 (10.03)	
Non-Hispanic	189 (87.50)	260 (89.97)	
BMI			0.0284[a]
Median	26	28	
Interquartile range	(23, 29)	(24, 32)	
BMI category			<0.001[b]
<18.5	7 (3.24)	2 (0.69)	
18.5 – 24.9	72 (33.33)	74 (25.61)	
25-29.9	87 (40.28)	112 (38.75)	
>30	50 (23.15)	101 (34.95)	
Education category			0.1343
8th grade or less	23 (10.65)	21 (7.27)	
8th grade to some college	177 (81.94)	255 (88.24)	
College degree or greater	16 (7.41)	13 (4.50)	
History of incarceration[d]			0.2690
Yes	77 (35.65)	117 (40.48)	
No	139 (64.35)	172 (59.52)	

Factor	Treatment Regimen 9H SAT n=216	Treatment Regimen 3HP DOT n=289	p-value
Unemployment			0.7655
Yes	140 (64.81)	191 (66.09)	
No	76 (35.19)	98 (33.91)	
Latent TB contact			0.0213
Yes	137 (63.43)	211 (73.01)	
No	79 (36.57)	78 (26.99)	
Latent TB fibrosis			0.5723[b]
Yes	0 (0)	1 (0.35)	
No	216 (100)	288 (99.65)	
Latent TB HIV positive			0.0754
Yes	19 (8.80)	14 (4.84)	
No	197 (91.20)	275 (95.16)	
Latent TB TST converter			0.8298
Yes	91 (42.13)	119 (41.18)	
No	125 (57.87)	170 (58.82)	
HIV status			0.3206
Positive	19 (8.80)	17 (5.88)	
Negative	126 (58.33)	184 (63.67)	
Unknown	71 (32.87)	88 (30.45)	
Smoking at Enrollment			0.7983
Yes	157 (72.69)	213 (73.70)	
No	59 (27.31)	76 (26.30)	
Alcohol Consumption [e]			0.0569[f]
Use	92 (42.59)	131 (45.33)	
Abuse	68 (31.48)	113 (39.10)	
No	56 (25.93)	45 (15.57)	
Injection drug use			0.5837
Yes	50 (23.15)	61 (21.11)	
No	166 (76.85)	228 (78.89)	
Methadone treatment			0.0089
Yes	17 (7.87)	8 (2.77)	
No	199 (92.13)	281 (97.23)	
Use of a translator			0.3388
Yes	13 (6.02)	12 (4.15)	
No	203 (93.98)	277 (95.85)	
Liver disease			0.0794
Yes	51 (23.61)	50 (17.30)	
No	165 (76.39)	239 (82.70)	

Abbreviations: LTBI: latent TB infection. HIV: human immunodeficiency virus. BMI: body mass index. TST: tuberculin skin test. 3HP-DOT: 3 months of directly observed, once-weekly rifapentine (maximum dose, 900 mg) plus isoniazid (maximum dose 300 mg); 9H-SAT, 9 months of daily self-administered isoniazid; LTBI: latent TB infection. HIV: human immunodeficiency virus. BMI: body mass index. TST: tuberculin skin test.

[a] Median Two-Sample Test

[b] Fisher's exact test

[c] Includes North American Indian and other participants in the United States and Canada.

[d] History of residing within a correctional institution for ≥ 1 month before enrollment.

[e] Use: affirmative response to a question asking whether the participant ever drank alcoholic beverages. Abuse: score of ≥2 on the CAGE questionnaire.

[f] Mantel-Haenszel Chi-Square

Table 3. LTBI Treatment Completion, Stratified by Homelessness and by Treatment Regimen (n=6232)

Treatment completion	**Homeless (n=505)**			**Non-homeless (n=5727)**		
	3HP n=289 (%)	**9H n=216 (%)**	p-value	**3HP n=2941 (%)**	**9H n=2786 (%)**	p-value
Completed	227 (79)	132 (61)	<0.0001	2435 (83)	2032 (73)	<0.0001
Did not complete	62 (21)	84 (39)		506 (17)	754 (27)	

Table 4A. Reasons for not Completing LTBI Treatment, Stratified by Homelessness Status Among Participants Assigned to the 9H Regimen (n=838)

Reason category –no. (%)	**Homeless n=82**	**Non-Homeless n=750**
Lost for more than 3 months	33 (40.24)	243 (32.40)
Other	21 (25.61)	97 (12.93)
Drug toxicities	10 (12.20)	119 (15.87)
Patient refused therapy	9 (10.98)	161 (21.47)
Patient withdrew consent	4 (4.88)	57 (7.60)
Out of window	3(3.66)	33 (4.40)
Prescription cancelled by MD	2 (2.44)	38 (5.07)
Patient died	0(0)	2 (0.27)
Missing	2	4

Table 4B. Reasons for not Completing Treatment, Stratified by Homelessness Status Among Participants Assigned to the 3HP Regimen (n=568)

Reason category –no. (%)	**Homeless n=59**	**Non-Homeless n=490**
Other	16 (27.12)	36 (7.35)
Drug toxicities	12 (20.34)	169 (34.49)
Lost for more than 3 months	12 (20.34)	44 (8.98)
Patient refused therapy	11 (18.64)	172 (35.10)
Out of window	4 (6.78)	13 (2.65)
Prescription cancelled by MD	3(5.08)	11 (2.24)
Patient withdrew consent	1 (1.69)	45 (9.18)
Missing	3	16

Table 4C. Classification of "Other" Reason for Non-completion of Treatment in the 9H Regimen, Stratified by Homeless Status (n=118)

Reason	Homeless (n=21)	Non-homeless (n=97)
Incarceration	6	9
Moved	3	20
Military deployment	0	5
Lost	0	3
Tx stopped	0	4
School/ work conflicts	0	3
Legal trouble	0	1
Unable to obtain meds in rehab	0	1
Non-compliant	0	1
MD wants to remove patient from study	0	1
No reason	12	49

Table 4D. Classification of "Other" Reason for Non-completion of Treatment in the 3HP Regimen, Stratified by Homeless Status (n=52)

Reason	Homeless (n=16)	Non-homeless (n=36)
Incarceration	3	6
Moved	1	9
Lost	1	1
Non-compliant	0	2
VISA expired	0	1
Fleeing to Mexico due to legal trouble	0	1
Unknown	11	16

Table 5. Factors Associated with Non-completion of LTBI Treatment in Homeless Participants – Univariate Analysis (n=505)

Factor		NCT (%)	Odds Ratio	Confidence Interval	P-value
Treatment Regimen	3HP-DOT (n=216) Ref. 9H-SAT (n=289)	21.45 38.89	Ref. 2.33	Ref. 1.57-3.45	Ref. <0.001
Age	<38 (n=89) ≥38 (n=416) Ref.	32.58 28.13	1.24 Ref.	0.76-2.02 Ref.	0.40 Ref.
Sex	Female (n=67) Ref. Male (n=438)	25.37 29.45	Ref. 1.23	Ref. 0.68-2.21	Ref. 0.49
Race	White (n=186) Ref. African descendent (n=268) Asian (n=11) Other[a] (n=40)	32.80 25.37 27.27 35	Ref. 0.70 0.77 1.10	Ref. 0.46-1.05 0.20-3.00 0.53-2.26	Ref 0.085 0.705 0.788
Site[b]	Site 70 (n=17) Ref. Other sites (n=488)	29.41 28.89	Ref. 0.98	Ref. 0.34-2.82	Ref. 0.96
Ethnicity	Non-Hispanic (n=449) Ref. Hispanic (n=56)	27.62 39.29	Ref. 1.70	Ref. 0.96-3.01	Ref. 0.072
HIV Status	Negative (n=310) Ref. Positive (n=36) Unknown (n=159)	29.68 33.33 26.42	Ref. 1.19 0.85	Ref. 0.57-2.47 0.55-1.31	Ref. 0.65 0.46
Birthplace	Non-U.S (n=65) U.S. (n=440) Ref.	38.46 27.50	1.65 Ref.	0.96-2.83 Ref.	0.07 Ref.
Body Mass Index	Underweight (n=9) Normal (n=146) Ref. Overweight (199) Obesity (n=151)	33.33 33.56 30.65 21.85	0.99 Ref. 0.88 0.55	0.24-4.13 Ref. 0.55-1.38 0.33-0.93	0.99 Ref. 0.57 0.03
Education	≤8th grade (n=44) 8th grade through some college (n=432) ≥college degree (n=29) Ref.	31.82 28.70 27.59	1.23 1.06 Ref.	0.44-3.44 0.46-2.45 Ref.	0.70 0.90 Ref.
Incarceration[c]	Yes (n=194) No (n=311) Ref.	33.51 26.05	1.635 Ref.	0.97-2.12 Ref.	0.07 Ref.
Unemployed	Yes (n=331) No (n=174) Ref.	28.10 30.46	0.87 Ref.	0.60 – 1.33 Ref.	0.58 Ref.
Alcohol Consumption[d]	No (n=101) Ref. Use (n=223) Abuse (n=181)	32.60 24.22 32.67	Ref. 0.66 1.00	Ref. 0.39-1.10 0.59-1.68	Ref. 0.11 0.99

Factor		NCT (%)	Odds Ratio	Confidence Interval	P-value
Intravenous drug user ever	No (n=394) Ref. Yes (n=111)	29.19 27.93	Ref. 0.94	Ref. 0.59-1.50	Ref. 0.80
Smoking at Enrollment	No (n=135) Ref. Yes (n=370)	28.15 29.19	Ref. 1.05	Ref. 0.68-1.63	Ref. 0.82
Use of Methadone	No (n=480) Ref. Yes (n=25)	28.75 32	Ref. 1.17	Ref. 0.49-2.77	Ref. 0.73
Concomitant medications	No (n=217) Ref. Yes (n=288)	31.80 26.74	Ref. 0.78	Ref. 0.53-1.15	Ref. 0.21
LTBI for contact TB	No (n=157) Ref. Yes (n=348)	22.93 31.61	Ref. 1.55	Ref. 1.01-2.40	Ref. 0.05
LTBI for TST converter	No (n=295) Ref. Yes (n=210)	31.19 25.71	Ref. 0.76	Ref. 0.51-1.13	Ref. 0.18
LTBI fibrosis	No (n=504) Ref. Yes (n=1)	28.97 0	Ref. <0.001	Ref. <0.001->999.999	Ref. 0.99
LTBI for HIV infection	No (n=472) Ref. Yes (n=33)	29.03 27.27	Ref. 0.92	Ref. 0.42-2.02	Ref. 0.83
Chronic Liver Disease	Yes (n=86) No (331) Ref.	31.68 28.22	1.18 Ref.	0.74-1.89 Ref.	0.49 Ref.
Missed clinic visit[e]	No (n=453) Ref. Yes (n=52)	25.17 61.54	Ref. 4.76	Ref. 2.62-8.65	Ref. <0.0001

Abbreviations: 3HP-DOT, 3 months of directly observed, once-weekly rifapentine (maximum dose, 900 mg) plus isoniazid (maximum dose 300 mg); 9H-SAT, 9 months of daily self-administered isoniazid; LTBI: latent TB infection. HIV: human immunodeficiency virus. BMI: body mass index. TST: tuberculin skin test. NCT: non-completion of treatment

[a] Includes North American Indian and other participants in the United States and Canada.

[b] The variable site was categorized arbitrarily taking site with the highest number (70) as the reference.

[c] History of residing within a correctional institution for ≥ 1 month before enrollment.

[d] Use: affirmative response to a question asking whether the participant ever drank alcoholic beverages. Abuse: score of ≥2 on the CAGE questionnaire.

[e] Missing ≥1 of the first 3 directly observed therapy (DOT) sessions for the 3HP regimen or ≥1 of the 3 monthly clinic visits for the 9H regimen, followed by a DOT or a monthly visit, respectively.

Table 6. Factors Associated with Non-completion of LTBI Treatment Among Homeless Participants – Multivariate Analysis (N=505)

Factor		**NCT (%)**	**Odds Ratio (95% CI)**	**p-value**
Treatment regimen	3HP (n=216) Ref. 9H (n=289)	12.28 16.63	Ref. 2.11 (1.40, 3.18)	Ref. 0.0003
Birthplace in the US	Non-US (n=65) US (n=440) Ref.	23.96 4.95	1.96 (1.11, 3.48) Ref.	0.0220 Ref.
Incarceration [a]	Yes (n=194) No (n=311) Ref.	12.87 16.04	1.69 (1.11, 2.57) Ref.	0.0148 Ref.
Missed clinic visit [b]	No (n=453) Ref. Yes (n=52)	22.57 6.34	4.57 (2.46, 8.49) Ref.	<0.0001 Ref.

Abbreviations: NCT: non-completion of treatment; 3HP-DOT, 3 months of directly observed, once-weekly rifapentine (maximum dose, 900 mg) plus isoniazid (maximum dose 300 mg); 9H-SAT, 9 months of daily self-administered isoniazid

[a] History of residing within a correctional institution for ≥ 1 month before enrollment.

[b] Missing ≥1 of the first 3 directly observed therapy (DOT) sessions for the 3HP regimen or ≥1 of the 3 monthly clinic visits for the 9H regimen, followed by a DOT or a monthly visit, respectively.

Table 7. Homeless Participants Stratified by Regimen and Site (n = 505)

Site	3HP n=**289 (%)**	9H n=**216** (%)
G (n=181)	110 (21.78)	71 (14.06)
L (n=78)	55 (10.89)	23 (4.55)
C (n=57)	30 (5.94)	27 (5.35)
J (n=40)	25 (4.95)	15 (2.97)
N (n=42)	17 (3.37)	25 (4.95)
V (n=17)	9 (1.78)	8 (1.58)
D (n=12)	7 (1.39)	5 (0.99)
T (n=7)	6 (1.19)	1 (0.20)
U (n=14)	6 (1.19)	8 (1.58)
P (n=13)	5 (0.99)	8 (1.58)
E (n=9)	4 (0.79)	5 (0.99)
R (n=6)	3 (0.59)	3 (0.59)
B (n=7)	2 (0.40)	5 (0.99)
H (n=2)	2 (0.40)	0 (0)
O (n=8)	2 (0.40)	6 (1.19)
A (n=1)	1 (0.20)	0 (0)
F (n=4)	1 (0.20)	3 (0.59)
I (n=2)	1 (0.20)	1 (0.20)
K (n=2)	1 (0.20)	1 (0.20)
M (n=1)	1 (0.20)	0 (0)
Q (n=1)	1 (0.20)	0 (0)
S (n=1)	0 (0)	1 (0.20)
Total = 505	**289 (8.94)**	**216 (7.20)**

Site key: A=12, B=13, C=14, D=15, E=16, F=17, G=20, H=21, I=22, J=23, K=24, L=26, M=27, N=28, O=53, P=54, Q=58, R=61, S=62, T=63, U=66, V=70

Table 8. Clusters of Participants Enrolled in the PREVENT TB Trial, Stratified by Homelessness Status (N=6232)

Clusters	**Homeless** (n=505)	**Non-Homeless** (n=5727)
1	399 (79.01)	4138 (72.25)
2	19 (3.76)	653 (11.40)
3	5 (0.99)	284 (4.96)
4	12 (2.38)	220 (3.84)
5	7 (1.39)	111 (1.94)
6	0 (0)	63 (1.10)
7	0 (0)	46 (0.80)
8	1 (0.20)	42 (0.73)
9	0 (0)	9 (0.16)
10	7 (1.39)	23 (0.40)
11	12 (2.38)	51 (0.89)
12	0 (0)	24 (0.42)
13	0 (0)	26 (0.45)
14	0 (0)	7 (0.12)
19	14 (2.77)	5 (0.09)
23	0 (0)	23 (0.40)
31	29 (5.74)	2 (0.03)

Table 9. Clusters of Homeless Participants Enrolled in the PREVENT TB Trial Stratified by Treatment Regimen (N=505)

Cluster	3HP (n=289)	9H (n=216)
1	200 (69.20)	199 (92.13)
2	14 (4.84)	5 (2.31)
3	5 (1.73)	0 (0)
4	6 (2.08)	6 (2.78)
5	2 (0.69)	5 (2.31)
8	0 (0)	1 (0.46)
10	7 (2.42)	0 (0)
11	12 (4.15)	0 (0)
19	14 (4.84)	0 (0)
31	29 (10.03)	0 (0)

SUPPLEMENT

Table S1. Demographic Characteristics Among First Participants Enrolled in a Cluster, Stratified by Homeless Status (N=5173)

Factor	**Homeless n=417 (%)**	**Non-Homeless n=4756 (%)**	**p-value**
Sex			<0.001
Male	354 (84.89)	2487 (52.29)	
Female	63 (15.11)	2269 (47.71)	
Age-years			<0.001[a]
Median	46	37	
Interquartile range	40,52	28,47	
Site [b]			<0.001
Site 70	16 (3.84)	305 (6.41)	
Other sites	401 (96.16)	4451 (93.59)	
Birthplace in the U. S.			<0.001
Yes	364 (87.29)	1879 (39.51)	
No	53 (12.71)	2877 (60.49)	
Race			<0.001
African descendent	243 (58.27)	1233(25.93)	
Asian	10 (2.40)	708 (14.89)	
White	154 (36.93)	2635 (55.40)	
Other [d]	10 (2.40)	180 (3.78)	
Ethnicity			<0.001
Hispanic	45 (10.79)	1912 (40.20)	
Non-Hispanic	372 (89.21)	2844 (59.80)	
BMI			0.3005[a]
Median	27	27	
Interquartile range	(24, 30)	(24, 31)	
BMI Category			0.0518
<18.5	7 (1.68)	76 (1.60)	
18.5 – 24.9	123 (29.50)	1366 (28.72)	
25-29.9	169 (40.53)	1669 (35.09)	
>30	118 (28.30)	1645 (34.59)	
Education category			<0.001
8th grade or less	37 (8.87)	751 (15.79)	
8th grade to some college	355 (85.13)	2937 (61.75)	
College degree or greater	25 (6)	1068 (22.46)	
History of incarceration [e]			<0.001
Yes	160 (38.37)	179 (3.76)	
No	257 (61.63)	4577 (96.24)	
Unemployment			<0.001
Yes	269 (64.51)	385 (8.10)	
No	148 (35.49)	4371 (91.90)	
Latent TB-contact			0.2645
Yes	261 (62.59)	2844 (59.80)	
No	156 (37.41)	1912 (40.20)	
Latent TB Fibrosis			<0.001[b]

Factor	Homeless n=417 (%)	Non-Homeless n=4756 (%)	p-value
Yes	1 (0.24)	177 (3.72)	
No	416 (99.76)	4579 (96.28)	
Latent TB – HIV positive			<0.001
Yes	33 (7.91)	105 (2.21)	
No	384 (92.09)	4651 (97.79)	
Latent TB –TST converter			0.0806
Yes	186 (44.60)	1913 (40.22)	
No	231 (55.40)	2843(59.78)	
HIV Status			<0.001
Positive	35 (8.39)	108 (2.27)	
Negative	246 (58.99)	2359 (49.60)	
Unknown	136 (32.61)	2289 (48.13)	
Smoking at Enrollment			<0.001
Yes	304 (72.90)	1306 (27.46)	
No	113 (27.10)	3450 (72.54)	
Alcohol Consumption [f]			<0.001[g]
use	187 (44.84)	2338 (49.16)	
abuse	141 (33.81)	245 (5.15)	
no	89 (21.34)	2173 (45.69)	
Injection Drug Use			<0.001
Yes	97 (23.26)	148 (3.11)	
No	320 (76.74)	4608 (96.89)	
Methadone treatment			<0.001
Yes	24 (5.76)	110 (2.31)	
No	393 (94.24)	4646 (97.69)	
Use of concomitant medications			0.0222
Yes	236 (56.59)	2414 (50.76)	
No	181 (43.41)	2342 (49.24)	
Use of a translator			<0.001
Yes	21 (5.04)	1150 (24.18)	
No	396 (94.96)	3606 (75.82)	
Liver disease			<0.001
Yes	86 (20.62)	136 (2.86)	
No	331 (79.38)	4620 (97.14)	

Abbreviations: LTBI: latent TB infection. HIV: human immunodeficiency virus. BMI: body mass index. TST: tuberculin skin test. 3HP-DOT, 3 months of directly observed, once-weekly rifapentine (maximum dose, 900 mg) plus isoniazid (maximum dose 300 mg); 9H-SAT, 9 months of daily self-administered isoniazid; LTBI: latent TB infection. HIV: human immunodeficiency virus. BMI: body mass index. TST: tuberculin skin test. A cluster represents a group setting; clustered participants represent the first person in a cluster. This first person underwent randomization and is representative of all participants in the cluster.

[a] Median Two-Sample Test using the proc npar1way SAS procedure.
[b] The variable site was categorized arbitrarily taking site with the highest number (70) as the reference
[c] Fisher's exact test

[d] Includes North American Indian and other participants in the United States and Canada.
[e] History of residing within a correctional institution for ≥ 1 month before enrollment.
[f] Use: affirmative response to a question asking whether the participant ever drank alcoholic beverages. Abuse: score of ≥2 on the CAGE questionnaire.
[g] Mantel-Haenszel Chi-Square

Table S2. Demographic Characteristics of the First Homeless Participants Enrolled in a Cluster, Stratified by Treatment Regimen (N= 417)

Factor	**Treatment Regimen 9H SAT n=204 (%)**	**Treatment Regimen 3HP DOT n=213 (%)**	**p-value**
Cluster			0.18
Yes	203 (99.5)	209 (98.12)	
No	1 (0.50)	4 (1.88)	
Sex			0.5510
Male	171 (83.82)	183 (85.92)	
Female	33 (16.18)	30 (14.08)	
Age – years			0.7358[a]
Median	45.5	47	
Interquartile range	40.5, 52.5	40, 52	
Birthplace in the U.S.			0.2311
Yes	174 (85.29)	190 (89.20)	
No	30 (14.71)	23 (10.80)	
Race			0.8330[b]
African descendent	120 (58.82)	123 (57.75)	
Asian	6 (2.94)	4 (1.88)	
White	74 (36.27)	80 (37.56)	
Other[c]	4 (1.96)	6 (2.82)	
Ethnicity			
Hispanic	24 (53.33)	21 (46.67)	0.5307
Non-Hispanic	180 (48.39)	192 (51.61)	
BMI			0.5944[a]
Median	26	27	
Interquartile Range	(23, 29)	(24, 32)	
BMI Category			0.0208[b]
<18.5	6 (2.94)	1 (0.47)	
18.5 – 24.9	68 (33.33)	55 (25.82)	
25-29.9	83 (40.69)	86 (40.38)	
>30	47 (23.04)	71 (33.33)	
Education category			0.1011
8th grade or less	22 (10.78)	15 (7.04)	
8th grade to some college	166 (81.37)	189 (88.73)	
College graduate or greater	16 (7.84)	9 (4.23)	
History of incarceration[d]			0.5096
Yes	75 (36.76)	85 (39.91)	
No	129 (63.24)	128 (60.09)	

Factor	Treatment Regimen 9H SAT n=204 (%)	Treatment Regimen 3HP DOT n=213 (%)	p-value
Unemployment			0.9343
Yes	132 (64.71)	137 (64.32)	
No	72 (35.29)	76 (35.68)	
Latent TB contact			0.5869
Yes	125 (61.27)	137 (64.32)	
No	79 (38.73)	76 (35.68)	
Latent TB fibrosis			0.5108e
Yes	0 (0)	1 (0.47)	
No	204 (100)	212 (99.53)	
Latent TB HIV positive			0.3000
Yes	19 (9.31)	14 (6.57)	
No	185 (90.69)	199 (93.43)	
Latent TB TST converter			0.6945
Yes	89 (43.63)	97 (45.54)	
No	115 (56.37)	116 (54.46)	
HIV Status			0.3453
Positive	19 (9.31)	17 (7.98)	
Negative	119 (58.33)	139 (65.26)	
Unknown	66 (32.35)	57 (26.76)	
Smoking at Enrollment			0.4696
Yes	152 (74.51)	153 (71.83)	
No	52 (25.49)	60 (28.17)	
Alcohol Consumption[e]			0.1692[f]
Use	88 (43.14)	99 (46.48)	
Abuse	65 (31.86)	76 (35.68)	
No	51 (25)	38 (17.84)	
Injection drug use			0.8614[b]
Yes	49 (24.02)	48 (22.54)	
No	155 (75.98)	164 (77)	
Unknown	0 (0)	1 (0.47)	
Methadone treatment			0.0270
Yes	17 (8.33)	7 (3.29)	
No	187 (91.67)	206 (96.71)	

Factor	Treatment Regimen 9H SAT n=204 (%)	Treatment Regimen 3HP DOT n=213 (%)	p-value
Use of a translator			0.5055
Yes	12 (5.88)	9 (4.23)	
No	192 (94.12)	204 (95.77)	
Liver disease			0.0935
Yes	49 (24.02)	37 (17.37)	
No	155 (75.98)	176 (82.63)	

Abbreviations: LTBI: latent TB infection. HIV: human immunodeficiency virus. BMI: body mass index. TST: tuberculin skin test. 3HP-DOT, 3 months of directly observed, once-weekly rifapentine (maximum dose, 900 mg) plus isoniazid (maximum dose 300 mg); 9H-SAT, 9 months of daily self-administered isoniazid; LTBI: latent TB infection. HIV: human immunodeficiency virus. BMI: body mass index. TST: tuberculin skin test. A cluster represents a group setting; clustered participants represent the first person in a cluster. This first person underwent randomization and is representative of all participants in the cluster.

[a] Median Two-Sample Test using the proc npar1way SAS procedure.

[b] Fisher's exact test

[c] Includes North American Indian and other participants in the United States and Canada.

[d] History of residing within a correctional institution for ≥ 1 month before enrollment.

[e] Use: affirmative response to a question asking whether the participant ever drank alcoholic beverages. Abuse: score of ≥2 on the CAGE questionnaire.

[f] Mantel-Haenszel Chi-Square

Table S3. Factors Associated with Non-completion of LTBI Treatment Among the First Homeless Participant Enrolled in a Cluster – Univariate Analysis (N=417)

Factor		NCT (%)	Odds Ratio	Confidence Interval	P-value
Treatment Regimen	3HP-DOT (n=204) Ref. 9H-SAT (n=213)	20.19 38.73	2.50 Ref.	1.61-3.87 Ref.	Ref. <0.001
Age	<38 (n=71) ≥38 (n=346) Ref.	31.43 28.82	1.13 Ref.	0.65-1.97 Ref.	0.66 Ref.
Sex	Female (n=62) Ref. Male (n=355)	23.81 30.23	Ref. 1.39	Ref. 0.74-2.58	Ref. 0.30
Race	White (n=155) Ref. African descendent (n=242) Asian (n=10) Other[a] (n=10)	32.47 26.34 30 50	Ref. 0.74 0.89 2.08	Ref. 0.48-1.16 0.22-3.59 0.58-7.51	Ref 0.19 0.87 0.26
Ethnicity	Non-Hispanic (n=371) Ref. Hispanic (n=46)	27.42 44.44	Ref. 2.12	Ref. 1.13-3.98	Ref. 0.02
Site[b]	Other sites (n=401) Site 70 (n=16)	29.18 31.25	0.91 Ref.	0.31-2.67 Ref.	0.86 Ref.
HIV Status	Negative (n=258) Ref. Positive (n=36) Unknown (n=123)	31.40 33.33 23.58	Ref. 1.09 0.67	Ref. 0.52-2.29 0.41-1.10	Ref. 0.81 0.12
Birthplace	Non-U.S (n=54) U.S. (n=363) Ref.	43.40 27.20	2.05 Ref.	1.14-3.70 Ref.	0.02 Ref.
Body Mass Index	Underweight (n=7) Normal (n=122) Ref. Overweight (168) Obesity (n=120)	42.86 33.33 30.77 22.03	1.50 Ref. 0.89 0.57	0.32-7.02 Ref. 0.54-1.46 0.32-1.00	0.61 Ref. 0.64 0.05
Education	≤8th grade (n=37) 8th grade through some college (n=354) ≥college degree (n=26) Ref.	35.14 28.73 28	1.39 1.04 Ref.	0.46-4.20 0.40-2.56 Ref.	0.56 0.94 Ref.
Incarceration[c]	Yes (n=159) No (n=258) Ref.	35.63 25.29	Ref. 1.64	Ref. 1.07-2.51	Ref. 0.02
Unemployed	Yes (n=270) Ref. No (n=147)	28.25 31.08	Ref. 1.15	Ref. 0.74-1.77	Ref. 0.54
Alcohol Consumption[d]	No (n=88) Ref. Use (n=188) Abuse (n=141)	26.20 31.21 32.58	Ref. 0.74 0.94	Ref. 0.42-1.27 0.53-1.66	Ref. 0.27 0.83
Intravenous drug user ever	No (n=320) Ref. Yes (n=97)	30 26.80	Ref. 0.85	Ref. 0.51-1.42	Ref. 0.54

Factor		NCT (%)	Odds Ratio	Confidence Interval	P-value
Smoking at Enrollment	No (n=112) Ref. Yes (n=305)	28.32 29.61	Ref. 1.07	Ref. 0.66-1.72	Ref. 0.80
Use of Methadone	No (n=393) Ref. Yes (n=24)	29.26 29.17	Ref. 1.00	Ref. 0.40-2.47	Ref. 0.99
Concomitant medications	No (n=181) Ref. Yes (n=236)	33.15 26.27	Ref. 0.72	Ref. 0.47-1.10	Ref. 0.17
LTBI for contact TB	No (n=155) Ref. Yes (n=262)	23.08 32.95	Ref. 1.64	Ref. 1.04-2.58	Ref. 0.03
LTBI for TST converter	No (n=231) Ref. Yes (n=186)	32.03 25.81	Ref. 0.74	Ref. 0.48-1.13	Ref. 0.17
LTBI fibrosis	No (n=416) Ref. Yes (n=1)	29.33 0	Ref. <0.001	Ref. <0.001->999.999	Ref. 0.99
LTBI for HIV infection	No (n=384) Ref. Yes (n=33)	29.43 27.27	Ref. 0.90	Ref. 0.41-2.00	Ref. 0.79
Missed clinic visit[e]	No (n=377) Ref. Yes (n=40)	25.33 64.29	Ref. 5.31	Ref. 2.71-10.40	Ref. <0.001

Abbreviations: NCT: non-completion of treatment; 3HP-DOT, 3 months of directly observed, once-weekly rifapentine (maximum dose, 900 mg) plus isoniazid (maximum dose 300 mg); 9H-SAT, 9 months of daily self-administered isoniazid; LTBI: latent TB infection. HIV: human immunodeficiency virus. BMI: body mass index. TST: tuberculin skin test. A cluster represents a group setting; clustered participants represent the first person in a cluster. This first person underwent randomization and is representative of all participants in the cluster.

[a] Includes North American Indian and other participants in the United States and Canada.

[b] The variable site was categorized arbitrarily taking site with the highest number (70) as the reference.

[c] History of residing within a correctional institution for ≥ 1 month before enrollment.

[d] Use: affirmative response to a question asking whether the participant ever drank alcoholic beverages. Abuse:
score of ≥2 on the CAGE questionnaire.

[e] Missing ≥1 of the first 3 directly observed therapy (DOT) sessions for the 3HP regimen or ≥1 of the 3 monthly clinic visits for the 9H regimen, followed by a DOT or a monthly visit, respectively.

Table S4. Factors Associated with LTBI Non-completion of Treatment Among the First Participant Enrolled in a Cluster - Multivariate Analysis (N=417)

Factor	Odds Ratio (95% CI)	p-value
Treatment Regimen		
3HP	Ref.	
9H	2.23 (1.41, 3.53)	0.0006
Birthplace in the U.S.		
Yes	Ref.	Ref.
No	2.81 (1.48, 5.35)	0.0016
Incarceration [a]		
Yes	2.06 (1.28, 3.32)	0.0029
No	Ref.	
Missed clinic visit		
Yes	5.16 (2.55, 10.46)	<0.0001
No	Ref.	

Abbreviations: 3HP-DOT, 3 months of directly observed, once-weekly rifapentine (maximum dose, 900 mg) plus isoniazid (maximum dose 300 mg); 9H-SAT, 9 months of daily self-administered isoniazid. A cluster represents a group setting; clustered participants represent the first person in a cluster. This first person underwent randomization and is representative of all participants in the cluster.

[a] History of residing within a correctional institution for ≥ 1 month before enrollment.