Recommendations for Strategies to Improve Adherence to Treatment for
Latent Tuberculosis Infections

by

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4/8/2016
ABSTRACT

While significant progress has been made toward the elimination of tuberculosis in the United States (U.S.), it remains a public health problem in other parts of the world (Centers for Disease Control and Prevention [CDC], 2016a). Completion of Latent Tuberculosis Infection (LTBI) treatment is essential to controlling and eliminating tuberculosis (TB). Treatment completion is determined by the number of doses ingested over a given period of time. Adherence to LTBI treatment is important because it can improve the control of disease transmission and it is a key strategy to reduce TB disease incidence in industrialized countries.

A literature review was conducted to assess ways to improve adherence to LTBI treatment and provide recommendations for implementation. The evaluation focused on three main strategies—healthcare provider-centered, clinic-centered, and patient-centered—to find ways to improve adherence to LTBI treatment regimens. Based on the results of the studies evaluated, directly observed therapy (DOT) showed an increase in adherence to LTBI treatment of approximately 70-80% especially when used in conjunction with other patient-centered strategies and innovative treatment regimens. DOT is when qualified healthcare staff observe TB patients taking their TB medication to ensure adherence to treatment; therefore, a recommendation is that DOT along with innovative regimens and patient-centered strategies be implemented to improve adherence.

Key words: LTBI treatment, DOT, adherence
ACKNOWLEDGEMENTS

I’d like to thank the following individuals for their support in encouraging me to become involved in TB control activities and the associated clinical and programmatic activities. Working with this team allowed me to gain more confidence and confirm my interest improving public health with a focus on TB control and the control of other infectious diseases.

**My Advisor**: Susan Randolph, MSN, RN, COHN-S, FAAOHN

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**Robeson County Health Department**: Tracy Jones, RN, TB Nurse

**Robeson County Health Department**: Tammy Jackson, RN, TB Nurse
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CHAPTER I
INTRODUCTION

Tuberculosis (TB) is one of the most infectious diseases in the world that infects approximately 9 million people every year (Center for Connected Health Policy, 2015). TB is also one of the leading killers of people with the human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) (CDC, 2016a). Significant progress has been made toward the elimination of TB in the United States; however, it remains a public health problem in other parts of the world (Lonnroth et al., 2015).

TB is caused by a bacterium called *Mycobacterium tuberculosis*. The bacterium primarily attacks the lungs; however, it can attack any part of the body. Once a person is exposed to the bacteria, active disease with symptoms can develop or a latent infection, where the bacteria live in the body without symptoms, can occur.

LTBI treatment for those at highest risk for TB disease (e.g., HIV/AIDS, injection drug users, previous active TB disease, diabetes, organ transplant, immunosuppressant medications) will help eliminate the disease because it reduces TB disease incidence and transmission. Non-completion of LTBI treatment increases the risk of disease activation and progression, transmission, development of drug resistance, or death (Center for Connected Health Policy, 2015).

Based on research and recommendations by CDC (2013a), directly observed therapy (DOT) is the most effective way to ensure adherence to treatment for active and latent TB infections. DOT involves having healthcare staff observe TB patients taking their medication to ensure adherence to treatment. It should be a collaborative effort
with county health departments to help reduce the cost and resource burden for each healthcare provider (CDC, 2013a). The health department works with other agencies and private physicians to plan effectively for the care of the person with TB disease and any other individuals who have been exposed to and/or infected with TB (N.C. DHHS, 2016). Patients may be managed in the private sector or by the public health department, or jointly, but in all cases the local health department is ultimately responsible for ensuring that adequate, appropriate diagnostic and treatment services are available, and for monitoring the results of therapy (CDC, 2003).

Treatment programs are clearly defined for active TB cases where DOT is required; however, for LTBI, the treatment is optional and DOT is not required. As a result, the development of active disease and transmission is still a high risk.

**Purpose of Paper**

The purpose of this paper is to summarize the findings of a literature review conducted to assess ways to improve adherence to LTBI treatment and provide recommendations for implementation. Adherence to LTBI treatment is important because it can improve the control of disease transmission. It is also a key strategy to reduce TB disease incidence in industrialized countries.
CHAPTER II
BACKGROUND

History

The bacterium that causes TB existed since ancient times (approximately 15,000-20,000 years ago) and was discovered in the late 1800s by Robert Koch (Mandal, 2014). TB disease has been referred to as consumption due severe weight loss of the infected, phthisis pulmonaris, the white plague because the infected had a pale appearance, “the captain of all men of death”, and “the King’s evil” because it was believed that Kings of France and England could touch the infected and cure them (Mandal, 2014).

The tubercle bacilli have a unique protein coat that made it difficult to visualize prior to the discovery of the Zeihl Neelson stain. Due to the tubercle bacilli’s retention of the acidic red dye, it was called acid-fast bacilli (AFB) because it stained red (Figure 2.1). In 1895 Wilhelm Roentgen developed X-rays to view the lungs. The Zeihl Neelson stain and X-rays further advanced diagnostics and allowed for early diagnosis and isolation of infected individuals (Mandal, 2014).

Once it was discovered that the disease could be transmitted by close contact, tuberculosis patients were isolated in a sanatorium for treatment with rest and improved nutrition (Mandal, 2014). Using the concepts (e.g., attenuation, genetic modification) from the development of other vaccines such as cholera, rabies, and anthrax, the Bacillus Calmette–Guérin (BCG) vaccine for the treatment of TB was developed and introduced in 1921.
FIGURE 2.1

ACID FAST STAIN

Source: Picture courtesy of microbeonline (2013)
Tuberculosis was treated by draining pleural effusion from around the lungs to prolong life; however, due to lack of efficacy, treatment by surgery diminished (Mandal, 2014). An antibiotic called streptomycin was discovered and used to treat tuberculosis for the first time in 1944. However, use of this antibiotic alone led to antibiotic resistance. Then with the development other drugs like isoniazid (INH) and rifampicin, better results were observed (Mandal, 2014). To date, there are approximately 20 antimicrobials with activity against Mycobacterium species.

**Epidemiology**

According to the World Health Organization (WHO) (2015a), TB now ranks alongside HIV/AIDS as a leading cause of death worldwide. In 2014, it is estimated that 1.2 million people died from HIV/AIDS and 0.4 million of those deaths were due to tuberculosis. Approximately 9.6 million people worldwide are estimated to have become sick with tuberculosis in 2014: 5.4 million men, 3.2 million women and 1 million children (CDC, 2014a). Nearly one-third of the world’s population has LTBI and greater than 11 million people in the U.S. have LTBI, which is about 4% of the total population (CDC, 2014a). It is estimated that 5-10% (550,000 to 1,100,000) of people with LTBI people will develop TB disease at some point in their life unless they receive adequate treatment.

**Tuberculosis**

TB is a disease caused by the bacterium *Mycobacterium tuberculosis* which has seven very closely related mycobacterial species – *M. bovis, M. africanum, M. microti, M. caprae, M. pinnipedii, M. canetti* – that cause disease in humans and together are known as the *M. tuberculosis* complex. *M. tuberculosis* is carried in airborne particles,
called droplet nuclei, that are generated when persons who have TB disease cough, sneeze, shout, or sing. Depending on the environment, these tiny particles can remain suspended in the air for several hours. *M. tuberculosis* is transmitted through the air when a person inhales droplet nuclei containing *M. tuberculosis*, and the droplet nuclei travel from the mouth or nasal passages, upper respiratory tract, and bronchi and reach the alveoli of the lungs (CDC, 2012a). Transmission of *M. tuberculosis* is dependent on the following:

- Susceptibility of the person who was exposed;
- Infectiousness of the person who transmitted the disease affects the number of bacilli that are expelled into the air;
- Environmental factors, like ventilation, that impacts the length of the time the bacilli remain in the air; and
- The proximity and length of exposure to the infected person.

**Definitions**

“Not everyone infected with TB bacteria becomes sick. As a result, two TB-related conditions exist: latent TB infection and TB disease” (CDC, 2012a, para 1) (Table 2.1).

**Latent TB Infection**

Most people who are exposed to the TB bacteria and become infected are able to fight the bacteria to stop them from growing resulting in a latent TB infection; however, progression from a latent TB infection to TB disease may occur at any time. Individuals with LTBI have the TB bacteria in the body but do not have symptoms and cannot transmit the infection to others.
### TABLE 2.1

**LATENT TB INFECTION VS. TB DISEASE**

<table>
<thead>
<tr>
<th>Latent TB Infection</th>
<th>TB Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>• TB bacteria in the body that are alive, but inactive</td>
<td>• Has a large amount of active TB bacteria in the body</td>
</tr>
<tr>
<td>• Cannot transmit infection</td>
<td>• Can transmit infection</td>
</tr>
<tr>
<td>• Asymptomatic. Can become sick if the bacteria become active due to changes in immunity</td>
<td>• May feel sick and may have mild or severe symptoms depending on the rate of progression of the disease</td>
</tr>
<tr>
<td>• Positive TB skin test or TB blood test</td>
<td>• Positive TB skin test or TB blood test</td>
</tr>
<tr>
<td>• Normal chest x-ray</td>
<td>• Abnormal chest x-ray</td>
</tr>
<tr>
<td>• Negative cultures from microbiology testing</td>
<td>• Sputum smears and cultures may be positive</td>
</tr>
<tr>
<td>• Should consider treatment for LTBI to prevent TB disease</td>
<td>• Needs treatment for TB disease</td>
</tr>
</tbody>
</table>

Source: CDC (2012a)
TB Disease

Individuals with active TB disease have symptoms (e.g., cough, fever, night sweats) and can spread the infection to others. The symptoms may be mild for many months before progressing to more severe symptoms.

Signs and Symptoms

The symptoms of TB disease may develop approximately 2-6 weeks after exposure and include a cough that lasts 3 weeks or longer, chest pain, coughing up blood or bloody mucous, weakness or fatigue, weight loss, loss of appetite, chills, night sweats, or low grade fever. Approximately 78% of individuals do not develop any infection because the body eliminates the bacterium by phagocytosis, which is an immune response. The remaining 22% of individuals will become infected. Of the 22% who become infected, 5% will develop TB disease whereas the other 95% will continue to have a latent TB infection. Without treatment there is a 10% chance of developing TB disease. Approximately 5% of individuals who have been infected with *M. tuberculosis* will develop disease after about 2 years of exposure and another 5% will develop disease sometime later in life (CDC, 2014a). If someone has HIV/AIDS, then the risk of developing TB disease increases to 10% annually (CDC, 2014a). Figure 2.2 shows the pathogenesis after exposure to TB.

Treatment

TB disease can be treated in phases by taking several drugs for 6 to 9 months using first line anti TB agents that include isoniazid (INH), rifampin (RIF), ethambutol (EMB), and pyrazinamide (PZA) (CDC, 2012b). Table 2.2 shows some of the recommended treatment regimens based on the clinical scenario. The initial phase of
FIGURE 2.2

EVENTS AFTER TB EXPOSURE

Source: Adapted from CDC (2014a)
# TABLE 2.2

**CDC RECOMMENDED TB DISEASE TREATMENT REGIMENS**

<table>
<thead>
<tr>
<th>Preferred Regimen</th>
<th>Alternative Regimen</th>
<th>Alternative Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Phase</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Daily INH, RIF, PZA, and EMB* for 56 doses (8 weeks)</td>
<td>• Daily INH, RIF, PZA, and EMB* for 14 doses (2 weeks), then twice weekly for 12 doses (6 weeks)</td>
<td>• Thrice-weekly INH, RIF, PZA, and EMB* for 24 doses (8 weeks)</td>
</tr>
<tr>
<td><strong>Continuation Phase</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Daily INH and RIF for 126 doses (18 weeks) or Twice-weekly INH and RIF for 36 doses (18 weeks)</td>
<td>• Twice-weekly INH and RIF for 36 doses (18 weeks)</td>
<td>• Thrice-weekly INH and RIF for 54 doses (18 weeks)</td>
</tr>
</tbody>
</table>

Source: CDC (2012b)
treatment is given for daily for 8 weeks and the continuation phase is given for 4 or 7 months. The 4-month treatment is more common because the 7-month treatment is recommended only for these groups (CDC, 2012b):

1. Patients with cavitary pulmonary tuberculosis caused by drug-susceptible organisms and whose sputum culture obtained at the time of completion of 2 months of treatment is positive;
2. Patients whose initial phase of treatment did not include PZA;
3. Patients being treated with once weekly INH and rifampentine and whose sputum culture obtained upon completion of the initial phase of treatment is positive; and
4. Patients being treated with once weekly INH and rifapentine and whose sputum culture obtained at the time of completion of the initial phase is positive.

Although basic TB regimens are broadly applicable, there are modifications (e.g., shorter or longer duration, fewer or more doses, other drug types) that should be made under special circumstances (e.g., HIV infection, drug resistance, pregnancy, or treatment of children).

As defined by the CDC (2012b), drug-resistant tuberculosis is resistant to at least one first-line anti-Tuberculosis drug. Multidrug-resistant tuberculosis (MDR TB) is resistant to more than one anti-Tuberculosis drug and at least isoniazid (INH) and rifampin (RIF) and extensively drug resistant tuberculosis (XDR TB) is resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs.
(i.e., amikacin, kanamycin, or capreomycin). Treatment of drug resistant tuberculosis is difficult and costly.

**Importance of LTBI Treatment Adherence**

Too many people in the U.S. and around the world still suffer from TB and anyone can get TB. The current efforts to find and treat LTBI and TB disease are not sufficient (CDC, 2016b). About one-third of the world population has LTBI, with 13 million people (4.2% of the population) affected in the U.S. (WHO, 2015b). TB epidemiology in most low-incidence countries (e.g., U.S. and Canada) is characterized by a low rate of transmission in the general population and occasional outbreaks with a majority of TB cases generated from progression of LTBI rather than transmission from active disease (WHO, 2015b).

LTBI treatment adherence is an important determinant to successful TB elimination (WHO, 2015b). Treatment of LTBI can substantially reduce the risk of development of active disease by as much as 60%, and is an important TB control strategy especially in low-TB incidence settings (Pai & Rodrigues, 2015). For those at highest risk for TB disease (e.g., HIV/AIDS, injection drug users, previous active TB disease, diabetes, organ transplant, immunosuppressant medications), LTBI treatment will also help eliminate the disease because it will reduce TB disease incidence and transmission resulting from TB disease activation or reactivation (CDC, 2013a). Lack of treatment means the infected person has an increased risk of disease activation, which may lead to disease transmission.

Even though persons with LTBI have no signs or symptoms of TB disease and are not infectious, they are still at risk for developing active TB disease and becoming
infectious. The lifetime risk of reactivation TB for a person with LTBI is estimated to be 5-10%, with the majority developing TB disease within the first five years after initial infection (WHO, 2015b). Activation or reactivation of TB disease can be averted by preventive treatment (WHO, 2015b). One of the barriers to LTBI treatment adherence is the side effects from the anti TB drugs; however, the benefits outweigh the harm from side effects especially for individuals who are at a greater risk of progression to active disease.

The management of LTBI requires a comprehensive package of interventions that includes identifying and testing those individuals who should be tested, delivering effective and safe treatment in a manner that will increase the rate of adherence while monitoring and evaluating of the process (WHO, 2015b). Current guidelines for the management of LTBI are focused on people living with HIV/AIDS and children below 5 years of age who are household contacts of TB cases. Therefore, written guidelines for the management of all cases of LTBI would be one of the necessary tools for facilitating the global TB elimination strategy (WHO, 2015b).

In 2014, the WHO developed guidelines for the management of LTBI after recognizing the importance of expanding the LTBI response. The guidelines are primarily targeted at high-income or upper middle-income countries with an estimated TB incidence rate of less than 100 per 100,000 population, because they are most likely to benefit from it due to their current TB epidemiology and resource availability (WHO, 2015b). The objective of the guidelines is to provide guidance for testing, treating, and managing individuals with LTBI and those at highest risk of progression to active disease.
Healthcare providers play a key role in achieving the goal of TB elimination because of their access to high-risk populations. Many variables can affect a patient’s adherence to LTBI treatment including scheduling, misinformation about tuberculosis, health beliefs and practices, income or social status, pre-existing medical conditions, medication side effects, language, and stigma (CDC, 2013a). People with latent TB infections have a low adherence to treatment because the perception is “no symptoms, no treatment needed” thus increasing the risk of developing the disease and transmitting it (T. Jackson R.N., personal communication, September 22, 2015). In addition, adherence to LTBI treatment regimens is low despite the individuals knowing that the treatment greatly reduces the risk that TB infection will progress to active TB disease (Table 2.3). The lack of adherence can be attributed to barriers such as drug costs, medication side effects, and loss of work time. Therefore, it is recommended that treatment for LTBI be conducted as DOT.

Once the diagnosis of LTBI has been made, healthcare providers must choose the most appropriate and effective treatment regimen, and make every effort to ensure those persons complete the entire course of treatment for LTBI. However, if exposed to and infected by a person with multidrug-resistant TB (MDR TB) or extensively drug-resistant TB (XDR TB), preventive treatment may not be an option.

**Reporting Requirements**

TB is a communicable disease; therefore, it must be reported as defined by Public Health Laws. The reporting structures are established in collaboration with tribal,
# TABLE 2.3

## CDC RECOMMENDED LATENT TB INFECTION TREATMENT REGIMENS

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Duration</th>
<th>Interval</th>
<th>Minimum Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>9 months</td>
<td>Daily</td>
<td>270</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly</td>
<td>76</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>6 months</td>
<td>Daily</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly</td>
<td>52</td>
</tr>
<tr>
<td>Isoniazid and Rifapentine</td>
<td>3 months</td>
<td>Once weekly</td>
<td>12</td>
</tr>
<tr>
<td>Rifampin</td>
<td>4 months</td>
<td>Daily</td>
<td>120</td>
</tr>
</tbody>
</table>

*Use Directly Observed Therapy (DOT)*

Source: CDC (2012b)
state, local public health departments, federal authorities, and private sector partners and may differ slightly for each country or state (CDC, 2012b).

According to the North Carolina (N.C.) Department of Health and Human Services (N.C. DHHS, 2016), tracking, treating and stopping the spread of tuberculosis requires the cooperation of all healthcare providers and health agencies, especially local public health departments in each county, private healthcare providers, N.C. Tuberculosis Control Program, Duke University Medical Center, Tuberculosis Medical Advisory Committee, American Lung Association of the Southeast, Southeastern National Tuberculosis Center, and the State Laboratory of Public Health (N.C. DHHS, 2016). Local public health departments in N.C. have the primary responsibility for TB control efforts in their own counties and should have a nurse who is responsible for TB control activities (N.C. DHHS, 2016). The local health department must be notified within 24 hours of any diagnosed or suspected case of tuberculosis (N.C. DHHS, 2016).
CHAPTER III
LITERATURE REVIEW

Approach

The focus of the literature review was primarily to review studies that compare or evaluated LTBI treatment strategies and utilized healthcare provider-centered, clinic-centered, and/or patient-centered strategies as recommended by the CDC (2012c). Healthcare provider-centered strategies included interventions conducted by the healthcare provider such as innovative treatment regimens, improved diagnostic methods, use of culturally sensitive case manager). Clinic-centered strategies included methods that are focused on improving adherence during clinic visits (e.g., providing incentives for showing up, flexible hours, transportation assistance). Patient-centered strategies are programs designed to focus on the patient and may consist of DOT, reminder systems, and/or collaboration.

Ten studies were reviewed. The purpose and findings for each study were categorized by determining if the information generated was healthcare provider-centered, clinic-centered strategies, or patient-centered. Then the data were summarized to compare the success rates of different LTBI adherence strategies (Table 3.1).

Inclusion Criteria

An Internet search was conducted using key words or phrases, such as LTBI treatment adherence, DOT, healthcare provider-centered strategies, clinic-centered
### TABLE 3.1

**SUMMARY OF LITERATURE**

<table>
<thead>
<tr>
<th>Healthcare Strategy</th>
<th>Literature Reviewed</th>
</tr>
</thead>
</table>
**Purpose:** The goal of this study was to evaluate the demographic, medical, behavioral, attitude-based, and geographic factors associated with LTBI treatment initiation and completion. This was a prospective cohort study of adults >17 years of age (n=496) that were previously treated for LTBI. In addition to traditional social and behavioral factors, a three-level medical risk variable (low, moderate, high), based on risk factors for both progression to and transmission of active tuberculosis, was included for analysis. LTBI therapy initiation and completion of 9 months of INH or 4 months of RIF were the outcomes evaluated.  
**Main Findings:** Investment in social support and access to regular primary care may lead to increased LTBI therapy adherence in high-risk populations. |
**Purpose:** The goal of this study was to determine the efficacy of coaching Latino adolescents with LTBI as compared to those that receive standard care. Health department staff coached the designated patients throughout the course of the study whereas the patients receiving standard care did not receive any coaching (n=286).  
**Conclusion:** Coaching can increase adolescents’ adherence to treatment for LTBI and should contribute to tuberculosis control for adolescents at high risk of contracting the disease. |
<table>
<thead>
<tr>
<th>Healthcare Strategy</th>
<th>Literature Reviewed</th>
</tr>
</thead>
</table>
| **Healthcare Provider**<br>**Clinic**<br>**Patient** | Li, J., Munsiff, S., Tarantino, T., & Dorsinville, M. (2010). Adherence to treatment of latent tuberculosis infection in a clinical population in New York City. *International Journal of Inf. Diseases.*  
**Purpose:** This study examined the LTBI treatment completion rate and factors associated with adherence of New York City Health department chest clinic patients (n=15,035).  
**Main findings:** Shorter regimen and DOT increased completion rates for LTBI. Though efforts to improve TLTBI completion need to address all groups, greater focus is needed for persons who are contacts and HIV-infected, as they have higher risk of developing TB. |
**Purpose:** This study compared the completion rates of two different LTBI treatment regimens, with and without DOT, among LTBI patients receiving 12 weekly doses of INH plus rifapentine (RPT) administered as DOT and patients with nine months of daily self-administered INH (n=139).  
**Conclusion:** High completion rates for LTBI treatment can be achieved at a community health center using INH-RPT administered via DOT. Greater success treating with INH-RPT may be attributed to DOT strategy and a shorter treatment regimen. |
**Purpose:** This study assessed the effects of reminder systems on improving attendance at TB diagnosis, prophylaxis, and treatment clinic appointments, and their effects on TB treatment outcomes. The study was conducted by evaluating investigations that used randomized controlled trials and controlled before-and-after studies comparing reminder systems with no reminders or an alternative reminder system for people with scheduled appointments (n= 4654). |
<table>
<thead>
<tr>
<th>Healthcare Strategy</th>
<th>Literature Reviewed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conclusion:</strong> Sending reminders to people pre-appointment, and contacting people who miss appointments, seem sensible additions to any TB program, and the limited evidence available suggests they have small but potentially important benefits.</td>
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<table>
<thead>
<tr>
<th>Clinic</th>
<th>Patient</th>
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**Purpose:** The purpose of this study was to evaluate the effects of material incentives and enablers given to patients undergoing diagnostic testing for TB, or receiving drug therapy to prevent or cure TB. This was a review of twelve randomized controlled trials of patients undergoing treatment for LTBI or TB disease.

**Conclusion:** Material incentives and enablers may have some positive short-term effects on clinic attendance, particularly for marginal populations such as drug users, recently released prisoners, and the homeless.

<table>
<thead>
<tr>
<th>Clinic</th>
<th>Patient</th>
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**Purpose:** The purpose of the present study was to determine the rate LTBI treatment completion in an inner-city population in Edmonton, Alberta, and to identify factors that correlated with treatment completion. A retrospective chart review was conducted involving patients with LTBI treatment regimens (n=77).

**Conclusion:** Treatment completion rates comparable with or better than those described in the general population (not homeless); it highlighted the need for continued emphasis on interventions aimed at improving outcomes within homeless populations.

<table>
<thead>
<tr>
<th>Clinic</th>
<th>Patient</th>
</tr>
</thead>
</table>

**Purpose:** This is a multi-centered randomized, open label trial that was geared towards comparing the frequency of adverse events and treatment completion in 2 treatment regimens for latent tuberculosis infection (n=422).
<table>
<thead>
<tr>
<th>Healthcare Strategy</th>
<th>Literature Reviewed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conclusion:</strong> Treatment of latent tuberculosis with 4 months of rifampin leads to better adherence than 9 months of isoniazid.</td>
<td></td>
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</tbody>
</table>
**Purpose:** This was a rapid review of two guidelines and one systematic review aimed at identifying effective strategies that physicians could use to increase LTBI treatment completion rates (n=717).  
**Conclusion:** Client education, patient reminder systems, provider education, patient involvement, and DOT are more likely to increase LTBI treatment adherence and incentives are least likely to improve adherence. |
**Purpose:** This was a prospective, two-group site randomized study conducted among 520 homeless adults. The goal of this study was to compare the effectiveness of an intervention program that compared nurse case management and incentives vs. standard care and incentives on completion of a 6-month INH LTBI treatment regimen and change in TB knowledge.  
**Main Findings:** The study demonstrated treatment completion rates comparable with or better than those described in the general population (not homeless), it highlighted the need for continued emphasis on interventions aimed at improving outcomes within homeless populations. |
strategies, patient-centered strategies, LTBI treatment improvement, and LTBI treatment regimens. The literature publications were retrieved from the University of North Carolina at Chapel Hill Library database and other sites/databases such as ScienceDirect, Medline or Elsevier.

Studies were included if they evaluated one or more of the treatment strategies (healthcare provider-centered, clinic-centered, or patient-centered) and compared DOT for LTBI treatment or focused on LTBI treatment adherence; was a controlled trial; discussed potential barriers or lessons learned; and/or used high risk populations (e.g., homeless, immigrants, patients with active disease or other co-infections). Studies were excluded if they focused on active TB disease treatment adherence and impact of different diagnostics for active TB disease and/or LTBI.

**Synthesis of Findings**

**Different Population Groups Studied**

- Homeless (Nyamathi et al., 2006)
- Chest clinic patients (Liu et al., 2014)
- Latino adolescents (Hovell et al., 2003)
- Inner city adults (Malejczyk et al., 2014)
- Patients undergoing LTBI or TB disease treatment (Liu et al., 2014; Lines et al., 2015)
- Patients previously treated for LTBI (Goswami et al., 2012)

**Factors that Increased Treatment Adherence**

- DOT (Lines et al., 2015; Li, Munsniff, Tarantino, & Dorsinville, 2010; Nguyen & Frenette, 2012)
- Patient involvement, coaching and education (Hovell et al., 2003; Malejczyk et al., 2014; Nyamathi et al., 2006)
- Innovative/shorter treatment regimens (Goswami et al., 2012; Li et al., 2010; Lines et al., 2015; Lutge et al., 2015; Menzies et al., 2008)

**Factors with Little or No Impact on Treatment Adherence**

- Incentives (Nguyen & Frenette, 2012; Lutge et al., 2015)
- Flexible clinic hours (Nguyen & Frenette, 2012)
- Reduced wait times (Nguyen & Frenette, 2012)
- Appointment reminders (Liu et al., 2014)
CHAPTER IV
LATENT TUBERCULOSIS INFECTION TREATMENT STRATEGIES

Healthcare provider-centered strategies that showed a 78% improvement in adherence rates included shorter, more innovative regimens that aim to reduce the length of treatment, the number of pills, drug side effects, and costs (Table 4.1). The rate of improvement noted here can also be attributed to a study that utilized DOT to administer the different treatment regimens (Lines et al., 2015). A 5-15% increase was observed with other strategies that included culture competence, improved/better diagnosis, and implementing changes based on patient feedback.

The clinic-centered strategy showed the least improvement because inconveniences, such as work-loss time and lack of transportation to and from clinics, have been identified as barriers to treatment. Only a 5-15% improvement in adherence was observed with clinic-centered strategies that included improved wait times, incentives, patient education, transportation assistance, and flexible hours (Table 4.2). Even though the clinic-centered strategies involve DOT, the barriers outweighed the ability to deliver treatment.

The patient-centered strategies varied in response (Table 4.3). The most improvement (70%) was seen with DOT and previously showed improvement with the healthcare provider-centered strategy study. A 5-15% improvement was observed with incentives and patient reminder systems, and patient involvement in decision-making; however, the improvement with incentives had a short-term effect due to funding limitations. Patient education about TB infections had a minimal effect (3-5%).
# TABLE 4.1

**HEALTHCARE PROVIDER-CENTERED STRATEGIES IMPROVEMENT SUMMARY**

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Magnitude of Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Innovative regimens to reduce side effects, pill burden, length of treatment, and costs</td>
<td>• 78% completion for shorter regimen vs. 52% for the longer regimen.</td>
</tr>
<tr>
<td>• Provide a case manager of the same cultural background</td>
<td>• 5-15% increased adherence when used in conjunction with other interventions.</td>
</tr>
<tr>
<td>• Patient needs assessment survey to determine areas of improvement</td>
<td></td>
</tr>
<tr>
<td>• Culturally sensitive interactions/culture competence</td>
<td></td>
</tr>
<tr>
<td>• Confidence in diagnosis</td>
<td></td>
</tr>
</tbody>
</table>

Source: refer to Table 3.1
<table>
<thead>
<tr>
<th>Strategy</th>
<th>Magnitude of Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce the number of required clinic visits</td>
<td>5-15%</td>
</tr>
<tr>
<td>Incentives for showing up</td>
<td>5-15%</td>
</tr>
<tr>
<td>Short wait times</td>
<td>5-15%</td>
</tr>
<tr>
<td>Flexible hours</td>
<td>5-15%</td>
</tr>
<tr>
<td>Transportation assistance to and from clinic</td>
<td>5-15%</td>
</tr>
</tbody>
</table>

Source: refer to Table 3.1
### TABLE 4.3

**PATIENT-CENTERED STRATEGIES IMPROVEMENT SUMMARY**

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Magnitude of Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coaching, educate, re-educate</td>
<td>Increased adherence by 3-5% depending on ethnicity, socioeconomic status, etc</td>
</tr>
<tr>
<td>Patient reminder systems</td>
<td>5-15% increase when used in conjunction with other activities or incentives</td>
</tr>
<tr>
<td>Patient involvement in decision-making</td>
<td>5-15% increase when used in conjunction with incentives</td>
</tr>
<tr>
<td>Incentives</td>
<td>Increased adherence by 5-10% vs. groups with no incentives. Short-term effect</td>
</tr>
<tr>
<td>DOT</td>
<td>73% completion rate vs. 47.9% for self-administered therapy</td>
</tr>
</tbody>
</table>

Source: refer to Table 3.1
CHAPTER V
CONCLUSIONS AND RECOMMENDATIONS

Challenges for high-income countries where the TB incidence is lower include lack of political commitment, funding, clinical expertise, and general awareness of TB (Lonnroth et al., 2015). As a result, implementation of DOT for LTBI will be more difficult, especially when there are limited resources and high demand for it with directly with active TB cases (i.e., outbreak). For areas where there is a higher incidence of TB, the focus is on treating TB disease rather than LTBI.

Directly observed therapy should be a collaborative effort with the county health departments to help reduce the cost and resource burden for each healthcare provider (CDC, 2013a). Length of treatment can range from 3 months for LTBI up to 24 months for multi-drug resistant TB (MDR-TB), and the cost of treating a single patient can range from $2,000 to $250,000 for just the medication (Center for Connected Health Policy, 2015). Therefore, shorter more innovative treatment regimens should be used to help reduce the costs. A cost-benefit analysis showed that while there is an increased up front cost associated with DOT, the use of shorter drug regimens (e.g., 4 months of RIF vs 9 months of INH) in conjunction with DOT could compensate for the higher up front cost by preventing more cases of active TB (Holland, Sanders, Hamilton, & Stout, 2009). Treatment of patients with tuberculosis is most successful within a comprehensive framework that addresses both clinical and social issues of relevance to the patient (CDC, 2003). It is essential that treatment and supervision be based on each patient’s clinical and social circumstances (CDC, 2003).
The studies discussed in this paper have demonstrated that patient-centered strategies are the most effective when coupled with incentives. However, the most likely scenario, to increase adherence to LTBI treatment, is to provide patient outreach or treatment options that are convenient to the patient since transportation and work time loss are some of the biggest barriers. These strategies require more resources, increased cost to the healthcare provider, and constant availability of anti TB drugs. However, the long-term benefit to decrease the transmission rates and work towards TB elimination, would outweigh the cost (Holland et al., 2009).
REFERENCES


