Management of Latent Tuberculosis Infection Among an Inner-city Population with Psychosocial Barriers to Treatment Adherence

By

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Abstract

BACKGROUND: In Canada, preventive therapy for LTBI has meant long durations and frequent dosing. This contributes to poor adherence and completion rates. In response, a shortened treatment regimen, once weekly rifapentine plus isoniazid for 3 months (3HP), is now available, though there has been no formal evaluation of it use. This study explored perceptions of latency and the need for preventive therapy, and barriers and facilitators to treatment adherence and completion in inner-city clients offered 3HP and their health care providers.

DESIGN/METHODS: This qualitative descriptive study involved semi-structured individual interviews. Unstably housed or homeless individuals in Edmonton and Fort McMurray, Alberta, Canada offered directly observed preventive therapy (DOPT) with 3HP, and their health care providers were eligible. The data were systematically organized and analyzed using latent content analysis.

RESULTS: Analysis of interviews revealed incomplete understandings of LTBI and the need for preventive therapy. Clients self-motivation and desire to be healthy, alongside education, health care outreach, relationships through DOPT, ease of treatment regimen, incentives and collaboration were described as supporting successful treatment outcomes. Competing priorities, difficulty in reaching clients, undesirable aspects of the regimen (e.g. side effects, pill burden and drug interactions) and arduousness related to obtaining and initiating 3HP were barriers to access, uptake, and completion. Perceptions of stigma related to LTBI and TB were described by clients as well as feelings of shame or embarrassment related to their diagnosis

CONCLUSIONS: This study was the first in Canada to qualitatively explore the use of 3HP. Our study used qualitative descriptive methods to explore the understandings of LTBI and the barriers and facilitators to preventive therapy access, uptake, and adherence among individuals experiencing homelessness and their health care providers. Our study provided insight into the knowledge and understandings of LTBI and the multiple interacting psychosocial factors that influence preventive therapy access, uptake, and adherence. Findings from this study can be used to inform health policy and TB programming aimed at removal of the LTBI reservoir and to address TB specific inequities among individuals experiencing homelessness.

Preface

This thesis is an original work by Amber Heyd. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, under study title "Management of LTBI among an inner-city population and those with psychosocial barriers to treatment" No. Pro00087572 (October 15, 2019, amended December 12, 2019, closed April 22, 2020).

Dedication

This thesis is dedicated to the inner-city clients in Edmonton and Fort McMurray and the outreach nurses and teams who serve them.

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List of Acronyms

LTBI: Latent Mycobacterium Tuberculosis Infection

TB: Tuberculosis

TST: Tuberculin Skin Test

IGRA: Interferon-Gamma Release Assays

INH: Isoniazid

RMP: Rifampicin

3HP: INH/Rifapentine

DOPT: Directly Observed Preventive Therapy

DOT: Directly Observed Therapy

HCP: Health Care Provider

DST: Drug Susceptibility Tests

NAAT: Nucleic Acid Amplification Tests

MDR-TB: Multidrug Resistant TB

XDR-TB: Extensively Drug Resistant TB

PPD: Purified Protein Derivative

BCG: Bacille Calmette-Guérin Vaccine

HIV: Human Immunodeficiency Virus

HBM: Health Belief Model

SAT: Self-administered Therapy

Chapter 1: Introduction

Latent Mycobacterium Tuberculosis Infection (LTBI)

It is now accepted as fact that the pathology of tuberculosis (TB) disease exists within a spectrum resulting from a complex interplay between bacterium, environment, and host.[1-3] Persons who are exposed to someone with active pulmonary TB may inhale the disease causing organism that has been expelled in an aerosol to which the body responds, first with an innate and then with, if the bacterium is not already eradicated and the host is immunocompetent, an acquired immune response.[2] If these early responses do not eradicate all viable bacteria, then rapid progression to disease may occur or the bacterium may be contained and a period of latency will follow.[1-4] This period usually lasts the lifetime of the host, however, in a subset of hosts with latent infection, progression to disease will occur. The latter is more likely in those who are immune-compromised.[1-3] In clinical latency, the immune response of the host predominates; whereas in active disease, bacterial replication is inadequately contained by the hosts immune response, often if not surpassing the threshold required to cause symptoms.[2]

Latent infection (LTBI) refers to a persistent state of (dormant) infection without evidence of active TB disease.[1,4] Diagnosis of LTBI is made indirectly through one of two immunologic tests, the tuberculin skin test (TST) or an interferon-gamma release assays (IGRA).[1,2] Both the TST and IGRA detect a memory T-cell response revealing the presence of host sensitization to *M. tuberculosis* antigens.[2] Individuals who are latently infected test TST or IGRA positive (this can be compromised by immune deficiency), are sputum smear and culture negative, non-infectious, and asymptomatic.[1]

Globally, it is estimated that 1.7 billion individuals are latently infected.[5] As above, while most individuals infected will remain asymptomatic and non-infectious, 5-15% of those with

LTBI will go on to develop active disease.[6] In high income, low TB incidence countries, it is estimated that a majority of active TB cases are a result of reactivation of LTBI, highlighting the significance of detecting and treating LTBI as an essential component of TB elimination efforts.[2,7,8] The likelihood of progression from LTBI to active TB disease is determined by bacterial, host, and environmental factors with certain population groups identified as having increased risk.[2,4] As above, individuals with suppressed cellular immunity (i.e. persons living with HIV, transplant recipients, persons taking tumor necrosis factor α inhibitors) have substantially higher risk of progression, as well as individuals with end-stage renal disease and those with silicosis or exposure to silica dust.[2,4] Other groups are placed at increased risk because of increased exposure to infection or through intermediate factors like malnutrition. These include individuals who are incarcerated, use illicit-drugs, are precariously housed or are healthcare workers, and migrants from high TB burden countries.[2,4] Individuals who are latently infected with increased risk of progression to active disease are recommended preventive therapy to prevent this progression. The removal of this LTBI reservoir, which has been referred to as the "seedbed" of tuberculosis, is key to elimination and a critical component of the World Health Organization's End TB strategy.[7]

Preventive Therapy and Treatment Access, Uptake, and Adherence

In Canada, the standard regimen for the treatment of LTBI has for many years been nine months of daily self-administered isoniazid (INH-9).[9] This regimen has efficacy rates of 69-93%, depending on how much of the regimen is completed. Toxicity and the duration of treatment limit completion rate.[9,10] As a result, there has been considerable interest and research into shorter regimens, several of which have proven to be as safe and efficacious as INH-9. Shorter treatment regimens include six months of INH, 3 months of weekly rifapentine plus isoniazid

(3HP), three to four months of isoniazid plus rifampicin (3-4INH/RMP), or four months of rifampicin alone (RMP).[9] For hard to reach populations, the most attractive of these is a combination of INH and rifapentine taken once weekly for 12 doses (3HP).[11] In order to monitor adverse events and hypersensitivity reactions closely, as well as to maximize adherence in a regimen that is only 12 doses (each dose represents a high proportion of the whole regimen) the treatment is administered as directly-observed preventive therapy (DOPT).[11,12] This drug regimen was approved by the United States Food and Drug Administration in 2014.[13] Based on a number of randomized control trials and observational studies, it has been found to be non-inferior in terms of efficacy and safety to standard INH-9 treatment and has demonstrated better or higher completion rates compared to other regimens of six months or longer.[10,14-17] In June of 2017, the Government of Canada arranged for the availability of rifapentine to meet an urgent public health need facilitating timely access to the medication among high risk subpopulations.[18]

Treatment of LTBI involves the challenge of convincing ostensibly healthy persons of the need to treat an infection that may never develop into active disease, with prolonged antibiotic therapy associated with non-negligible side effects.[19] Levels of adherence to preventive therapy within high-income, low-incidence countries remain low with suboptimal treatment completion rates across high-risk groups.[19] The cascade of care in diagnosis and treatment of LTBI is multifaceted. Individuals must first be identified and screened through TST or IGRA testing, receive a positive result, and have a medical evaluation and chest radiograph to rule out active disease. This is then followed with recommendation of therapy by a provider, and subsequent acceptance, adherence, and completion of that therapy.[19] Losses occur at each stage of the cascade of care and barriers to treatment access, uptake, and adherence occur at multiple levels in all settings and across multiple study populations.[19-21] The most commonly reported client-

level barriers to treatment acceptance and completion include long treatment durations, fear or experience of adverse events, financial and other barriers related to poverty and competing priorities, and ignorance about LTBI. Provider and system level barriers include insufficient prioritization of and resources for LTBI diagnosis and treatment as efforts tend to focus on active TB diagnosis and treatment.[19-21] Identifying barriers and facilitators of LTBI treatment completion at each stage of the cascade of care is integral to the effort to remove the reservoir of latent infection.

Demographic and Geographical Context

TB is as much a social disease as it is a biomedical condition. The burden of TB follows a social gradient both within and between countries and communities: those who are poorest are at highest risk of both exposure to *M. tuberculosis* and progression from latent infection to active disease.[22] As a result, successful TB control efforts must include interventions that address social, economic, and environmental conditions in addition to biomedical advances.[22] When examining the social determinants of health, the link between TB, poverty, and homelessness cannot be ignored.[23] Physical and mental health conditions such as malnutrition and substance use among individuals experiencing homelessness may contribute to susceptibility to TB and progression from latent infection to active disease.[22,24] Moreover, overcrowding and poor ventilation of residential facilities or homeless shelters fuel transmission and confound elimination efforts.[22,24] It has been demonstrated that those who use inner-city shelters or drop-in centres experience much higher prevalence rates of LTBI in comparison to the general population (30-40%vs 5-10%, respectively) and homelessness has been identified as a significant factor in determining LTBI treatment outcomes.[24-26] Among those experiencing homelessness there is increased risk of progression to disease and potential of infecting both members of the

general public and others experiencing homelessness.[22,23] This represents a plausible source for inner-city transmission and risk of a future TB outbreak.[23,24]

There were 1,796 cases of active TB reported in Canada in 2017, a 2.6% increase from 1,750 cases reported in 2016, corresponding to an incidence rate of 4.9 per 100,000.[27] While this is a low overall rate, there remains disproportionately higher rates in two populations groups: Indigenous peoples (21.5 per 100,000) and foreign-born individuals (14.7 per 100,000).[27] Across Canada, the incidence of TB varies by province/territory. In Prince Edward Island there were no cases of TB reported and incidence rates were below the national rate (4.9 per 100,000) in Newfoundland and Labrador (2.5 per 100,000), Nova Scotia (0.9), New Brunswick (1.1), Quebec (2.6) and Ontario (4.8).[27] Rates were slightly higher than the national rate in the Northwest Territories (6.7 per 100,000), British Columbia (5.3 per 100,000), and Alberta (5.3 per 100,000).[27] The highest TB incidence rates were reported in Saskatchewan (8.1), Manitoba (14.0), Yukon (20.8) and Nunavut (265.8).[27] The majority of cases (64.4%) occurred in Ontario (37.6%), British Columbia (14.1%) and Alberta (12.6%).[27]

This study reported herein was conducted in two cities within the Province of Alberta: Edmonton and Fort McMurray, respective populations of 946,945 and 75,615 in 2018.[28,29] In that same year, Edmonton had a crude incidence of tuberculosis disease of 9.7/100,000 population with 2.2% of cases notified among persons experiencing homelessness at diagnosis, while Fort McMurray had a crude incidence rate of 13.2/100,000 population with 10% of cases notified among persons experiencing homelessness at diagnosis. During the ten-year period 2008-2018, 3.1% (n=24) of total active cases in Edmonton (n=777, 9.0 per 100,000) were among those experiencing homelessness and 27.7% (n=18) of total active cases (n=65, 9.1 per 100,000) in Fort McMurray were among those experiencing homelessness. It is difficult to estimate the

incidence rate of latent infection as data primarily only confirm LTBI in contacts of active disease in this sub-population.

In Alberta, Canada, the Provincial TB Program has supported the use of rifapentine/INH (3HP) for treatment of LTBI in inner-city populations who are at increased risk of developing active disease in Edmonton and Fort McMurray. Edmonton and Fort McMurray are cities both located in the northern half of the province of Alberta. Edmonton is a substantially larger city and is approximately 435kms south of Fort McMurray.[30] In 2016, it was estimated that 1752 individuals were experiencing homelessness in Edmonton's inner-city.[31] Of those, 57% identified as Indigenous, while only representing 5.7% of Edmonton's total population.[30,31]A recent study that examined factors associated with noncompletion of LTBI treatment among an inner-city population in Edmonton revealed homelessness to be the only significantly predictor of noncompletion.[25]

Fort McMurray is in the municipality of Wood Buffalo and is one of the fastest growing industrial communities in Canada due to the rich oil sands deposits in the region.[32,33] A 2018 point-in-time homeless count identified that approximately 200 individuals are experiencing homelessness in Fort McMurray, with 60% of those individuals considered chronically homeless (e.g. continuously homeless for a year or more or have had at least four episodes of homelessness in the past three years).[34] Of those, 60% had moved to Fort McMurray seeking employment.[34] Although Indigenous peoples only represent 7.8% of Fort McMurray's population, 46% of those experiencing homelessness self-identified as being Indigenous.[32,34] Over the past 10 years, unstably housed inner-city residents of Fort McMurray have experienced a protracted outbreak of TB, largely as a result of reactivation of latent infection. In response, a pilot project, known as the "community mobilization project" was provincially funded in 2018. This project aims to

actively case find and screen for latent infection among those living in inner-city Fort McMurray. Screening took place at the Centre of Hope, a daytime drop in centre for homeless and near homeless adults. To date, 42 individuals have been screened and 12 (21.4%) were diagnosed with latent infection using IGRA. Of those, 5 have completed treatment for LTBI with 3HP and 7 are waiting for assessment and/or to start treatment. Screening is ongoing with plans of expanding to other inner-city agencies and surrounding First Nations communities with historically high rates of TB incidence.

Study Rationale

LTBI must be treated effectively in order to meet TB elimination goals. In order to improve outcomes related to LTBI preventive therapy it is important to understand the perceptions of barriers and facilitators of treatment uptake and adherence among populations at greatest risk. Although it is known that a broad range of factors can impact treatment adherence, a knowledge gap exists in defining these factors in the context of a shorter treatment regimen, (3HP), specifically administered as directly-observed therapy (DOT), a route of administration that is uncommon for preventive therapy. Furthermore, there is lack of qualitative research on the topic of LTBI perceptions and treatment adherence among populations who are unstably housed or homeless (i.e. both harder to reach) and at greater risk of progressing to active TB. Features of this regimen (e.g. shorter treatment duration, administered as DOT) appear promising to populations who face challenges to treatment adherence, however, exploring this from the perspective of those offered treatment is key. As opined in a recent Lancet series on TB elimination, biomedical advances such as shorter treatment regimens, need to be supported by qualitative work to explore individual and community understandings of latency and the need for preventive therapy.[7] This study proposes to address this call for research by exploring

understandings of LTBI and the need for preventive therapy. As well, this study aims to identify the barriers and facilitators of treatment access, uptake, and adherence using a shortened regimen, among a population that is often, as evidenced by the lack of literature, neglected. In addition to exploring client experiences and perspectives, exploring health care providers (HCP) programmatic experiences of using the regimen can support a more thorough understanding of the regimen and identify barriers and facilitators from a systems perspective. HCPs can provide additional contextual information and provide insight into the programmatic processes of using 3HP as directly observed therapy to treat LTBI, a mode of administration that is new for preventive therapy. By including both HCPs and clients in our study, this will enable us to gain a comprehensive understanding of the use of the new regimen, and barriers and facilitators to it use, from both a patient and programmatic perspective.

Study Objectives and Research Questions

This study is embedded within the Alberta provincial TB program and their efforts to offer a shorter treatment regimen (3HP) to individuals who encounter psychosocial barriers to treatment completion. The first objective of this study is to describe the context of latent TB and the need for preventive therapy among those who are unstably housed or homeless and at risk of progressing to active disease. The second objective is to describe the identified barriers and facilitators of LTBI treatment access, uptake, and adherence in this target population using a shortened treatment regimen (3HP). With this platform of client perspectives, we aim to improve preventive therapy programming and adherence in inner-city populations in Alberta. The third objective is to enhance our understanding of the use of the regimen by exploring perspectives of HCPs experienced in providing preventive therapy with 3HP to the study population.

Objective #1

To describe the individual understandings of latent tuberculosis infection and the need for treatment with preventive therapy among an inner-city population.

Research Question

What are the understandings of latent infection and the need for preventive therapy among LTBI+ homeless or unstably housed residents of Edmonton's and/or Fort McMurray's inner-city?

Objective #2

To identify barriers and facilitators of LTBI preventive therapy access, uptake, and adherence, using a shortened treatment regimen (3HP), among an inner-city population.

Research Question

What barriers and facilitators to treatment access, uptake, and adherence are reported by LTBI+ homeless or unstably housed residents living in Edmonton's and/or Fort McMurray's inner-city who have been offered preventive therapy with a shorter treatment regimen (3HP)?

Objective #3

To explore health care providers (HCP) programmatic experiences of using the regimen and identify barriers and facilitators from a systems perspective.

Research Question

Among health care providers who provide outreach TB management and care, what are the perspectives and programmatic experiences of using 3HP among individuals who are unstably housed or homeless?

Conceptual Framework

This study employs qualitative methods and is exploratory in nature. Qualitative description, a method that provides a basic description and summary of the phenomenon from the perspective of those who live it, is used in this study.[35] Using this method, the goal is to provide a summary of events while staying close to data, resulting in less interpretive findings. Qualitative description is guided by the theoretical perspective of naturalistic inquiry, which is a commitment to studying something in its natural shape wherein the naturalist inquirer seeks to use techniques that will allow the phenomena to present itself as if it were not under study.[35,36] This perspective is underpinned by a relativist ontology, meaning that realities are multiple, constructed and holistic, and a subjectivist epistemology, where the researcher and participant are interactive and inseparable.[36] Within this paradigm the aim of the study is idiographic and seeks to describe the phenomenon, rather than establishing general laws or generalizations.[36]

Structure of Thesis

This thesis is divided into five chapters. Chapter one introduces the problem and the research objectives and questions. Chapter two provides a literature review on background information relevant to the objectives of this thesis. Chapter three is an overview of the methods used and evaluation of rigor. Chapter four presents the results of the study. Chapter five provides a final discussion including an overview of the main findings, strengths and limitations and public health practice and policy implications.

Chapter 2: Literature Review

Tuberculosis Disease, Transmission, and Treatment

Etiology

Tuberculosis is an airborne communicable disease caused by organisms of the *Mycobacterium tuberculosis* complex.[37] The majority of cases result from *M. tuberculosis* and the closely related species *africanum*; a minority of cases result from zoonotic members of this complex namely *bovis* or *caprae*.[37,38] Robert Koch first discovered the bacterium in 1882 facilitating the identification of important diagnostic tools, the development of a live attenuated vaccine- the bacilli Calmette-Guerin or BCG, and the discovery of effective antimicrobial agents against a once highly lethal and untreatable infection.[38]*M. tuberculosis* is aerobic, requiring oxygen to survive and develops comparatively slowly, replicating over approximately 24 hours.[37,38] After inhalation, the bacterium is transported to the lower respiratory tract where it targets the alveolar tissue.[37] *M. tuberculosis* most commonly affects the lungs and conducting airways, with pulmonary TB representing more than 80% of all cases.[37,39] Extrapulmonary TB disease outside of the lungs occurs in approximately 10-20% of diagnosed cases of TB and includes sites such as the lymph nodes, abdominal organs, bones, joints, and the blood stream.[39,40]

Transmission

The reservoir for *M. tuberculosis* is human and infection is acquired almost exclusively through inhalation of airborne particles, known as droplet nuclei, which contain the bacterium. [40,41] These droplets (1-5 microns in size) are dispersed during forced respiratory maneuvers, such as singing, coughing, and sneezing by individuals with active pulmonary disease.[40,41] Each droplet nuclei are estimated to contain only a few bacteria and have an incredibly slow settling

rate, enabling the droplet to remain suspended in the air and transported by air currents, increasing the possibility of spread.[40,41] These small droplet nuclei containing the organism bypass the mucociliary system and reach the terminal air spaces or alveoli where they initiate infection in the host.[39-41] It is understood that several patient, pathogen, and environmental factors influence whether transmission occurs.[41] Patient level factors include disease type (e.g. pulmonary [smear positive/smear negative, cavitary/noncavitary on chest x-ray, typical/atypical on chest x-ray, laryngeal] or extrapulmonary), symptomatology (e.g. coughing), delayed diagnosis, and treatment.[41] Inherent factors which influence a host's resistance or susceptibility to TB after exposure are still unclear; however, hereditary defects in cell-mediated immunity or a genetic susceptibility are likely to play a role.[37,39,41] From a pathogen perspective it has been suggested that certain virulence properties of *M. tuberculosis* strains may affect its ability to be transmitted, influencing extent of contagion in human populations.[37,41] Environmental determinants of transmission include prolonged exposure indoors in poorly ventilated and overcrowded spaces. This suggests that those living in poverty or institutions are at particular risk.[40,41] Outdoor exposures are very unlikely to result in transmission as bacillary dispersion is immediate and ultraviolet light rapidly kills any viable bacteria.[40] Estimates of contagion vary widely; however, the World Health Organization (WHO) estimates that each untreated person with pulmonary TB may infect 10-15 people per year.[42] The infectiousness of TB diminishes rapidly once effective treatment is initiated.[40]

Pathophysiology and Diagnosis

Most of those infected will not develop active disease, however, of those who develop pulmonary TB, many will manifest pulmonary findings with classical symptoms such as persistent cough with or without hemoptysis, fevers, fatigue, night sweats, poor appetite and

weight loss.[37,39] Those with extrapulmonary TB can experience various systemic and localized manifestations depending on organ or area of body involved.[41] TB damages tissues through a T-cell mediated delayed hypersensitivity reaction.[40] This causes damage to tissues from direct toxic effects or through release of cytokines, which activate eosinophils, monocytes and macrophages, neutrophils, or natural killer cells.[40] Depending on the stage of TB infection (latent, primary disease, or adult-type pulmonary TB) these damages may present as cavitary lung lesions, pleural effusions, empyema, hemoptysis, and in rare cases acute respiratory distress syndrome. [40] Presentation depends on age as individuals under age 10 may have minimally symptomatic pulmonary TB; those under age 5 and persons who are immunocompromised are more likely to present with extrapulmonary TB. Diagnosis of active TB varies depending on patient risk and clinical characteristics. In Canada, the standard testing algorithm when pulmonary TB is suspected includes a chest radiograph, sputum smear microscopy, mycobacterial culture and sensitivity and nucleic acid amplification tests (NAAT).[43] Canadian TB Standards recommend that every effort be made to obtain a microbiological diagnosis which requires demonstration of acid-fast bacilli on smear microscopy and positive culture of *Mycobacterium tuberculosis*.[43]

Treatment and Prognosis

Once diagnosed, treatment of active drug sensitive TB involves measures to prevent transmission: medical isolation and antibiotic therapy.[40] There are three main goals of antibiotic therapy: 1) to rapidly kill replicating bacteria in order to improve the clinical condition of the patient, prevent death, and prevent transmission; 2) to prevent the emergence or worsening of drug resistance; and 3) to eliminate subpopulations of persisting bacteria in order to prevent relapse of disease after completion of therapy.[9,44] In order to achieve these goals, treatment for TB involves the use of combination therapy – concurrent use of multiple antibiotics at the same

time.[9,44] The current first-line treatment for drug-sensitive active TB is a minimum of 6 months of drug therapy. This is usually divided into an intensive phase of treatment (first 2 months) with rifampicin, isoniazid, pyrazinamide, and ethambutol, followed by a continuation phase of treatment (remaining 4 months) with rifampicin and isoniazid.[9,37] Duration of treatment ranges from six to twelve months, dependant on hosts response to therapy and prescriber preference. Therapy is given five days per week during the intensive phase, then three times per week if appropriate during the continuation phase.[9] Resistance to anti-tuberculosis drugs can emerge; multidrug-resistant TB (MDR-TB) described as *M. tuberculosis* resistant to at least isoniazid and rifampicin is rare in the Canadian-born but not uncommon in the foreign-born. The majority of extensively drug-resistant TB (XDR-TB) cases (resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs), have been reported in India, Ukraine, and the Russian Federation.[37,45]

The most common approach to treatment administration, and the approach taken in many provinces and all of the territories in Canada, is that treatment be provided through DOT.[9,37] DOT involves the witnessed ingestion of every dose of treatment by a health care professional and is increasingly becoming a part of comprehensive patient care and case management.[9,40] This approach to treatment administration increases the likelihood that the full treatment course will be completed and is especially important for patients with risk factors for non-adherence or who may face barriers to treatment completion (e.g. poverty, unstable housing, mental illness, and addictions).[9,40] Outreach teams that aggressively seek out and treat clients who face the greatest barriers (i.e. those listed above) to present for DOT is a critical component of case management and ensuring treatment completion, however, DOT may be seen as intrusive or paternalistic. Alternative approaches to treatment adherence include methods such as mobile phone reminders,

smart pill boxes, video DOT, and the use of call centres for follow up.[37] Irrespective of method used, it is acknowledged that using a team-based patient centered approach which incorporates education, counselling, and empowerment of patients with TB is integral.[46]

Of immunocompetent individuals with drug susceptible TB, TB is a treatable and curable disease when medications are provided and completed in full. The vast majority of TB cases are cured, and between 2000 and 2017 an estimated 54 million lives were saved through diagnosis and treatment.[42] Nevertheless, in those who are treated, TB causes or contributes to death in up to 10% of cases, often among patients with comorbidities.[40] Poorer outcomes and treatment failure are more common in immunocompromised patients as well as among individuals with MDR-TB and XDR-TB.[40,42] In the absence of treatment, TB is often fatal; among individuals who have developed active disease, approximately 50% will succumb to the infection.[37,47]

Latent Tuberculosis Infection

Etiology and Pathogenesis

LTBI is described as having evidence of TB infection with no clinical, radiological, or microbiological evidence of active disease.[2] In this state, there has been exposure to the *M. tuberculosis*; however, it is understood to be metabolically inactive or latent in the host.[2] For clinical purposes and simplicity, patients are categorized as either having latent or active TB; recent research suggests this is an oversimplification, and instead posits that latent infection and tuberculosis disease can be better understood as occurring along a spectrum.[2,37,48] This new approach suggests that additional stages of infection can be defined between latent and active TB.[2]

Following exposure to *M. tuberculosis*, interaction between the organism and the host's innate or acquired immunity influence progression to disease (Figure 1). Infection can be

eliminated through either the innate or acquired T cell immune response of the host.[2,37] These individuals have eliminated the pathogen and no longer have viable TB bacteria but may still have immunological evidence of prior infection. When the pathogen has been eliminated, there is no benefit of LTBI preventive therapy.[37] If the pathogen has not been eliminated, bacteria persist in a latent state where progression to TB disease may occur in the future, especially in the presence of immunological compromise.[2,37] This is detected as a positive result using tests that elicit T cell responses against *M. tuberculosis* antigens (TST or IGRA). In this latent state, benefits from preventive therapy are expected.[37] Individuals with incipient TB are infected with viable *M. tuberculosis* that is likely to progress to active disease in the absence of further intervention.[2] The infection has not yet induced clinical symptoms, radiographic abnormalities, or microbiological evidence consistent with active TB disease.[2] These individuals are more likely than any others to benefit from preventive therapy. However, there is currently no diagnostic available to distinguish between phases of latent and intermediate states.[37,48,49] Subclinical TB disease refers to disease caused by viable *M.tuberculosis* bacteria that does not elicit clinical TB symptoms but can be detected through existing radiological or microbiological assays.[2] Individuals with active TB disease experience clinical symptoms such as cough, fever, weight loss, with coinciding radiographic abnormalities and microbiologic evidence consistent with active disease.[37] Individuals with subclinical or active TB disease should receive one of the recommended treatment regimens for active TB disease.[37]

TST	Positive or Negative*	Positive	Positive	Positive	Positive
IGRA	Positive or Negative*	Positive	Positive	Positive	Positive
CULTURE	Negative	Negative	Negative	Intermittently Positive	Positive
SPUTUM SMEAR	Negative	Negative	Negative	Usually Negative	Positive
INFECTIOUS	No	No	No	Sporadically	Yes
SYMPTOMS	None	None	None	Mild or None	Usually (Mild to Severe)
RECOMMENDED TX	None	Preventive Therapy	Preventive Therapy	Multidrug Therapy	Multidrug Therapy

Figure 1. Spectrum of M. tuberculosis Infection [2,37] *Individuals who have eliminated the infection through innate immune response without t-cell priming have negative TST and/or IGRA. Those who have eliminated the infection from acquired immune response and memory t-cell activation will test positive on TST and/or IGRA.

Diagnosis

Testing for LTBI involves identifying individuals with evidence of prior exposure to *M. tuberculosis*. There are two tests available to diagnose LTBI: the tuberculin skin test (TST) and the interferon-gamma release assays (IGRAs).[50] The TST consists of an intradermal injection of purified protein derivative (PPD) that is interpreted 48-72 hours after implantation.[50] In a person who has cell-mediated immunity to the antigens present in the PPD, a delayed hypersensitivity reaction will occur at the site of implantation.[37] Interpretation of the test, completed by a health care provider, considers the size of induration, the pre-test probability of M. *tuberculosis* infection and the risk of developing active disease if the person was actually infected.[50] Although there are advantages to using the TST for identifying LTBI, including low reagent and equipment costs and limited laboratory and other skills required, major limitations exist.[37]

Firstly, its specificity is compromised due to the fact that the PPD contains antigens that cross react with non-pathogenic mycobacteria and false positives can occur, for example, in individuals previously vaccinated with *Mycobacterium bovis* (BCG) vaccine or exposed to non-tuberculosis mycobacteria.[37,49,50] Secondly, it has limited predictive value as most individuals with positive TST results do not advance to active disease.[37,48,49] Furthermore, in individuals who are at greatest risk of developing disseminated TB, which include very young children and immunocompromised individuals (e.g. those living with HIV), false negatives occur.[49] Finally, as the test requires interpretation 48-72 hours after implantation, failure to present for reading and loss to follow up can occur.

Established as an advancement in the diagnosis of LTBI, the IGRA test was introduced in the early 2000's.[37] With IGRA testing, individuals may be tested in a single visit, using standard phlebotomy procedures for whole blood collection, with analysis available 16-24 hours after collection.[51] The Quantiferon TB Gold Plus is the IGRA that is used in Alberta. It is an *in vitro* blood test which measure the cell-mediated immune response; it measures T cell release of the cytokine interferon-*y* (INF*y*) after exposure to peptide antigens associated with *M.tuberculosis* infection.[37,49,51] IGRA tests have high sensitivity (94%) and specificity (97%) that is not affected by BCG vaccination.[37,50,51] Since the test is not affected by BCG vaccination status, IGRAs are useful for evaluating LTBI in those vaccinated with BCG, especially in settings where routine vaccination is administered in infancy or when multiple (booster) BCG vaccines are given.[37,50] As with TSTs, however, IGRAs also have limitations. The sensitivity of the test is diminished in those living with HIV, with a correlation between decreasing CD4 counts and the likelihood of indeterminate results.[37,50,52] Additionally, similarly to a drawback of TSTs, IGRAs also have poor predictive value.

Both the TST and IGRA are acceptable, yet flawed tests to detect LTBI. Both have reduced sensitivity in those who are immunocompromised, are unable to distinguish between active and latent infection, and do not provide any direct evidence of the presence of viable bacilli.[37,49] Furthermore, and arguably their biggest problem, is that they poorly predict who is at greatest risk of progression to active disease.[48] Each test simply determines that exposure has at some point led to an acquired immune response that is detectable following re-challenge with an antigen.[49] With poor predictive value, widespread screenings of low-risk populations is counterproductive, and LTBI screening should only be performed if it is supported by the intent to provide preventive therapy if positive.[37] The above limitations underscore the need for a highly predictive test that can identify individuals at greatest risk for progression to active disease and who will benefit the most from preventive therapy.

Progression to Active TB Disease

In most individuals with LTBI the innate or acquired cellular immune response is enough to maintain a controlled, asymptomatic infection.[37] However, in a subset of hosts, progression to active TB disease is more likely. Of the estimated 1.7 billion individuals with LTBI worldwide, it is predicted that 5-10% will progress through the spectrum to active disease, while the majority will remain at minimal risk of developing clinical disease (reactivation) (Figure 1.2).[5] The likelihood of developing clinical disease is influenced by biological, environmental, and host factors.[2] The initial bacterial load, inferred by the severity of disease in the index case, and the level of close contact are direct determinants of risk of progressing to active disease.[2] From a host perspective, the most important factor limiting a contributing progression of infection is an intact cellular-mediated immune response.[2,37,49] Individuals with suppressed cellular immunity (for example, persons living with HIV and persons taking tumor necrosis factor α inhibitors)

have substantially higher risk of progression to active disease.[2,4,7,37] Individuals with end-stage renal disease on dialysis, those receiving transplant immunosuppression, those with silicosis or exposure to silica dust, and those who are recently infected are at increased risk of reactivation.[2,4,7,37] Diabetes, malnutrition, alcohol misuse, and tobacco use are factors which increase the relative risk of developing active disease.[9] Other groups have a high prevalence of infection; these include those who are incarcerated, use illicit-drugs, are precariously housed, are elderly or are healthcare workers and immigrants from high TB burden countries.[2,4,7,37] In low incidence countries, such as Canada, reactivation of LTBI accounts for the majority of new active TB cases.[53] Targeting screening for LTBI in populations at high risk of progression to disease and treatment of those testing positive is key to preventing disease.

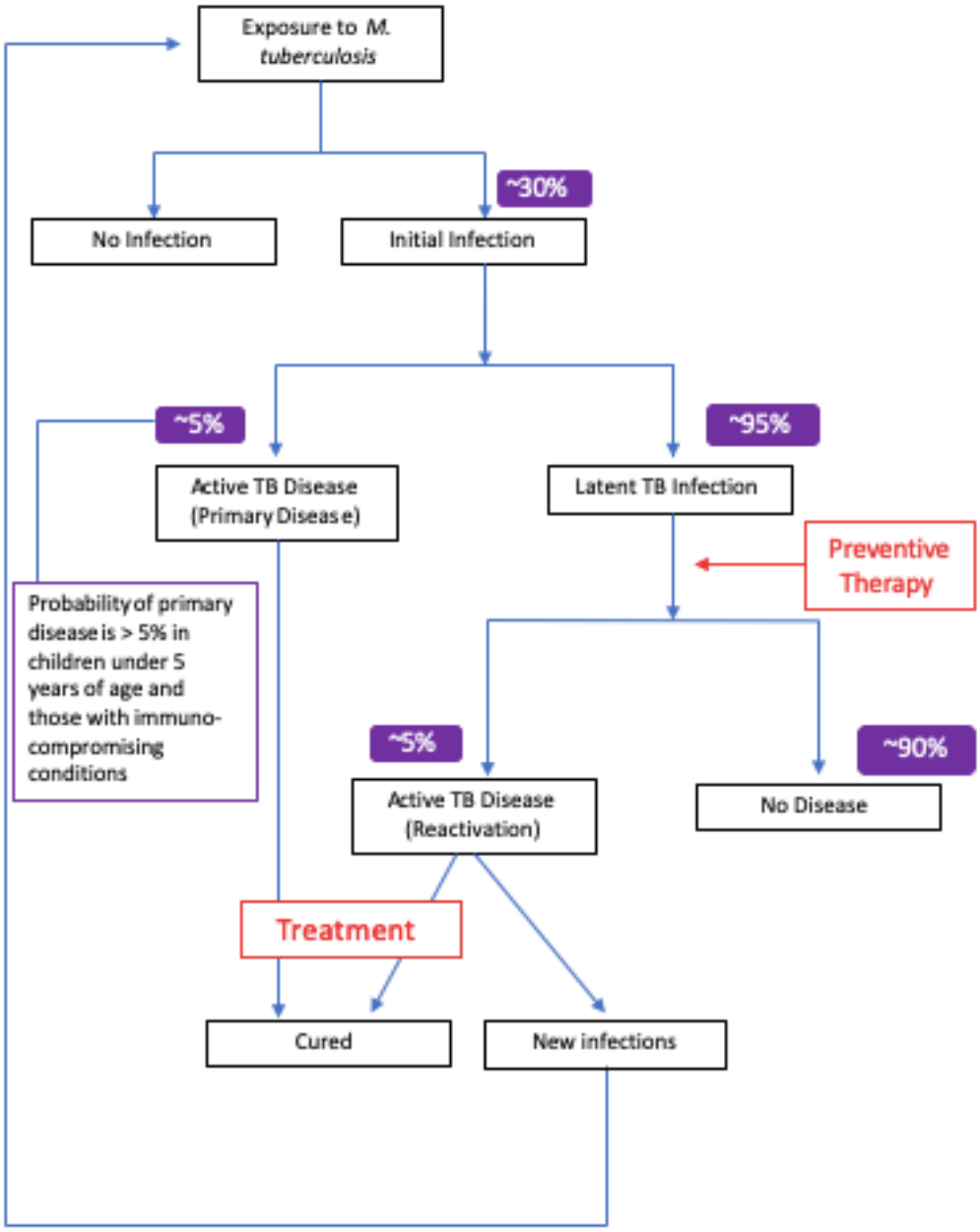

Figure 2. Pathogenesis of TB [41,45]

Preventive Therapy

The aim of treatment for LTBI is to prevent the progression of infection to clinical disease in those at highest risk. When given to those at highest risk of progressing to disease,

preventive therapy can offer both individual and public health benefits.[54] Early studies demonstrate evidence of the efficacy of preventive therapy in reducing active TB disease among diverse populations, including children, Alaskan Natives, those living in congregated facilities, and recent contacts of active cases.[7,55-58] More recent systematic reviews validate the individual-level benefit of preventive therapy.[7,59,60] In HIV negative, immunocompetent individuals, the risk of developing active TB disease is reduced by 60% in those that received 3-12 months preventive therapy in comparison to their untreated counterparts.[7,59,60] Among individuals living with HIV, the risk of developing TB disease is reduced by 32-62% when treated.[7,59,60]At a population level, incidence rates of active TB have declined 15-20% following interventions that included preventive therapy.[7,61-64] In geographic areas known for high rates of TB transmission and re-infection, the benefits of preventive therapy decline as protective efficacy seems to weaken after discontinuation of therapy.[2,7,65,66] This suggests that preventive therapy can provide short to medium term protection, however, in high transmission areas long term protection might be better achieved when transmission is controlled through active case finding and treatment.[7]

Before preventive therapy is offered, active TB disease must be ruled out through history, physical examination, and chest radiography.[54] Sputum smear microscopy and bacterial culture are also collected. Deciding to treat LTBI with preventive therapy is individualized; clinicians consider the risk of adverse events from therapy, including hepatotoxicity, balanced against the risk of developing active disease.[54] In Canada, the standard treatment regimen of first choice for LTBI is 9 months of daily self-administered INH therapy, which has shown protective efficacy of up to 90%.[54,67] However, serious side effects, including hepatotoxicity, which when severe can be fatal, and long duration contribute to poor acceptance of the regimen by both providers and patients.[54] A systematic review of studies that assessed adherence to LTBI treatment in

Canada and the US between 1997 and 2007 found that, although adherence rates varied across patient populations (19-82%), overall rates are low.[19] Furthermore, this may not reflect true adherence rates that may be seen in a program setting. An additional retrospective randomized two-stage cross-sectional survey of treatment and completion of LTBI at public and private clinics in 19 regions of the United States and Canada in 2002 found that 42.9% of patients prescribed 9-month INH failed to complete at least 6 months of treatment and treatment initiation with 9-months INH in comparison to shorter regimens was associated with failure to complete treatment.[68] The authors found the major risk factor for treatment noncompletion was being prescribed 9-month INH regimen (OR 2.08 95% CI, 1.23-3.57, p=0.008) and that an inverse relationship was found between length of regimen provided and completion rates.[68] The authors suggest the most important advancement to LTBI treatment effectiveness are regimens of shorter duration.[68] Existing alternate recommended shorter treatment regimens include daily self-administered INH for 6 months (6INH), and daily self-administered INH and rifampin (RMP) for 3-4 months, three months of once weekly, directly observed INH and rifapentine (3INH/RPT) and four months of daily, self-administered RMP (4RMP).[54] Regardless of the regimen used, treatment must be provided from a patient centered approach to ensure adherence and provide adequate care.[37]

A recent *Lancet* series suggested that preventive therapy is an essential, yet poorly used method, for removing the reservoir of LTBI.[7] The authors proposed that challenges at clinical, health systems, and policy levels all contribute to modest use of preventive therapy. From a clinical and individual standpoint, providers may be reluctant to offer LTBI due to diagnostic challenges in immunocompromised patients and ethical concerns related to drug toxicity or resistance development.[7] Additionally, patients may be reluctant to accept and complete therapy

for an asymptomatic infection. This is reviewed in more detail later in this chapter. At the health-system level absence of consistent guidelines, inadequately trained staff, lack of diagnostics or drugs available, insufficient surveillance and reporting, and poor funding all limit use of preventive therapy.[7,21] At the policy level the failure of TB control programs to prioritize prevention, choosing instead to focus efforts on active case finding and treatment, as well as inadequate funding and investment into basic, clinical, and implementation research hampers use of preventive therapy.[7,21] Furthermore, a lack of advocacy and low-level engagement and demand from communities and groups most at risk of TB, restricts progress.[7]

The World Health Organization (WHO) has identified preventive therapy as a key component of the End TB Strategy.[69] An integration of preventive therapy with improved active case finding and treatment, control of transmission, and health-systems strengthening may represent a comprehensive control strategy that could ultimately achieve global TB elimination.[7,53,69]

TB Epidemiology

Globally

Worldwide TB is one of the top 10 causes of death and is the leading cause of death from a single infectious agent.[45] In 2018 an estimated 10 million (range, 9.0–11.1 million) people fell ill with TB and of those, approximately, 1.2 million (range, 1.1-1.3 million) deaths were attributed to TB among HIV negative people.[45] An additional estimated 251,000 deaths (range, 223,000-281,000) occurred among HIV positive individuals. Although TB does not discriminate by age or sex, the highest burden of disease (57%) in 2019 was among men over 14 years of age, followed by women (32%) and children (11%, aged <15).[45] Among all cases of disease, 8.6% occurred in people living with HIV. The burden of TB disease varies significantly between and

within countries. Rates are as low as less than 5 per 100,000 to more than 500 new cases per 100,000 per year, with a global average estimated at 130 per 100,000.[45] Geographically, most TB cases in 2018 were in the WHO regions of South-East Asia (44%), Africa (24%), and the Western Pacific (18%), with lesser percentages in the Eastern-Mediterranean (8%), the Americas (3%) and Europe (3%).[45] Eight countries: India (27%), China (9%), Indonesia (8%), the Philippines (6%), Pakistan (6%), Nigeria (4%), Bangladesh (4%) and South Africa (3%) accounted for two-thirds of all TB cases in 2018.[45] Together, these and 22 other countries (WHO's list of 30 TB high burden), account for 87% of the world's cases.[45]

TB in Canada

In 2017 there were 1796 active TB cases reported in Canada.[27] This represents a 2.6% increase in the total number of cases since 2016 and brings Canada's incidence rate to 4.9 per 100,000 population.[27] Rates of TB vary widely by province/territory, sex, age, and population group. Prince Edward Island had zero cases, and incidence rates were below the national average in Newfoundland and Labrador (2.5 per 100,000), Nova Scotia (0.9 per 100,000), New Brunswick (1.1 per 100,000), Quebec (2.6 per 100,000), and Ontario (4.8 per 100,000).[27] Provinces with rates higher than the national average include Manitoba (14.0 per 100,000), Saskatchewan (8.1 per 100,000), Alberta (5.3 per 100,000), British Columbia (5.3 per 100,000), Yukon (20.8 per 100,000), Northwest Territories (6.7 per 100,000) and Nunavut (265.8 per 100,000).[27] Males accounted for 1,004 (55.9%) of cases and 792 (44.1%) cases were female, corresponding to an incidence rate of 5.5 among males and 4.3 among females, which has been consistent since 2007.[27] The incidence rate between males and females begins to widen after 44 years of age; among individuals aged 75 years and older, TB incidence rates among males were almost double that of females (13.8 versus 7.2 cases per 100,000).[27] Rates of TB incidence

increase with age, with the highest being among those 75 years and older (10.0 cases per 100,000), followed by those aged 25-34 years old (6.0 per 100,000), and the lowest rate among those aged 5-14 (1.7 per 100,000).[27] The incidence rate increased from 2.1 per 100,000 in 2016 to 4.1 cases per 100,000 in 2017 among infants younger than one year of age.[27] Although the highest incidence rate is among those aged 75 and over, the largest number of cases (n=309, 17.2% of total cases) were in those aged 25-34.[27] Trends among TB cases by age have remained relatively stable over the past ten years.

Although the national incidence rate of TB (4.9 per 100,000) is one of the lowest in the world, this rate masks disproportionately higher rates in two subpopulations: Canadian-born Indigenous peoples and immigrants. Rates of TB are 43 times higher (21.5 per 100,000) among Canadian-born Indigenous peoples and 29.4 times higher (14.7 per 100,000) among foreign-born individuals in comparison to Canadian-born non-Indigenous peoples (0.5 per 100,000).[27] Of Indigenous cases, 49.2% (n=154, 17.1 per 100,000) were First Nations, 45.4% (n=142, 205.8 per 100,000) were Inuit and 5.4% (n=17, 3.5 per 100,000) were Metis. There was a 25.7% increase in the number of cases among the Inuit in 2017 compared to 2016; 113 to 142 cases.[27] Incidence rates among the Inuit population have ranged from 85.2 per 100,000 in 2007 to 251.8 per 100,000 in 2012, but have consistently remained higher than any other population group in Canada since 2007.[27] Foreign-born persons carry the largest burden of TB in Canada, where 71.8% (n=1290) of total cases in 2017 were foreign-born.[27] Although the incidence rate of TB among foreign-born persons in Canada has remained relatively stable since 2007, the total number of cases continues to rise.[27] Reported countries of origin with the greatest number of cases included the Philippines (n=276, 21.4%), India (n=262, 20.3%), China (n=186, 14.4%), Vietnam (n=60, 4.7%), and Pakistan (n=46, 3.6%).[27] Inequitable access to health care and

complex social determinants of health, including stressful living conditions, language and cultural barriers, poverty, food insecurity and poor nutrition, contribute to the disproportionately high rates among both Indigenous peoples and the foreign-born in Canada.[27,70]

TB/LTBI in Persons Experiencing Homelessness

Homelessness is an extremely important risk factor for TB disease. Individuals who are marginalized (including those living in shelters or congregated facilities) have increased risk of exposure to *M. tuberculosis.* As well, physical and mental health conditions occurring among individuals experiencing homelessness may contribute to susceptibility to TB as well as progression from latent TB to active disease.[71,72] Moreover, overcrowding and poor ventilation of homeless shelters confound TB elimination efforts.[72,73] Tan de Bibiane et al reported that homeless individuals in Montreal were significantly more likely than non-homeless individuals to have pulmonary TB, smear-positive disease, HIV co-infection, and a history of substance use.[73] Their retrospective analysis also showed that homeless individuals experienced delayed diagnosis of TB, with mean duration from symptom onset to diagnosis of 61 days for homeless people vs. 28 days for non-homeless people ($p=0.022$). The results of their study highlighted concerns about delay in TB diagnosis and ongoing transmission within and beyond those experiencing homelessness.

A more recent study identified similar findings in examining an ongoing TB outbreak within underprivileged neighborhoods of Montreal.[74] Between January 2003 and February 2016, 35 individuals met the case definition of this outbreak, with the number of cases tripling between 2010 and 2016. Outbreak cases were divided into two groups: with risk factors (n=28) and without risk factors (n=7), all cases with risk factors had more than one risk factor. The most common risk factor was substance use (93%) followed by alcohol abuse (64%), tobacco use

(54%), and homelessness (46%). The results of this study echoed previous findings and suggested that TB outbreaks occur in marginalized Canadian-born urban populations and predominantly among those who use substances and are experiencing homelessness. Further validating the health inequities among this population, a longitudinal study based in Toronto demonstrated that one in five individuals who are homeless will die within one year of a diagnosis of active TB, a rate that is almost three times that of all individuals diagnosed with TB during the same time period.[75] These studies demonstrate how homelessness and substance misuse not only contribute to increased risk of acquiring TB, but also lead to delays in diagnosis and complicate treatment efforts.

In findings specific to latent infection, Aldridge et al examined the prevalence of LTBI through a cross-sectional survey in London, UK and found that individuals experiencing homelessness had a very high prevalence of LTBI, co-infection with hepatitis B (HBV) and HCV, and poor engagement with care.[26] Consistent with previous literature described above, substance use was common among participants, with 193/491 (39.3%) participants reporting crack cocaine or heroin use, and 202/491 (42.3%) of participants reporting concerns related to alcohol use. The overall prevalence of LTBI was estimated at 81/491 (16.5%; 95% CI 13.2 to 19.8) which was substantially higher than the prevalence found in a comparison group screened for LTBI in the UK (1.6% (95% CI 0.2 to 5.7%). Due to treatment guidelines at the time, of all patients who screened LTBI positive only three were referred to preventive therapy, and notably, none of the three were engaged with or completed treatment.[26]

In individuals experiencing homelessness, adherence to LTBI treatment is poor. Presenting for TB examination after referral has shown to be modest (53%) and homelessness was identified as the only significant factor determining LTBI treatment outcomes among an

inner-city population in Edmonton, Alberta.[25,76] Additionally, in a study that offered twice weekly, directly observed INH therapy (DOT) to homeless men in Seattle, 47 (73%) began therapy, while only 23 (49%) completed the six to 12-month regimen.[77] In a more recent evaluation of preventative therapy for LTBI, offering 6-months of isoniazid therapy in homeless adults in San Francisco, only 36 (31%) individuals completed therapy.[78] However, this randomized control trial did demonstrate that those in an incentive arm were significantly more likely to complete treatment than those in the peer health advisor arm (p=0.01) or usual care arm (p-0.04). Despite their high risk, deficiencies in TB and LTBI treatment among homeless individuals is demonstrated. Furthermore, individuals experiencing homeless are likely to prioritize other needs, such as shelter, food, and for some with addiction, alcohol and substance use.[79] The above literature reinforces the need for integrated screening and treatment for LTBI and highlights the complexity of this unique and underserved population.

3HP Use

In Canada, the standard treatment regimen of first choice for LTBI has heretofore been nine months of daily self-administered isoniazid (INH-9).[54] This medication has efficacy rates of 69-93%; however, toxicity and long treatment durations with frequent dosing complicate treatment completion rates.[54] As a result, there has been considerable interest and research into shorter regimens. Several of these have proven to be as safe and efficacious as INH-9. For hard to reach populations, the most attractive of these is a combination of INH and rifapentine taken once weekly for 12 doses (3HP), usually as directly-observed preventive therapy (DOPT).[11] In the 3HP regimen for adults, 900mg rifapentine (6 x150mg tablets) is taken with 900mg isoniazid (3 x 300mg tablets) alongside vitamin B6 for a total of 10 or 11 tablets per week. This drug regimen was approved by the United States Food and Drug Administration in 2014 and, in June

of 2017, the Government of Canada arranged for the availability of rifapentine to meet an urgent public health need, facilitating timely access to the medication in high incidence areas.[13,18]

In a landmark open-label, randomized noninferiority trial comparing 3 months of directly-observed once-weekly therapy with rifapentine plus isoniazid (3HP) with 9 months of self-administered daily isoniazid (INH-9) in subjects at increased risk for tuberculosis, 3HP was found to be non-inferior to standard INH-9 treatment.[10] 8053 subjects were enrolled from the United States, Canada, Brazil and Spain and followed for 33 months. Treatment completion rates were higher (82.1% in 3HP group vs. 69.0% in INH only group, $p<0.001$) and effectively prevented TB reactivation. Although rates of hepatotoxicity were significantly higher among the INH only group (2.7% in INH only vs. 0.6% in 3HP group, $p< 0.001$) rates of discontinuation of therapy due to adverse events were greater among the 3HP group in comparison to those who received INH only (4.9% in 3HP group vs. 3.7%, $p<0.009$).[10]

In New York City, four health department TB clinics retrospectively assessed the effectiveness of preferentially offering two shorter treatment regimens, 4 months of Rifampin (4R) and 3 months of once weekly isoniazid and rifapentine (3HP), in comparison to 9 months of isoniazid (INH-9).[80] Most individuals were placed on shorter treatment regimens and the health departments found that, when adjusted for age, sex, and TB risk factors, those on 4R (adjusted risk ratio [aRR] 1.39, 95%CI 1.07–1.81) or 3HP (aRR 1.67, 95%CI 1.27–2.19) were more likely to complete therapy then those on INH-9. The authors suggested that offering shorter treatment regimens may help reduce overall disease burden in a high-volume public health setting.[80]

In a study that investigated treatment discontinuation rates and associated characteristics of persons experiencing homelessness treated with 3HP for LTBI, the authors suggested that, 3HP is a successful option for the treatment of LTBI among this population.[81] Although neither

sociodemographic, behavioural or medical factors were found to be significantly associated with treatment discontinuation, in comparison to historic LTBI treatment rates using 6-12-month INH among those experiencing homelessness (25-33%), the authors report higher completion rates using 3HP (77%). Through key informant interviews with health care providers, the authors proposed that shorter treatment duration, low rates of adverse events, and the use of enablers (e.g. food or transportation vouchers) contribute to high completion rates among this population.[81]

The results reviewed above are supported in a recent systematic review which found no significant differences in efficacy between 3HP and standard preventive therapy regimens (OR.0.89, 95% CI.0.46, 1.70), as well as higher treatment completion using 3HP (87.5%, 95% CI.83.2%-91.3%) compared to other regimens (65.9%, 95% CI.53.5%-77.3%).[16] A systematic review conducted by Pease et al is also consistent, showing no significant differences in efficacy between 3HP and other standard treatment regimens, and that completion rates were higher for shorter rifamycin-based regimens compared to other regimens of six months or longer.[14]

In regards to the safety profile of 3HP, a systematic review which aimed to determine whether the regimen had similar or lesser rates of adverse events compared to standard treatments, including isoniazid daily for 9 months (INH-9), isoniazid daily for 6 months (INH-6), Rifampicin daily for 4 months (RMP 4), and Rifampicin plus isoniazid daily for 3-4 months (INH/RMP 3-4), found that 3HP had the lowest median rate of any adverse events (11.5% vs. INH-6 36.1%, INH-9 17.6%, RMP 3-4 20.0%, INH/RMP 3-4 29.7%).[15] The shorter regimen had the second highest rate of experiencing a grade 3 or 4 adverse event[1] (6.0% vs. INH-6 8.2%,

[1] Grade 3 adverse event = medically significant but not imminently life-threatening event; grade 4 adverse event = life-threatening event

INH-9 3.3%, RMP 3-4 1.7.%, INH/RMP 3-4 2.3%) and the lowest number of patients withdrawing from a study because of an adverse event (1.7% vs. INH 6- 3.8%, INH-9 6.4%, RMP 3-4 2.8%, INH/RMP 3-4 2.2%). Among both randomized and non-randomized studies included in the review, lower median rates of hepatotoxicity among those given the 3HP regimens in comparison to the standard treatment regimens were reported. However, increased frequency of flu like reactions among those given 3HP was reported, suggesting that further research and reporting on adverse reactions experienced by those treated with 3HP is needed.[15]

Barriers and Facilitators to LTBI Treatment Access and Adherence: A Review of Psychosocial Factors

Treatment of LTBI involves the challenge of convincing otherwise healthy persons of the need to treat an infection, one that may never develop into active disease, with prolonged antibiotic therapy that may have side effects.[21] There is relatively limited data accumulated on LTBI treatment access and adherence, with most research focused on improving treatment outcomes pertaining to active TB disease. However, existing research on LTBI treatment outcomes suggests that treatment is suboptimal, resulting from a complex interaction of psychosocial factors impeding treatment access, uptake, and adherence.[21,82]

Social-Ecological Perspective

A socio-ecological perspective is useful in understanding LTBI treatment related outcomes and health behaviour change. Included in this perspective is the acknowledgement that multiple levels of factors including individual, interpersonal, organization, community, and policy influence health behaviour.[83] These influences interact across all levels in creation of barriers or facilitators to health behaviour change.[83] A review of qualitative literature related to LTBI treatment outcomes follows, with a distinction between individual and social level factors which influence access, uptake, and adherence to preventive therapy.

Individual level factors. For LTBI preventive therapy to be offered, individuals first need to be identified as positively exposed and then assessed for active disease or latent infection. Barriers to accessing health care services and resulting TB diagnosis, treatment or prophylaxis, include limited awareness and knowledge of free existing TB screening and diagnosis service.[84,85] More generally, limited knowledge and understanding of LTBI pathology as a barrier is well supported in the qualitative literature. Findings in the literature reflect poor understanding of the difference between latent infection and active disease, as well as the use and need for preventive therapy.[21,84,86-91] Existing studies indicate that most individuals were aware of TB disease but were unfamiliar with latent infection, with participants often disclosing a misunderstanding of BCG vaccine, believing that a positive TST or latent infection was the result of vaccination, a belief that has some basis, given that the vaccine consists of live, attenuated *Mycobacterium (*bovis).[85,88-90] Further complicating this matter is that individuals with latent infection are asymptomatic and thus dis-inclined to accept therapy with little to no perceived benefit of treatment.[21,88,89,91]Through focus group discussion, Weiland et al reported that many participants were unaware that they could have latent infection without symptoms, with participants citing this lack of knowledge as a primary factor underlying not being tested and/or treated.[89] Fear or experience of side effects are additional individual level factors which impact treatment adherence and completion, as well as competing priorities with commitment to long treatment durations of uncertain efficacy.[21,87,88,90] Given that those impacted by TB are often at a socio-economic disadvantage, financial and nonfinancial barriers, such as missing work to attend a clinic appointment, have also been identified in the literature as additional barriers to treatment acceptance and adherence.[90,92] Individual level facilitators identified for increasing

access, uptake, and adherence for preventive therapy focused on improving awareness and knowledge of latent infection, treatment, and TB services among at-risk populations.[85,91]

Social level factors. Individual level factors influencing treatment decisions for LTBI exist within social contexts that also influence uptake and adherence to preventive therapy. Stigma was a recurring theme uncovered in the literature affecting both treatment access and adherence to LTBI preventive therapy.[21,84,85,87,90] Fear of the social consequences of a positive result (e.g. social and economic isolation) and the visibility of attending a "TB clinic" were barriers to screening and diagnosis, the initial steps of accessing preventive therapy.[84,85,87] This was revealed in a study that explored the perceptions of TB among Haitian immigrants in the United States, where several participants stated that people will avoid going to clinics that are designated for HIV or TB because of the stigma attached to the disease.[85] The association of TB with HIV compounds the stigma connected with TB, with TB at the community level being viewed as shameful, dirty, sinful, or as a result of "wrongful behaviour".[21,85] With regards to LTBI, acceptance or adherence to preventive therapy was impeded by the fear of the individual's family, friends, or community members finding out and resulting in ostracism, demonstrating a lack of understanding of the distinction between latent infection and active disease, with individuals expressing the view that if you take pills, you are sick.[85] It is interesting to note, however, that among an urban Indigenous population in Canada, although there were concerns regarding stigma this did not emerge as a major issue in their findings. This suggests that TB seems to have been normalized in some high incidence communities, as a result of its presence throughout many generations.[86]

At an interpersonal level, a number of studies indicate that supportive trusting relationships with health care providers and existing family and social support positively

influenced LTBI treatment adherence and completion.[82,84,85,87,89,91]Unsatisfactory relationships with health care providers were seen as a barrier to LTBI treatment adherence, with participants expressing the need for a multifaceted, holistic approach to patient care which extends beyond TB related concerns. The literature revealed that language and cultural barriers were commonly reported by migrant populations as factors that hinder relationship development and impact treatment adherence.[84,89,91,92] In a study examining cultural feasibility of a TB prevention program, migrant participants expressed the need for more bilingual-bicultural clinic staff and a personalized approach based on respect, sensitivity, and trust in order to connect with the community effectively.[84] Improving social supports for clients who have accepted preventive therapy through peer counselling and comprehensive case management were also identified as ways to improve treatment adherence. [90]

At the organizational and systems level, multiple barriers associated with accessing TB clinics and costs associated with preventive therapy have been reported. Restricted clinic hours were reported as a barrier with several studies revealing that conflict between clinic hours and work schedules prohibited people from accessing LTBI care and preventive therapy.[7,21,84,85,89] In addition to rigid clinic hours, geographical location of the clinics and challenges associated with transportation were noted.[7,21,84-86,89]Many participants reported facing difficulties in arranging transportation to the clinics and this was identified as a barrier in both accessing and adhering to treatment.[7,21,84-86,89] Direct costs associated with obtaining treatment or indirect costs as a result of missing work, transportation related costs, or associated investigational or monitoring costs (e.g. x-ray, liver function tests) that were not covered by insurance presented as barrier.[21,84,86,89,90]

Health Belief Model (HBM) and Preventive Therapy Uptake and Adherence

Health Belief Model (HBM)

Theoretical models can be used to further understand what people believe about health, why they act, and how health behaviour change is sustained.[93] The Health Belief Model (HBM) is the most frequently used model in studies of health behaviour and adherence, and was initially developed in the 1950s to explain why people fail to engage in preventive health behaviours.[93] This theory focuses on individual level behaviour change and focuses on beliefs and perceptions.[94,95] Mental processes such as thinking, reasoning, hypothesizing, or expecting are critical components of cognitive theories.[96] It is proposed that behaviour is determined by the degree to which individuals value an outcome and their assessment of the probability or expectation that a particular action will achieve that outcome, also referred to as *value-expectancy* models.[96] In relation to health behaviour the *value* is avoiding illness or maintaining health, and the *expectation* is that a specific health action may prevent or ameliorate an illness or condition for which individuals believe they are at risk.[96]

In the field of TB research, the HBM has been used to examine TB screening, prevention, treatment, and health education.[97] The model suggests that the likelihood of one completing the recommended health behaviour, in this instance, accepting and adhering to preventive therapy, is dependent on beliefs about perceived susceptibility, severity, benefits, and barriers. LTBI treatment falls into the category of secondary prevention as individuals do not currently have active TB disease, yet, they are identified to be at risk because of the presence of latent infection and one or more factors that increase the chances of its progression.[97] Preventive therapy is recommended to reduce this risk and the health belief model is useful for understanding LTBI treatment uptake and adherence. Findings from a study that examined participation in TB screening demonstrate its utility. Among individuals who believed they were more susceptible to TB and that there were benefits to early detection, 82 percent had at least one voluntary chest x-

ray.[96,98] Among those who perceived lower susceptibility and benefit of early detection, only 21 percent completed voluntary chest x-rays. In addition to its use for screening, use of this model may further our understanding of adherence to preventive therapy, a voluntary action taken to reduce threat of disease.

In relation to LTBI, perceived susceptibility includes the individual's perception of the risk of contracting the disease or negative health outcome (active TB), and perceived severity includes beliefs about how severe an illness or negative the health outcome might be (physical and social consequences of active TB, e.g. death, inability to work, feeling stigmatized); together these are known as perceived threat.[99] In addition to determining the level of perceived threat, the individual weighs the perceived benefits of an action (e.g. preventive therapy is effective, feasible, or beneficial) against the perceived barriers of an action (e.g. competing priorities, duration of treatment and time constraints, side effects).[99] Cues to action are internal (e.g. develop a cough or symptoms of TB that increase perceived threat) or external (e.g. physician recommends preventive therapy or recent known exposure to TB) factors which trigger the health behaviour. More recently this model has expanded to include the impact of demographic, structural, and psychosocial factors on individual perceptions and likelihood of health-related action. For example, social normalization of TB may indirectly influence behaviour by altering perceptions of susceptibility, severity, benefits, and barriers.[86,96] Albert Bandura's concept of self-efficacy, the belief in one's ability to successfully execute a behaviour, was incorporated into the model as a separate construct after 1988.[99] Components of the HBM and their interactions are depicted in Figure 1.3.

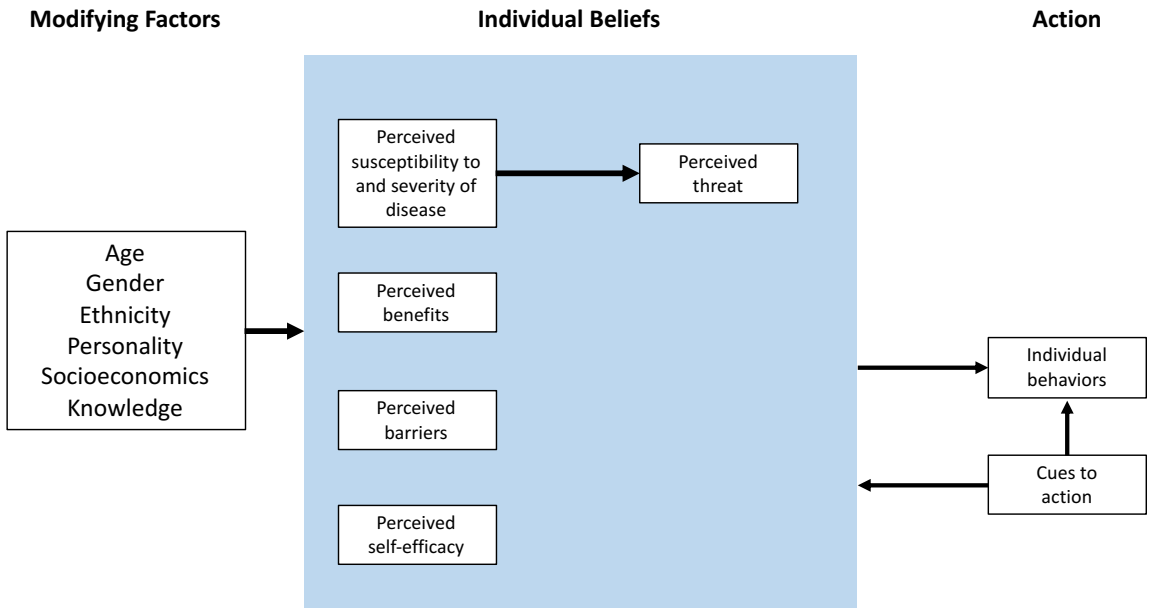

Figure 3. Components and Interactions of the Health Belief Model from Skinner CS, Tiro J, Champion VL. The health belief model. In: Glanz K, Rimer BK, Viswanath K, editors. Health behaviour. Theory, research, and practice. 5th ed.

Using the HBM it is understood that individual level behaviour is a component of health behaviour change, however, it is critical to also consider the relevant social and community contexts in which behaviour occurs. There are two main criticisms of the HBM, the first is that the relationships between the variables in the model have not been clearly examined; it is assumed that the variables are not moderated by each other but rather have an additive effect.[94] The model also assumes the variables affect health behaviour directly and are unaffected by behavioural intentions. Secondly, the model does not consider important determinants of health behaviour such as positive effects of negative behaviour and social influences.[94] Furthermore, the model fails to address behaviours which are based on habits (e.g. smoking) rather than decisions, making it a poor predictor of adherence in situations where behaviour is socially determined or linked to unconscious motivations.[94] Although limitations exist, critical reviews provide empirical evidence and support for the HBM and its variables (perceived susceptibility,

perceived severity, perceived benefits, perceived barriers) however, the magnitude of each of these variables individually is small.[96] Carpenter measured the average magnitude of the relationship between each variable and behavioural outcome across 18 studies from 1982 to 2007 and generally found strengths of association to be small (*r* 0.05 to 0.30).[100] Perceived barriers had the largest association (*r*=0.30) followed by perceived benefits (r=0.27), perceived susceptibility (r=0.15) and lastly perceived severity (r=0.05). Furthermore, the author argued that future research should abandon the simple four-variable additive model and instead examine more complex models (e.g. including self-efficacy) and possible mediation and moderation among variables.[100] Overall, more research is needed on the application of the health belief model in interventions aimed at health behaviour change as well as on determining the relationships between constructs and the relationships of constructs to the behaviour they are predicting.[96]

Study Rationale

LTBI must be treated effectively in order to meet TB elimination goals. It is suggested that 3HP holds promise for increasing preventive therapy adherence and completion rates, especially among populations who face psychosocial barriers to treatment completion. However, research in this area is limited. Although it is known that a broad range of factors can impact treatment adherence, this literature review reveals gaps in knowledge in defining these factors in the context of a shorter treatment regimen, (3HP), specifically administered as DOT, a route of administration that is uncommon for preventive therapy and among individuals at greater risk. Furthermore, there is lack of qualitative research on the topic of LTBI perceptions and treatment adherence among populations who are unstably housed or homeless (i.e. both harder to reach) and at greater risk of progressing to active TB. Although features of this regimen (e.g. shorter

treatment duration, administered as DOT) appear promising to populations who face challenges to treatment adherence, qualitatively exploring this from the perspective of those offered treatment is key. As opined in a recent Lancet series on TB elimination, biomedical advances such as shorter treatment regimens, need to be supported by qualitative work to explore individual and community understandings of latency and the need for preventive therapy.[7]

In order to improve outcomes related to LTBI preventive therapy it is important to understand the perceptions of barriers and facilitators of treatment uptake and adherence among populations at greatest risk. The study described in Chapter 3 proposes to address this call for research using qualitative descriptive method to explore understandings of latent infection, the need for preventive therapy and identify barriers and facilitators to preventive therapy uptake and adherence using a shortened treatment regimen (3HP) among individuals who are unstably housed or experiencing homelessness in Edmonton and Fort McMurray, where risk of TB reactivation is high. In addition to exploring patient experiences and perspectives, in-depth interviews with health care providers experienced in providing preventive therapy with 3HP to the study population will be conducted. HCPs can provide additional contextual information and provide insight into the programmatic experiences of using 3HP as directly observed therapy to treat LTBI, a mode of administration that is new for preventive therapy. By interviewing both HCPs and patients, this will enable us to gain a comprehensive understanding of 3HP, and barriers and facilitators to use. It is anticipated that findings from this study will be applicable to other settings of high TB burden in Canada and support advocacy efforts related to shorter treatment regimens for underserved populations and in those who may face psychosocial barriers to treatment uptake and completion.

Chapter 3: Methodology

Preamble

Although the following chapter provides a comprehensive overview of the methods used in this study, and the processes for participant recruitment, data generation and analysis, it is important to provide insight into some of the challenges faced during this research project. Initially we aimed to recruit only the clients of this study, those who were unstably housed or experiencing homelessness, and who had been offered treatment with 3HP, however, we experienced challenges with this approach. Firstly, there was a very small number of clients who were offered treatment with 3HP, due to provincial programming and logistical challenges (reviewed later in this thesis). Additionally, due to the instability of clients' lives, this led to difficulties in reaching out or connecting with clients for recruitment and completion of an interview. During recruitment, I relied heavily on the relationships that the care providers had developed with their clients. Due to recruitment challenges, we expanded this study to explore HCPs programmatic experiences with 3HP and to identify barriers and facilitators of LTBI treatment access, uptake, and adherence from a systems perspective. I used a personal journal, discussed further in the rigour section of this chapter, to reflect on what was going well in the study and also some of the challenges I faced. This included learning how to navigate the "muddiness" of qualitative research (what is a theoretical position?) and the researcher-participant relationship. As well as sometimes having to do 4 interviews in a day, back-to-back because of the limited time I had in the community, specifically in Fort McMurray. Overall, although not comprehensive, this preamble provides insight into some of the challenges I faced while completing this thesis. While I hoped to provide an extensive and clear picture of the

methods of this study, it is critical to engage and bring awareness to this broader research experiences and some of the difficulties experienced.

Overview of Qualitative Descriptive Research

This study is exploratory in nature and employs a qualitative approach. Qualitative description, a method that provides a basic description and summary of a phenomenon from the perspective of those who live it, was used in this study.[35]

Qualitative research uses inductive methods, working from the data and not from a commitment to a pre-existing framework or theory, in order to interpret or make sense of the meaning people attach to their experiences or to understand a particular phenomenon.[101] The qualitative descriptive study, as Sandelowski describes it, is best used when clear descriptions of phenomena are invited and the researcher wishes to know the who, what, and where of events.[35,102] Qualitative descriptive studies can draw on the tenets of naturalistic inquiry, an orientation to inquiry which commits to studying a phenomena in its natural shape, without pre-selection of variables, manipulation of variables, or an a priori commitment to one theoretical view of a target experience.[35] The method is often used when researchers are looking to obtain clear, unadorned answer to questions of relevance to health practitioners and policy makers.[35] Examples of such questions may include what are people's feelings, thoughts or attitudes towards an event; or why may some individuals use a service and others not? And in our study, why do some individuals accept and complete preventive therapy and what barriers and facilitators support this process? Purposive sampling is used in qualitative descriptive studies to obtain cases deemed information-rich for the purpose of the study; in our case, individuals who were diagnosed with LTBI and offered preventive therapy with 3HP, but who faced psychosocial barriers to treatment completion (e.g. homelessness) and their health care providers.[35] Data

generation strategies may include minimally to moderately structured interviews, focus groups and/or observations of events or examination of artifacts in order to discover the who, what, and where of events or experiences.[35] Variants of inductive qualitative content analysis are the analytical strategies of choice for qualitative descriptive studies and are data driven.[35,101,102] Codes and coding frameworks are generated from the data themselves and systematically applied during the analysis process. The resulting outcome of a qualitative descriptive study is a direct descriptive summary of the informational contents of the data, organized in a way that best fits the data.[35]

Theoretical Perspective

It is essential that a researcher situates her or himself both ontologically and epistemologically in their approach to the research study. The epistemological perspective I hold is that data is obtained dialogically and is co-constructed between myself and the participant, in other words, a subjectivist epistemology. Within this perspective, I believe that the participant and I co-create understanding a phenomenon and the process of data generation is relational. Additionally, I assume that there are multiple realities and truth on the phenomenon of interest, informed by historical, cultural and social constructs, reflecting a relativist ontology.[101] These perspectives can be described as constructivist, and align with the underpinnings of naturalistic inquiry, the characteristic theoretical foundation of a qualitative descriptive study.[36,102] Moreover, I recognized the importance of reflecting on my positionality in the research study, while collaborating with underserved populations. As well as the inherent biases I brought to the research process, including experience as a Registered Nurse and practice in communicable disease.

My own clinical practice as well as a review of literature and discussion with colleagues informed my interview guide, exploring areas or themes that I had encountered in my practice at the Edmonton TB clinic and in working with underserved populations. After completing my first couple of interviews and where I revealed that I was nurse, I felt impelled to reflect on this and how it may have impacted the data and the relationship formed between the participant and myself. I felt that when I disclosed that I was a nurse, the relationship or power dynamic of the interview changed, and I took on more of an "expert" or educator role. I engaged in teaching and provided education around LTBI and TB and felt that this was not reflecting the positionality that I wanted to approach the research with. Through an iterative process, I reflected on how I wanted to present myself to participants and how this may impact the data collected, the relationship and the interview process. As a student researcher, I wanted to take the role of inquiry, I wanted to learn from the participants and hear their story and perspective. In subsequent interviews, I intentionally positioned myself as a student throughout the interview and described the research study as a component of my degree. I emphasized that I was there to learn and to hear their story, they were the "experts" and I feel that this actually changed the participant/researcher relationship. I felt the power dynamics shifted, I wasn't taking on a health care provider role, confirming or renouncing what they were sharing, but rather took on a learner perspective, withholding knowledge related to my clinical experience. Following the data generation phase, I felt that I was then able to synthesis both the participants and my knowledge and experiences to make sense of the data during the analysis and writing of this thesis.

Sample, Recruitment, and Consent

Patient Recruitment

Purposeful homogenous sampling was used to recruit participants who could provide rich information on the phenomenon of interest.[103] Homogenous sampling is an appropriate sampling strategy, as this study aimed to describe the phenomenon of interest (understanding of latent infection, the need for preventive treatment, and barriers and facilitators to preventive treatment access, uptake, and adherence) among a particular sub-group, those who are unstably housed or experiencing homelessness.[103] Participants were eligible for the interview component of the study if they were English-speaking adults (individuals over the age of 17), living in inner-city Edmonton and/or Fort McMurray who experienced homelessness or unstable housing within the last 12 months, had a positive tuberculin skin test or interferon gamma release assay, and who have been offered and may currently be on, treatment with 3HP. Homelessness describes the situation of an individual, family, or community without access to stable, safe, appropriate, and permanent housing.[104] Homelessness exists within a range, with people without any shelter at one end and being insecurely housed at the other.[104] For the purpose of this study, participants were eligible if within the last 12 months they were (1) unsheltered or absolutely homeless (living in the street or in places not intended for human habitation), (2) emergency sheltered (those staying in emergency overnight shelters), and (3) provisionally accommodated (those who are living in transitional housing where accommodation is temporary).

In order to identify the full range of barriers and facilitators to 3HP treatment adherence we decided it would be helpful to study the treatment experiences of three groups: those who declined, those who accepted but did not complete, and those who completed treatment. As such, those invited to participate included homeless LTBI-positive individuals who (a) were offered treatment for LTBI with 3HP but who declined this treatment, (b) were offered 3HP treatment and accepted but who did not complete treatment (<11 3HP doses taken within 16 weeks of

treatment initiation), and (c) were been offered 3HP treatment and completed treatment (≥ 11 3HP doses taken within 16 weeks of treatment initiation). We thought it would be noteworthy to explore the understanding of latency and the need for preventive therapy among these three groups, as they would each have varying levels of interaction with health care providers. Additionally, interviewing those who declined treatment could provide more insight into the barriers related to the uptake of preventive treatment, even though a shorter treatment regimen is being offered. Completing interviews with those who had accepted but did not complete treatment would enable us to gather more information and further our understanding of what factors imped treatment completion and what factors facilitate completion of the treatment course. Participants were compensated with a $20 gift card from 7/11 stores to acknowledge their time and sharing of their experiences.

Health Care Provider (HCP) Recruitment

To supplement the patient data and provide programmatic insight, a diverse range of health care providers, including physicians, nurse practitioners, registered nurse, social workers, and cultural liaisons were recruited. To be eligible for the study, HCPs had to have been from Edmonton and/or Fort McMurray, be familiar with outreach and underserved populations, and to have had direct experience in providing 3HP to the clients in the study population.

Procedures

An overview of the study's research objectives and questions were presented to key stakeholders and members of the Provincial TB Program, and the Street Connect team and Centre of Hope shelter in Fort McMurray prior to recruitment. To recruit patients, health care providers identified potential study participants who met the study inclusion criteria in confidence without the researcher's knowledge of the identity of the patient. In Fort McMurray,

a TB outreach nurse or nurse practitioner informed and offered clients treatment for LTBI, and in Edmonton, a physician, nurse, or pharmacist did the same. Eligible patients were provided with information by their health care provider regarding the study and invited to participate. At this point, if the participant agreed, consent to contact was obtained (Appendix A). With the participant's consent, I met with the client in person and reviewed the study information sheet and eligibility. Following review of the information sheet, if patients were still interested and met the eligibility criteria described above, I completed the informed consent process (Appendix B).

To recruit health care providers, the Edmonton TB Clinic, the Provincial TB Clinic, and the Street Connect team in Fort McMurray were contacted by email and invited to participate in the study. If HCPs expressed interest in participating, I reviewed the information sheet and completed the consent process either in person, or in some cases, over the phone. All participants (clients and HCPs) were made aware that they could revoke consent and withdraw from the study at any time before or during the interview process and were offered a $20 gift card to 7/11 or Starbucks (participant choice) to acknowledge their time and sharing of experiences.

Data Collection

Interviews were conducted from June 2019 to January 2020. A semi-structured interview approach was used, as I felt I knew enough about the phenomena through review of literature and clinical practice experience to develop questions about the topic in advance of the interview.[105] The interview guide was informed by the literature review conducted for this study, as well as through feedback provided from experienced TB researchers and my own experience in practicing as a registered nurse at the Edmonton TB Clinic and with underserved populations. Each participant was able to share their unique story of their understanding of LTBI and treatment experience if treated, while also ensuring that topics related to the research objectives

were discussed. Tailored interview guides were developed for each client group (declined treatment, initiated but discontinued, completed treatment) (Appendix C) and also for HCPs (Appendix D). Although a set of guiding questions were used, the interview guides evolved throughout the data collection phase in an effort to explore developing themes and rich data points. Examples of interview questions for clients included: Can you tell me what you know about TB? Can you describe to me the difference between latent and active TB? Can you tell me about when you were first told that you had LTBI? Is LTBI something you discuss with friends or family? For HCPs, examples of interviews questions included: What were the perceptions and expectations of using 3HP before your program started using it? What do you like best about using 3HP in comparison to other treatment regimens for LTBI among persons experiencing homelessness? What do you find challenging about using 3HP in persons experiencing homelessness? Interviews were staggered, as individuals initiated and completed or discontinued treatment and were dependent on health care provider availability. Review of the data generated through interviews with a TB physician and a qualitative researcher external to the project, occurred during the first phase of interviews as well as after all interviews had been conducted. This debriefing process assisted the researcher in organizing her findings and identifying areas to explore deeper in future interviews. This checking is discussed more below in an evaluation of the study's rigour.

Interviews were completed in English and conducted in a variety of settings, for the convenience of the participant and safety of the researcher. This included participants homes, an inner-city pharmacy, a vehicle, Centre of Hope shelter, and TB services in Fort McMurray. Four of the nine interviews with health care providers were conducted over the phone, all interviews with clients were conducted in person. In two of the ten interviews completed with clients, a

member of the “Street Connect” team were present in the room for safety. Consent was obtained for the interviews to be audio-recorded and they lasted 14 to 31 minutes. Audio files were sent for transcription and then reviewed and cleaned. Any identifying information was removed. A personal journal was kept where I recorded my thoughts, impressions, and reflections following each interview. It included assumptions and perspectives on how the research was unfolding, and the challenges and frustrations I encountered.[101]

Data Analysis

Inductive content analysis has been described as the most fitting analytical technique for an exploratory or descriptive qualitative study.[101] The technique is a method for systematically describing the meaning of qualitative data and includes three key features: it reduces data, it is systematic, and it is flexible.[106] Inductive qualitative latent content analysis was the analysis technique used in this study and ATLAS.ti the software used to manage and organize the data. Latent content analysis includes the process of identifying, coding, and categorizing key patterns in the data.[101] The first step of my analysis was to become familiar with the data. This included, first, recording personal reflections and field notes, documenting my overall impression of the interview, what went well and what to watch for, as well reflecting on what the participant was trying to convey through the interview, a “key statement” immediately or as soon as possible after each interview. Following this I listened to the audio recording of the interview and reviewed and cleaned transcripts to maintain confidentiality and correct any spelling, punctuation, grammar or mishearing that occurred during transcription.[107] At this stage, I made notes of any interesting words, phrases or ideas that came up in the interviews or that seemed to be repeated across interviews. This enabled me to follow up on these points in succeeding interviews. After the transcripts were cleaned and I felt acquainted with the data, I then began the

process of generating open codes for each transcript. This included reviewing and rereading the data, highlighting sections of the text and making comments in the margins of anything striking.[101] I then assembled these "codes" into categories or groups of related ideas. Once I had grouped my codes into categories, I then reviewed each category, merging and collapsing them to ensure each code fit within that category and that categories themselves were distinct from each other- described by Mayan as internal and external homogeneity.[101] Once the categories were developed, I created a "coding framework" which I then applied to existing and subsequent transcripts. Because my interviews were staggered and there was a break between data collection, I completed this process twice, first for the initial set of interviews and then again for the second set about four months later. I then adapted the coding framework developed and the organization of categories to include new and additional findings, which I then applied to the earlier transcripts. The analysis occurred iteratively during the data generation phase, and informed revisions of my interview guides, allowing me to explore themes or topics that were being uncovered.

Once I completed the first set of interviews and analysis, I met with two experienced qualitative researchers, external to my study, to review my findings and work through category development and organization of data. I also reviewed these preliminary findings with a TB physician familiar with the project, for feedback. Due to the community-based nature of the work and the relationships developed with HCPs over the study period, once I had completed the final analysis of all study data, I completed member checking with the HCPs who participated in the study. This was an opportunity for them to review the main findings and organization of data, including the results of both the patient and HCP interviews; feedback was provided and incorporated into the final results and discussion of this thesis.

Rigour

Rigour is the process of demonstrating how and why the findings of an inquiry are worth paying attention to, that is, are they sound and of high quality?[101] The concept of qualitative rigour began with the efforts to establish criteria for evaluating research that were equal in form and intent to those criteria revered in quantitative research.[108] The notion that a single set of criteria, used to evaluate qualitative rigour, can be applied across all interpretative contexts has been disputed.[108] Rather, it is suggested that different qualitative approaches, based on different principles, need an approach to rigour that is methodologically sound and philosophically congruent with the inquiry.[108] This project followed the set of criteria proposed by Lincoln and Guba developed in 1985 and explored by Tracy (2010), to maintain trustworthiness (rigour), and includes credibility, transferability, dependability, and confirmability.[102,109,110] The topic of ethics is also reviewed as a criteria of rigour, as described by Tracy (2010).[109] I selected these criteria as I felt they fit best within the research paradigm and overall project.

Credibility

Credibility examines whether the findings make sense and if they provide a rich, accurate representation of the participants and/or data.[102,109] Credible reports are those that readers feel trustworthy enough to act and base decisions on.[109] Strategies such as spending prolonged engagement in the setting and with the population, triangulation, and member checking support credibility of the research and findings.[102,109] The main strategies I used were extensive experience or exposure in the field, peer debriefing and member checking. Although the time I had available to spend in Fort McMurrary was fixed and limited, I did spend time with the Street Connect team and at the Centre of Hope, familiarizing myself with the setting and population under study prior to conducting interviews. In addition to this, I have extensive experience in

working with underserved populations and those experiencing homelessness. This provided me with *tacit knowledge*, an understanding of the culture of the study population, their vocabulary, jokes and idioms.[109] Peer debriefing includes engaging with another research colleague in an extensive discussion of one's process of working with the data.[102] I completed peer debriefing at different stages throughout the research process, firstly, after my initial interviews were completed and secondly after my data generation phase was complete. Peer debriefing was completed with researchers external to the project and included two public health qualitatively trained researchers and one anthropology researcher experienced in TB. This process is described in more detail under confirmability. Member checking is the process of obtaining feedback and verification from participants on developing hypotheses or interpretations of the data.[102] Although member checking aligns more with a post positivist perspective, as a novice researcher, I felt that this strategy supported my confidence in the research findings. I invited the HCPs who participated to review my findings to ensure that I had represented the data in an accurate way and to highlight any areas where they felt I wasn't quite capturing what was shared or where I may have missed something. This was completed once all interviews were completed and my findings were established, as I offered all HCPs who participated in the study an opportunity to review the results for both patients and HCPs. Logistical constraints and feasibility were such that member checking was only completed with health care providers of the study. Due to this study being informed by and nested in the Provincial TB Program, I felt that the invitation to review my findings and provide feedback was in line with this community-based approach. This feedback was reflected on and incorporated into my final results and discussion.

Transferability

Transferability assesses the applicability of the findings to other settings and is acquired by providing a rich overview and detailed description of the setting and participants of the research study.[102] Elevated rates of TB among inner-city populations is not unique to cities in Alberta. Rather every major city in Canada, and globally, faces similar challenges. The setting and population of this research study is described in detail in this thesis. By providing this rich description, these results and experiences may be generalizable to similar high incidence communities in Canada, or among populations that experience barriers in accessing care and completing treatment for LTBI.

Dependability

Dependability refers to the ability to describe how and why decisions were made throughout the research process and is usually attained through the use of an audit trail.[102] Linked to dependability, is the concept of sincerity, explored by Tracy (2010).[109] This includes transparency of the methods and challenges experienced, as well as self-reflection of the subjective values, biases, and inclinations of the researcher.[109] The two main strategies I used to achieve dependability and sincerity are the use of an audit trail and a personal journal. I used the audit trail to record a detailed description of the why, when, and how decisions were made throughout the research process. A personal journal was used to record my reflections on how the research was unfolding, interactions with the participants during interviews, biases and theoretical assumptions, as well as challenges and highlights. This journal fostered reflexivity during the research process. I discussed my reflections with colleagues and mentors, including classmates, and individuals external to the project, to solicit an "outsider" perspective.

Confirmability

Confirmability is used during the data collection and analysis phase to ensure that the findings are logical.[102] The technique includes the use of an audit trail, as well as the opportunity to examine data and resulting interpretations.[102] As described earlier, in addition to the use of an audit trail, I also used a verification strategy of peer debriefing, to attain confirmability.[102] I engaged three research colleagues, all external to the research project and experienced in qualitative research, two masters-level trained (MSc and MPH in Public Health) and one PhD-level trained in Anthropology. I discussed my process for working with and organization of the data, as well as my findings and interpretations with two of these colleagues. As a novice researcher, peer debriefing was a way for me to think through my findings. I provided a copy of transcripts and preliminary results from both HCPs and patient interviews to the MSc trained researcher external to the project. The purpose of this was not to confirm my findings, but rather to provider a critical perspective on my organization and interpretation of the data. This was a way to ensure that I hadn't missed anything major or 'forced' anything onto the data. Having qualitatively trained colleagues critically evaluate my process and discuss my tentative analysis and interpretations supported the rigour of this study.[102]

Ethics

As outlined by Tracy (2010) a variety of practices can attend to ethics in qualitative research and add rigour to the research study.[109] This includes procedural, situational, relational and exiting ethics.[109] Procedural ethics ensure that participants are protected for any risk associated with involvement in the study, including anonymity, confidentiality and privacy.[109] Procedural ethics includes the approval of the research proposal, which outlines how the rights of participants will be respected and how participants will be protected from harm, by appropriate research ethics boards.[102,109] Prior to any data gathering, the research proposal and all

amendments for this study were approved by both the University of Alberta REB 3 (ref PROPro00087572) and the Northern Alberta Clinical Trials + Research Centre (NACTRC), a joint venture of Alberta Health Services and the University of Alberta (ref PB85954). The information sheet and consent form were developed based on REB recommendations with input from the research unit and supervisory team. All identifying information was removed from the transcripts prior to uploading to ATLAS.ti and analysis of data, participants were coded with a number, and all data for this study was secured under double lock and key, and on a password protected computer at the University of Alberta.

Situational ethics refers to the unpredictable situations that may arise during the research process, and that the researcher must continually reflect upon, critique, and lead them to question their ethical decisions.[109] Prior to data generation, a presentation of the proposed research study was provided to the provincial TB clinic stakeholders. At this presentation, ethics-related issues concerning the topic and support for participants should emotional or psychological trauma occur during the interview process was arranged. This is linked to Morse, Niehaus et al (2008) ways of understanding risk related to interviewing: risk related to the participant, the topic, the relationship, the environment, the outcome of the research, and the researcher.[110] I reflected on ways to mitigate and respond to these risks during the research process and through conversations with the research unit and my supervisors.

Relational ethics refers to the dynamic relationship between the participant and the researcher, and the way the researcher is mindful of their character, actions, and consequences on others.[102] Being unfamiliar to the participants and an outsider, I had to build on the relationships and trust that the HCPs had developed with the clients. The HCPs acted as “gatekeepers” and facilitated access to the clients for the study. I spent time in the community, with members of the

street outreach teams, to build rapport and trust with the clients prior to conducting interviews. I also introduced myself to participants as a student, not as a health care provider, to challenge power dynamics that are often present in the interview process between the researcher and the participant. I emphasized that the participant was the expert and that I was there to listen and learn.

Lastly, exiting ethics refers to the ways in which the researcher concludes the research relationship, leaves the setting and shares the findings with the participants in a meaningful way.[109] Ensuring that my results appropriately reflected my research objectives and questions, as well as delivering the findings in an accessible way, both within and outside of academia is critical. I plan on sharing my findings with the provincial TB team, either in person or through an online presentation, and also producing a presentation, poster or infographic to be shared with participants. Although I cannot fully control how my work will be read or interpreted, it is important to consider how best to present the research to avoid unjust or unintended consequences, such as perpetuating negative associations or stereotypes of this underserved population.

Chapter 4: Results

Study Participants

This chapter presents results of 19 interviews (10 clients, and 9 health care providers [HCP]). Table 1, below, presents the demographic characteristics of clients; the mean age was 47 and 60% were male.

Of the 10 clients who were interviewed all reported a history of unstable housing or homelessness within one year: seven were provisionally housed at the time of the interview, while three were experiencing current homelessness.[2] There was also some variability in the stages of therapy at which these clients were at during the time of interview. Six clients completed treatment, one discontinued treatment, and three clients either declined, or delayed treatment. Treatment completion was defined as witnessed ingestion of 11 or 12 doses within 16 weeks of treatment initiation. Delayed treatment refers to an agreement to therapy without having immediately initiated treatment. Seven of the ten interviewees reported previous or current alcohol and/or substance use.

HCPs included two physicians, one nurse practitioner, four registered nurses, one social worker, and one Indigenous cultural helper employed by Alberta Health Services (AHS). All reported experience working with inner-city populations, and with clients and patients experiencing homelessness. All had direct involvement, and experience in providing preventive therapy with 3HP to the study population.

[2] Persons who were provisionally housed had supportive housing through outreach programming, or in low income housing; homelessness included staying at emergency shelters, couch surfing, and/or sleeping rough.

Table 1 Demographic characteristics of clients (n = 10*)*

	n	*percent*
Sex		
Female	4	40
Male	6	60
Age, years		
All clients, mean (SD) (range 17-64)	47 (14)	
Population Group		
Canadian-born non-Indigenous	4	40.0
Canadian-born Indigenous	3	30.0
Foreign-born	3	30.0
Housing Status		
Low-income housing	5	50.0
Housing first program	2	20.0
Homeless (emergency shelter use, couch surfing or sleeping rough)	3	30.0
Reported previous or current alcohol and/or substance misuse	7	70.0

The results of this study are presented in two sections. This first section reports on the knowledge and understandings of LTBI and preventive therapy from client interviews. The second section reports on the identified barriers and facilitators to treatment uptake and completion from both client and HCP perspectives.

Knowledge and Understandings of TB, LTBI and the Need for Preventive Therapy

Analyses of client interviews revealed four main thematic categories: (1)TB disease, (2) diagnosis, (3) need for preventive treatment , and (4) a desire to learn more. These categories and subcategories are summarized in Figure 1 and presented in more detail below.

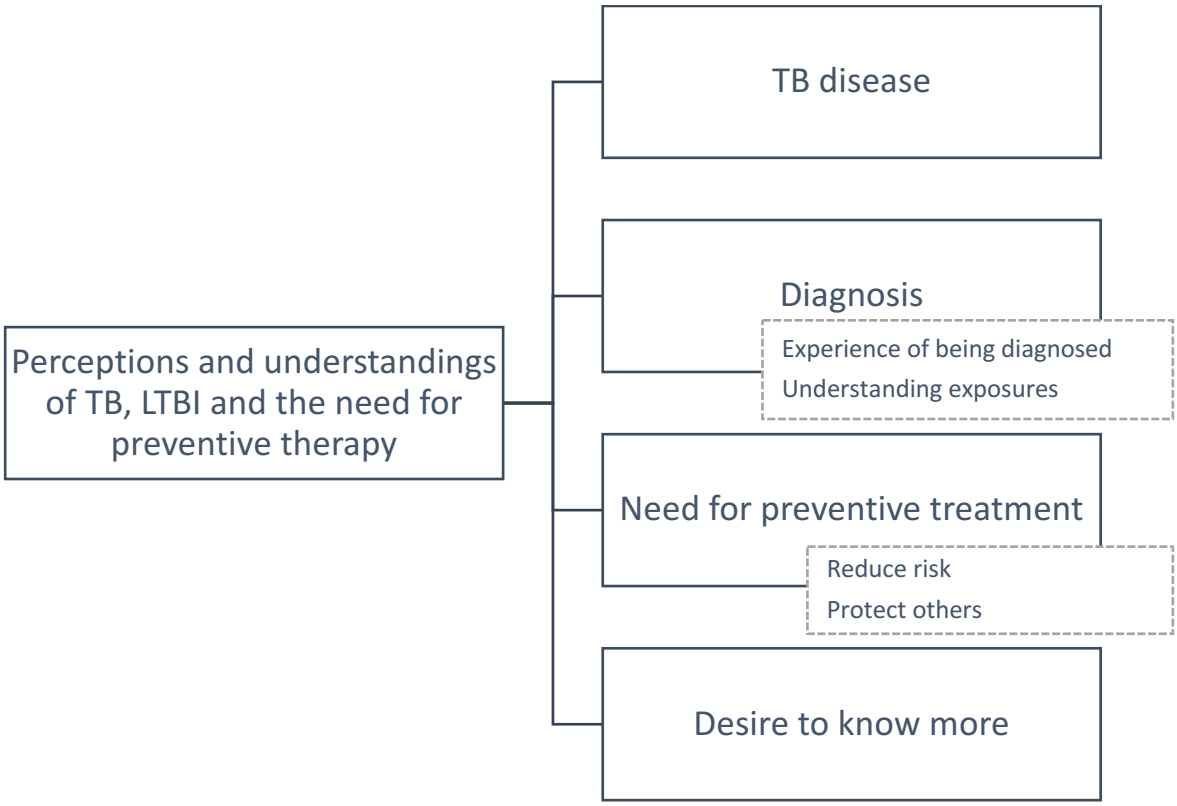

Figure 4. Overview of Themes Identified from Client Interviews

TB Disease

Knowledge of TB, LTBI and the difference between active disease and latency varied among clients. When prompted to share their knowledge of TB, some clients described TB as a germ, virus, bacteria or disease that affects the lungs, while others reported that they had heard of it, but did not know much. When asked to describe the differences between active TB disease and LTBI, about half of participants understood a latent infection to be "dormant", and made reference to the terms "sleeping TB" and at risk of "waking up." As two participants described:

> Well active… active you'll get really sick... if you just got the latent germs in your lungs right and they're dormant... like they can be dormant for years… then all of sudden start up. (P3, client [completed])

> You have it but it's not contagious. It's not active. It's not woke up. It's kind of dormant but you have it. You're a carrier. Just like some other diseases. You are a carrier and not fucking know. (P12, Client [declined])

Other participants reported that they had heard the term "sleeping TB" from their health care provider but were unable to describe what this meant, and how it is different from active TB disease. In describing their understanding of the difference between TB and LTBI, participants noted how "TB can kill you" (P1, client [declined]) remarking about the progression, and ultimate risk of dying from the disease.

Diagnosis

The conversation with clients about a diagnosis of LTBI revealed subthemes around the experience of being diagnosed and understanding of exposure.

Experience of being diagnosed: When asked to share their experience of being diagnosed and how this made them feel, many clients described initial feelings of shock and worry. Many were especially worried that that they could potentially die from TB disease. As two clients indicated:

> Yeah... I was worried…I was scared... I was like... what if you can die and stuff. (P1, client [declined])

> I'm totally worried. I was, like, "big guy, where else would you take me?" He had me a few times. I've been hit by vans and trucks and none of those stopped me. (P8, client [delayed])

While clients described initial feelings of shock and worry, some went on to share how they felt reassured after learning that the infection was latent, what this meant and how it could be treated before becoming active:

> You tested positive... and what the hell... and it was a shock to me hey.... what the hell is going on here…went and met with the doctor... ohhhh but it's TB... but it's dormant. She explained that it was dormant. Okay… do this pill program. Okay… I'm not going to miss nothin. (P3, client [completed])

> I just didn't worry about it after because they told me it's not like … gonna wake up right away, it's still sleeping, you can take the medicines and you can be better. (P1, client [declined])

> I just wanted to get cured. I didn't want to worry myself. When they said I had to take the medication, I was like, "At least I know I'm going to get cured from that." (P10, client [completed])

Understanding TB Exposures: Many clients shifted the conversation to describing their understanding of different exposures that may have led to their diagnosis. These exposures included factors outside of clients' control, such as their environment, and also factors over which the participants felt some sort of responsibility, such as behaviour and choices. Many identified the relationship between being around someone who is coughing and exposure to TB. Four clients discussed exposure from a close contact (i.e. family member and friend) while others did not list a contact, however, stated they were around people who were sick often and coughing. As two interviews revealed:

> Cuz TB like goes around right? They gotta be coughing around you in order for you to catch the germs in your lungs. (P1, client [declined])

> Interviewer: Do you know if you were around somebody with TB?
> Participant: I probably was.
> Interviewer: Not anyone you know?
> Participant: No…but lots of coughing and everything. I've been around people with lots and lots of coughing. (P5, client [completed])

In addition to identifying the connection between coughing and exposure to TB, clients also described the perception that transmission may have occurred through the sharing of drinks and bottles, cigarettes and other drug equipment:

> A few guys were fucking passing it around… I was sharing pipes with them…crack pipes. Two guys here ended up in the hospital with TB. They were…like I said…sharing pipes. (P8, client [delayed])

> I thought it was just from smoking, and sharing everything with everybody, whatever, because someone else might have and you don't know. It's pretty serious. (P12, client [delayed])

Exposure through sharing of items, including the ones described above, were described in the broader context of exposure to TB through being homeless and spending time on the street. Many participants relayed their belief that experiences associated with homelessness, such as environmental exposure through shelter use, sharing items, or being around people who are generally unwell exposed them to TB. Two people described this as follows:

> I was quite surprised because I knew they said this [diagnosed with LTBI] but I didn't know who had it. I shared a bottle and cigarette. You can't finish a cigarette outside the door anyway without sharing when you're on the streets. Probably everybody's just passing it on to people or whatever, don't realize they have it. Being homeless on the streets, lots of that is going on. (P13, client [completed])

> You go through the same shit at these centers daily, same circumstances at the Salvation Army daily. People cough and up all night. Cough, cough, cough, cough, cough. You got to breathe that in afterwards. After they cough, you breathe it in, irritating. (P5, client [completed])

Aside from environmental exposures, some expressed a sense of personal responsibly, where infection was associated with "being a bad apple" (P6, client [completed]), while others felt that they were blamed for acquiring the infection "they blamed me… I run a good life…I don't live a bad life…" (P3, client [completed]). Expanding on personal responsibility, exposure and subsequent infection were connected to alcohol and substance use and being involved in street life. As one client explains it:

> I'm a heavy smoker and I kind of led a real hardcore life. I'm not going to lie. I'm on the fucking streets. Partied, did a lot of drugs and shared pipes and shit like that so I probably might have it myself right? Probably one of the reasons why I fucking got it. My addiction led to me getting tuberculosis. I know it was because of the addiction, sharing pipes, smokes, pots, picking buts, sharing smokes and drinks, bottles and whatever else. I

> don't use needles, I smoke. [laughs] Maybe the occasional snort. The party life led me to have TB and I want to get rid of it. (P12, client [delayed])

Need for preventive treatment

Most clients described knowing that treatment was needed in order to "kill bacteria" (P2, client [completed]). They shared the perception that preventive treatment provides a means to both reduce risk and protect others from exposure to infection. For reducing risk, some described how taking treatment while the infection is latent can reduce the threat of developing active TB and becoming sick, as revealed in the following quotes from the interviews:

> I jumped right into it. Instead of catching it, they cured me before I caught it. (P5, client [completed])

> Interviewer: Can you tell me what you know about the differences between latent or sleeping TB and active TB?
> Participant: I know the first one…I didn't know I had it until I went for blood work and I found out that I had it. Before I got live active TB, they caught it right away, so I was on medication before it got active.
> Interviewer: Okay, so they caught it before you were sick?
> Participant: Ya, before it got active…they gave me medication…I had to take about eight pills, all different kinds. (P13, client [completed])

With regard to protecting others from exposure, some clients shared that receiving treatment for latent infection would prevent them from "passing it on" to others, describing this perception of either LTBI as infectious or as a way to avoid active infection and subsequent transmission:

> I'd rather know if I have it, so I can get cured of it, then go around passing it on to others. (P5, client [completed])

> Interviewer: Can you tell me a little bit about why you said yes to taking treatment?
> Participant: I don't know…I just feel like maybe I'm worried that if it got active I can pass it on, I just don't want to pass it on and give it to somebody else, right? (P8, client [delayed])

> I don't want to pass it on to anybody else, even though it's latent it can flare up. It could be active right fucking now and I don't even know. (P12, client [delayed])

Desire to know more

During the interview process almost all clients conveyed a desire to know more about TB. All asked questions about TB and latent infection and were eager to learn. Most reported that they received information about TB from their health care providers, however, a few reported that they learned about it from either a friend or family member. Some reported that although their health care provider communicated that they had latent infection, it was still unclear as to what this meant, and they sought clarification of their diagnosis during the interview process. Two clients share:

> Do I have TB... I want to see the doctor you know? I want to know 100% whether or not I have TB? (P4, client [discontinued])

> Participant: I don't have TB?
> Interviewer: No.
> Participant: How do you know?
> Interviewer: Because the medication that you were given, it's for sleeping TB, which means that it's inactive in your body. (P5, Client [completed])

Other clients suggested that more information should be made available about TB and LTBI to increase awareness and understanding of the need for treatment:

> Interviewer: So what I'm hearing is that providing a bit more education on TB would be helpful?
> Participant: Get more in-depth about TB because it could lead to other shit…that I didn't know… if it's not treated. I said, "Oh, fuck, this is serious" I'm learning shit about it that I didn't even fucking know. That's what I mean. You've got to explain more about TB and what it can do, like fuck, woah. (P12, client [delayed]

Barriers and Facilitators to Treatment Access, Uptake, and Adherence

Interviews with health care providers and clients identified several individual and social level barriers and facilitators to treatment access, uptake, and completion. A total of seven barriers and eight facilitators were identified. These themes and subthemes are summarized in Table 2 and results are presented in more detail below.

Table 2 Barriers and Facilitators to Treatment Access, Uptake, and Adherence

	Barriers	Facilitators
Individual level	• Competing priorities (e.g. addiction and substance use, unemployment, housing) • Side effects • Reaching clients	• Self-motivation • Desire to be healthy • Education
Social level	• Pill burden • Drug-interactions • Logistical challenges • Stigma and disease-related shame	• Health care outreach • DOPT • Ease of treatment regimen (e.g. dosing, duration, tolerated well) • Incentives • Collaboration

Barriers

Competing priorities: Instability related to homelessness and competing priorities were challenges to treatment uptake. One client discussed being "too busy doing other things," (P8, client [delayed]) which delayed treatment uptake. Another client described this as "too much shit in my head to worry about what's coming in the future or any sicknesses" (P5, client [completed]) when he was first offered preventive therapy. Many participants noted how

addiction and substance use inhibited them from accessing care, testing, and treatment for LTBI. One client, who reported that he was currently in recovery, offered insight into his priorities when he was using substances:

> When I was using, my drugs and alcohol were first, everything else was second. I think, before, when I was in addiction and drinking, I'd make a doctor's appointment and party-- Well, I guess I'll just miss that today. Well, I got five bucks, but I don't need bread and milk. I'd go to the liquor store and get three cans of beer. I'll worry about that later. (P6, client [completed])

In addition to addiction and substance use both clients and health care providers described how competing priorities related to unstable housing, unemployment and overall lack of a routine were barriers to starting treatment for LTBI. Participants noted how they felt the need to address these basic needs first before beginning treatment:

> I was trying to find money or work. Kind of saving. Just trying to stay clean. It's hard just to keep your sobriety when you're around everyone that's fucking doing it. It's hard. It's not like going to your house and cooking the meal and watching TV and go to bed. I got to live with that right now, buddy's helping me out with a place to stay, I'm helping him out, so kind of worked out a deal. Now I've got this housing, I'm making steps to get this TB-- but you got to get on the schedule and I got to get a place and then so have somewhere to go and I can get myself into that routine and then I can absolutely get on these medicines. Get rid of this TB. Get back my health. So I can get back to what I want to do. Right? (P12, client [delayed])

Health care providers provided confirming evidence that competing priorities and the unstable nature of client's lives were barriers to treatment initiation and completion. Many described how LTBI treatment is not always a priority for clients, and how that it can be a challenge for clients to maintain a schedule because of the unstable nature of their lives. One health care provider shared:

> It's hard for me to remember to take pills and I have a pretty structured, stable life. I was thinking, I guess you have your lack of housing or substance use, I think it's many orders of magnitude harder to remember to take a pill and to complete that pill just because it's not a priority and you don't have structure and order in your life. I think that's why I expected it to improve adherence. (P17, HCP [physician])

Side effects: A few clients who had initiated treatment reported intolerable side effects from taking 3HP. One in particular reported feeling abdominal pain, dizziness, and nausea while on treatment. This client stopped her treatment after one month and switching to an alternate regimen before she began a one-month religious fast (P4, client[discontinued]). Another client reported that he experienced diarrhea after starting treatment with 3HP, however, this resolved after the first few doses. Yet another client reported general pain and feelings of joint discomfort while on the regimen, which a HCP confirmed and reported was being managed with pharmacological treatment. HCPs all reported assessing clients for side-effects at each weekly dose in addition to monitoring routine bloodwork to assess for abnormalities. Most described the regimen as one that is well-tolerated. In line with the description of side-effects clients offered, however, a few HCPs indicated that nausea and abdominal discomfort were the most frequently reported complaints while completing the regimen.

Reaching clients: Almost all HCPs reported that connecting with clients each week, or "tracking them down," was a main barrier to treatment completion. HCPs described how, due to the transient nature of their clients' lives, they experienced difficulties in reaching the clients in order to dispense 3HP doses weekly. HCPs described the manpower required to find the clients each week, and reported that this took up a notable amount of their time. Locations for DOPT ranged from shelters, personal residences, public health centres, to meeting people on the street or local hangout spots. HCPs explained the need to be both resourceful and flexible in the process in order to complete the treatment regimen. As one HCP mentioned:

> The challenges would be just to connect with people. There's no stable address that we can always find them. Most of our clients don't have cell phones. Contacting them to try to arrange administering the medication is also a challenge. We spend a lot of time calling clients, old phone numbers, or their friends' phone numbers. Just try to connect. Then sometimes we might run into the client and not have the medication. Then we're running around to make it the most efficient as possible. I think also trying to not make it

> a huge inconvenience to the client. We want it to be something that they don't dread doing every week and we're not picking at them all the time to try to make sure it's finished. Because that can be annoying and then people don't want to do it. (P7, HCP [Indigenous cultural helper])

Pill burden: The number of pills taken at each dose was identified as a barrier to treatment initiation and completion. Many HCPs reported concerns regarding pill burden, stating "I knew the pill burden would be a big hurdle to overcome" (P18, HCP [registered nurse]) and described surprised or hesitant reactions of clients when they were made aware of number of pills required to take at each dose. In addition to concerns regarding the impact of pill burden on treatment completion, one physician also described the number of pills as being a deterrent to treatment acceptance and uptake:

> The biggest thing that limited people wanting to take or ability to finish the 3HP regimen, was the amount of pills. So, a lot of people, at least I can think of two people that didn't want to take it because there were just too many pills. (P19, HCP [physician]).

In keeping with HCPs, some clients reported concerns with the number of pills required at each dose. During the interviews, a client reported that it was "a lot of medication 1…2…3…4…5…12 at once," (P4, client [completed]) and some reported how they often felt unwell after their dose. One client shared the following:

> I think it was just the shock of the pills right…it might be a whole different situation for someone else, but for me that's a lot of pills. (P3, client [completed])

Drug interactions: A few HCPs made remarks related to drug-drug interactions, reporting that clients in the inner-city are often on multiple medications. Concerns with interactions between medications such as mood stabilizers and agonist therapies, including methadone and suboxone were reported. Because of the relative novelty and limited use of 3HP in Canada, physicians and nurses recalled not offering the regimen to clients because of these concerns.

> The unique challenges were mostly related to the physician's decision. Because with the clientele that we work with, this regimen interferes with the absorption of methadone and

> suboxone and mood stabilizing medication. The inner-city population has a high number of people being treated for addictions and mental health problems, and those are the most likely to be the ones that are stabilized through daily dosing at a pharmacy. They are already going to the pharmacy, that's part of the routine. Piggy backing 3HP on top of their regular daily travels is likely to be the most successful, but just due to how new the treatment was to us and how devastating it could be for people with mental health concerns or addictions to have their treatment interrupted by falling off the rails because of malabsorption of their medications. She [the physician] didn't want to have that influence on the community. (P18, HCP [registered nurse])

Logistical challenges: Logistical challenges related to both obtaining 3HP in Alberta and also pre-treatment requirements were barriers to access and uptake of 3HP. Prescribers (physicians and nurse practitioners) described the challenges with accessing 3HP as rifapentine is not yet licensed in Canada. Federal and provincial approvals were recounted as delaying access to treatment, as one provider described:

> First, we had to get access and go through- there was a special grant process because rifapentine is not licensed in Canada. We had to get access through this special mechanism hrough the federal government that allows us to import rifapentine. As part of that, we had to get approval from the Chief Medical Officer of Health in Alberta and to get approval from Medical Officer of Health in Canada we had to demonstrate that we had a protocol in place that would allow close follow-up with each patient. We had to develop a protocol, and because these patients were localized both in inner-city Edmonton and inner-city Fort McMurray, and the protocols for screening for this drug didn't exist, we had to develop them. It was a bit more difficult in Fort McMurray as well, because we hadn’t done a location based LTBI screening before, so it was a new process for us. (P17, HCP [physician])

Completing pre-treatment requirements were identified as factors that delayed treatment uptake. As one HCP (P9 [nurse practitioner]) explains “from a health systems approach, the availability of the lab, testing, and X-ray, are barriers to care.” Supply challenges in Fort McMurray, including delays in receiving QFT collection tubes and the medication itself, as well as the support clients required for completing pre-treatment tasks were factors that contributed to a delayed treatment start. HCPs noted how the more steps required and the longer treatment start is delayed, the more the risk of losing clients, or clients being unable to complete the regimen.

> Some of the pre-treatment stuff is a bit challenging. Trying to get anyone to do chest X-rays, sputum, blood work, it is a bit cumbersome, but it's manageable. It just takes time. I think for me that part of it I wish we could find a different way to get these people on treatment, without some of these major delays because with anything, you lose people along the way and the longer things are delayed, especially in an unstable population, you miss opportunities.(P18, HCP [registered nurse])

Stigma and disease-related shame: Perceptions of stigma related to LTBI and TB were described by clients as well as feelings of disease-related shame related to their diagnosis. When asked whether or not clients shared their diagnosis with others, the majority reported that they kept it private and that TB was not discussed among their peers. A few participants shared:

> No, because the way I see it here, if anybody got anything, they don't tell nobody, because that way, they are not embarrassed themselves-- or where do you get it? That's the way it is here. I know of somebody else who was taking the same thing I was, but we never sat down and talked about it or anything. I haven't seen her for a while, but I know she's around. She was pretty well going in the same time I was in. I knew, without saying a word. (P6, Client [completed])

> Interviewer: When you were first told that you had the latent or the dormant infection did you share that with anyone?
> Participant: I don't tell anybody's anything like that. They will tell me, “Ah you gotta a disease- Get away from me." That’s why I don’t, you know? (P8, client [delayed])

> Interviewer: Can you tell me a bit more about why you don’t talk about it with friends or family?
> Participant: You have TB you know? That’s why... you don’t tell anybody (P2, client [completed])

In relation to stigma, some clients described feelings of shame connected to their diagnosis of LTBI. One described a sense of guilt and “feeling bad” (P2, client) when told of his diagnosis while another became emotional as he described how his relationship had changed with his partner after he shared his diagnosis:

> Interviewer: Did you tell any of your friends or family when you were first told you had sleeping TB?
> Participant: Ahh… I told my common law
> Interviewer: Oh yeah, and did that affect your relationship at all?
> Participant: Yeah it did
> Interviewer: It did? How so?

> Participant: [crying] it was them… not me… was them... they blamed me... [crying] like I got a fuckin disease... like I'm fucking the worst fucking person in the world... I had fuck all to do with it… nothin to do with it... here I'm getting the brunt of everything. (P3, client [completed])

Although most participants described satisfaction with directly observed preventive therapy (DOPT), which is described in more detail below, a couple of participants spoke to the need for a more "private" space in order to maintain confidentiality and reduce experiences of stigma.

Facilitators

Self-motivation: When clients were asked to share what factors made treatment easier to complete, many went on to describe how they were self-motivated to complete preventive therapy. Clients relayed how the choice to accept treatment was made by themselves. This helped to contribute to a sense of determination to complete therapy despite competing priorities. Two shared:

> It doesn't matter if I'm drinking beer or whatever… I'm going to go do all those pills. If you got the will you got the way, right? (P3, client [completed])

> Interviewer: Is there anything that made taking the medication easier for you?
> Participant: No. Just like if that was going to help, that was whatever I was going to do. Even if I wasn't housed, I probably would have done it. Like I mean… I bought myself a new mountain bike. It meant cutting back on a couple things on groceries, but I got lots in the fridge, because that's what I wanted. If you want it, you go for it. Otherwise, I wouldn't have done it [taking treatment]. If you don't look after yourself, nobody else is going to. (P6, client [completed])

Related to this description of self-motivation for completing therapy, participants also shared how they felt a sense of accomplishment and pride once they finished their treatment. As one participant expressed:

> I'm proud that I completed all the medications, taking them all. Because of all the pain that I went through, but I still pushed myself. I feel happy I completed those medications. (P14, client [completed])

A few HCPs also made comments regarding the self-motivation of their clients as a determining factor for treatment completion. HCPs noted how clients expressed a drive to complete their treatment and shared a sense of accomplishment once completed. HCPs reinforced this by helping clients to celebrate the end of treatment. As one HCP described:

> The ones that continued to the end were the most focused on preventing TB before we even got started. You can tell when people are motivated and saying, "Yes, I want to do this." "You know there's a lot of pills," and they go, "That's okay. I want to do this and I want to get it over as soon as possible." The duration of treatment was important to people and they weren't easily swayed from their target by possible side effects. The ones that were the most motivated to prevent TB in the future were the ones that were successful. (P18, HCP [registered nurse])

Desire to be healthy: Clients conveyed that taking treatment for LTBI fit within the bigger picture of a desire to achieve and maintain health. They often described how they were ready to "get back to being healthy" (P12, client [delayed]) and how taking treatment was a part of that process. One participant described that taking medication is "good for you and good for your health" (P2, client [completed]) while another conveyed "I'm getting up in age, so I want everything checked… everything. Make sure I can get an extra week out of my life. I want to try to get as healthy or know what's wrong before I hit 65" (P6, client [completed]). Participants described using the treatment regimen as an opportunity to put themselves and their health first, while also describing a history of disregard for their health while living on the street, being in active addiction and attending to other priorities. One participant shared why he accepted treatment, although he had not yet started:

> Because I wanted to get cured. I wanted to know my health will be okay, to be fine. That's why I decided to take it. This has got to change my life. Good things that are happening so I want to be all focused on that. Stay clear on liquor. I got to stay clear from liquor and drugs, that's that. I also have-- I'm a diabetic type two and I also have Crohn's disease and COPD. So there's a whole bunch of other stuff, like I'm on puffers and I haven't been taking nothing [laughs]. That's bad right…but it's time to smarten up. Right? That's why I'm here today. To get my meds, get this all on track. Enough is enough right? (P12, client [delayed])

Education: HCPs highlighted that education about LTBI and preventive therapy facilitates treatment acceptance, and completion. Providers reported that clients were receptive to education and more likely to accept preventive therapy if they understood latency, the need for treatment and the difference between latent and active disease. As one HCP shared:

> I think they [nurses] did a really good job of just helping the clients understand what the medications were for. Helping them understand the difference between latent and active I think is a big one for getting a lot of the clients on board because their immediate reaction is like, "ah I have this," so just that education piece is important. (P10, HCP [social worker])

When discussing education, most HCPs reported that one on one education, and using plain language were the most effective strategies. In addition to one-on-one education between provider and client during a clinic appointment, supplementary resources are provided to be read off-site – these are mostly in the form of information sheets and pamphlets; these resources are often lost by clients experiencing homelessness. As a result, the information provided during appointments is the most critical.

Health care outreach: Programs that provide mobile outreach health care at shelters and drop-in centres accessed by participants facilitated LTBI testing, and treatment uptake and completion. Clients noted how they first learned about TB screening through outreach services either at a drop-in centre, or mobile outreach. Some shared their experiences in accessing care through the shelter or at sites they frequently visited, and how these services supported adherence and completion of their treatment:

> I would take the medication in the afternoon…I go for lunch at the salvation army church. So then I see the nurses there and say, "Oh, are you coming in this afternoon?" Then I know it's open and I can take my medication. (P14, client [completed])

> I didn't know about the medication until I come here. If I didn't come here. I wouldn't have taken it. I would have stayed at my stepmom's. I didn't like it up there either, that's why I stay at the shelter. (P5, client [completed])

Likewise, HCPs commented that outreach and meeting clients "where they are at" helps to facilitate treatment completion. As previously described, HCPs reported great diversity in the locations and environments where weekly treatments are provided, and noted the importance of services being accessible. As two indicated:

> Bringing the medication to them. In my case, I haven't had anybody that's gone to a pharmacy to get it, but a convenient location. Convenient location for them to go to with convenient hours or myself or an outreach team going to them and providing them the medication (P16, HCP [registered nurse])

> We would try to organize the clients to always administer it on Tuesdays because we're at the shelter then. If we didn't see them, we would go to places we knew they stayed at and see if they're around to take it. We'd sometimes just carry it [3HP dose] in our vehicle so that we would always have it in case we ran into them, to give it to them within the closest time frame that we could. All over town, which is the nature of our team anyways so it makes sense for us. (P7, HCP [Indigenous cultural helper])

DOPT: Clients reported positive experiences of DOPT, which helped with treatment adherence and completion. Clients reported that the continuity of receiving their treatment by weekly DOPT provided an opportunity to develop more meaningful relationships with their providers, ensured that treatment was completed and administered correctly, and overall improved their treatment experience. As one patient described:

> Interviewer: What was your relationship like with the outreach nurse?
> Participant: Well, she's a friend afterwards. She started to give me the medication over and over and over and again and again and again. We became friends, and that's more important to me than anything else. I'd rather have friends than enemies. (P5, client [completed])

Many clients shared their appreciation of the caring attitudes of the health care team and described how this encouraged them to complete their treatment:

> Interviewer: Having the nurse and the outreach team come meet you to give you the medication, do you think that helped you to complete the treatment?

> Participant: Oh definitely. I realized how caring they are too and you know it's like they're taking the time for me and I'm not going to be wasting somebody's time that cares… very much. (P14, client [completed])

When asked if they would have preferred to take treatment on their own, as self-administered therapy (SAT), almost all participants expressed that it was unlikely they would take it on their own and preferred the support provided by receiving the treatment through direct observation. HCPs reported that DOPT is critical for ensuring that treatment was completed in whole among those who have risk factors for treatment non-completion. Both clients and providers noted how the instability in their lives, such as substance use, forgetfulness and not having a secure place to store their medications, would make it challenging to complete on their own:

> Yes, it's a lot like-- the people on the streets, yes, they should do that [DOPT] because they're giving the pills to them… because most of them will still be drinking, wouldn't even bother taking the pills or nothing. Yes, I recommend. (P13, client [completed])

> I think with our population it would be really hard to know what the compliance looked like if it wasn't directly observed, not because our clients aren't capable of doing it but because those things are just sometimes easily forgotten or the importance of it isn't understood at the time or they also if they're homeless you don't always have a place to go and so when the client says, "I don't feel like taking it right now," but it could get lost between now and an hour from now and you don't have a solid place to put down your personal items, I think that's a big piece that's actually really important for this population which is to actually see is the only way to know that is actually taken. (P10, HCP [social worker])

Both HCPs and clients relayed how receiving DOPT weekly also provided a means to connect and follow up on other needs as well, such as housing, employment or other health-related concerns. As one HCP shared:

> It was nice to have a motivation to see them and they have a reason to see us. It's a link and we might be there to administer the medication, but you end up providing supports for housing or bringing warm clothes or something like that. I definitely don't think that the challenges are a reason to stop doing it, but I do think that there needs to be teams like this one or community support services in place. (P7, HCP [Indigenous cultural helper])

Ease of 3HP regimen: Both HCPs and clients appreciated the once weekly dosing, and the shortened duration of the 3HP regimen relative to other options for preventive therapy. Most clients tolerated the regime well when asked to describe their treatment experience. Clients reported that taking treatment was "easy" and "just like anything else" (P6, client [completed]) and appreciated that you complete the regimen once and then it's done. When asked if they were offered conventional therapy (e.g. 4 months of rifampin or 6-9 months of daily isoniazid self-administered) instead of 3HP, some clients reported that it was unlikely they would be able to complete these regimens on their own:

> There's no way. I know I'd fuck up, forget a day or whatever. I hate pills, right? (P12, client [delayed])

HCPs also reported their preference for the 3HP regimen in comparison to treatment regimens with more frequent dosing and longer durations. They shared how the once per week dosing was more manageable. In inner-city Fort McMurray, one provider shared how she felt that the regimen facilitated treatment completion in individuals that likely would not have succeeded on conventional treatment:

> I'd say that this 3HP regimen is very attractive for anyone that would—it's the regimen itself is fast. It's not pills every day. It's pills once a week. We've successfully completed five, we have a couple that are waiting. It's a small population and I do think that those little successes-- It doesn't seem like lots of numbers, but that's five more people than we ever would've gotten on treatment before. I guarantee it. (P11, HCP [registered nurse])

Overall all HCPs reported that the regimen, which includes a greatly shortened duration and less frequent dosing, can improve treatment acceptance, uptake, and completion in populations with psychosocial barriers to treatment completion especially. As one provider indicated:

> I see it [3HP] as being a way to improve adherence to LTBI in high risk populations. I feel that its target group is those populations where frequent dosing or frequent DOPT is more difficult or labor intensive. With this, it's just the 12 doses, it makes it easier on

> outreach staff as well as on the patient. That's where I see it targeting. I find that trying to get in the 12 doses is a lot easier than a longer LTBI regimen. (P19, HCP [physician])

Collaboration: HCPs expressed the importance of collaboration both within the team, and with outside organizations or agencies as key to supporting treatment access, uptake, and adherence among clients. Different members offered unique supports to clients, in collaboration with other agencies such as pharmacies, additional shelters and treatment centres and health services including diagnostics and imaging was required for treatment completion. As one provider shared:

> The healthcare resources were our team. We used the recovery workers or we worked a lot with the nurses. We had to use the lab for doing routine bloodwork. We had to use the diagnostic imaging when we were doing our first screening to make sure that it's not active. The medication which specifically came from Edmonton and the TB nurse herself. Then the physician is involved so quite a lot of resources for one client but collaboratively ends up with good results. I think that that just shows, that's what you need for a good result. (P9, HCP [nurse practitioner])

Incentives: Providers reported that the use of incentives supported treatment adherence and completion. Although there were no formal incentives used in either Fort McMurray or Edmonton, HCPs reported that often informal incentives, such as coffee, bus tickets, a small meal or transportation often motivated clients to meet for their weekly dose. One provider shares how incentives can be used to encourage treatment completion:

> I really believe in incentives as well. You may not think about it, but $10 gift card or whatever every two weeks or every time you get your blood work done, somebody that has to live on $30 a week grocery money, that's a big chunk of money. You're talking about 10% increase in your grocery budget if you have to go twice a month for blood work, so it doesn't sound like a lot to us, but in cases where communities have an increased TB rate, so I think it's a great idea to encourage people with incentives, just to keep it in their mind. (P18, HCP [registered nurse])

Chapter 5: Discussion

This study sought to qualitatively explore the knowledge and understanding of LTBI and the barriers and facilitators of preventive therapy access, uptake and adherence, using a shortened regimen, (3HP), among individuals experiencing homelessness and their health care providers. The study is novel in that it is the first study in Canada to qualitatively explore the use of 3HP. Using a qualitative descriptive approach, ten individuals offered treatment with 3HP as well as nine health care providers with direct experience in administering the regimen were interviewed. Interviews with clients and health care providers provided insight into a wide range of individual and social level factors impacting preventive therapy access, uptake and completion.

The findings revealed that knowledge of LTBI varied among individuals offered treatment for preventive therapy. Interviews suggested only a moderate understanding of the difference between active TB disease and latent infection, and even poorer understanding of transmission risks. Although some clients associated transmission with coughing, many described transmission to be influenced by behaviours, such as sharing cigarettes and alcohol, and overall involvement in street life. Clients indicated an understanding of the need for treatment to "kill" TB bacteria, however, many also implied that this would reduce their risk of "passing it on," indicating a misunderstanding of the lack of infectiousness associated with LTBI. Clients requested additional information about LTBI during the interview process and raised questions regarding the difference between active TB and latent infection, transmission, treatment and prognosis. These results are consistent with a modest understanding of LTBI identified in other studies. This includes limited knowledge of LTBI shown among both HCP and patients, as well as study participants engaging with TB education and identifying how

education can support treatment uptake and adherence.[21,89,90,111,112] In this study, clients identified how receiving education on LTBI from their HCP improved their understanding of their diagnosis and the use of preventive therapy. Some clients indicated that an increased awareness of the seriousness of LTBI as it pertains to TB disease, and the value of preventive therapy to halt that transition could improve uptake and adherence.

Findings from interviews with clients and HCPs revealed multiple barriers and facilitators to 3HP treatment access, uptake and adherence. Competing priorities, difficulty in reaching clients, undesirable aspects of the regimen (e.g. side effects, pill burden and drug interactions) and arduousness related to obtaining and initiating 3HP were identified as barriers to access, uptake, and completion. These results are consistent with barriers identified in other studies. In a study that examined multi-level barriers to LTBI treatment among Latino adolescents, Hill et al highlighted that many participants required numerous contact attempts for prompting and assistance to complete pre-treatment tasks, suggesting an increased risk of loss to follow up at each stage of the LTBI cascade of care.[111] This was true in our study as well, with HCPs remarking on how pre-treatment requirements delayed treatment uptake and reduced the chance of treatment initiation. In studies exploring LTBI treatment adherence among individuals experiencing homelessness, it has been shown that competing priorities related to meeting basic needs and/or addiction and substance misuse can hinder adherence and completion.[79,81] In our study, many clients stated that competing priorities related to finding housing, employment or addiction and substance misuse were reasons for declining or delaying 3HP uptake and/or treatment interruptions. HCPs also reported difficulty in reaching clients often related to instability in their lives and lack of attention to LTBI. Specifically to 3HP, HCPs in a mixed methods study in the United States identified similar programmatic and follow up challenges

encountered as well as patient difficulty with the pill burden of the regimen.[81] Although clients and HCPs reported on the positive aspects of DOPT, which is described in more detail below, the requirement of 3HP to be directly-observed can be interpreted as a policy barrier to treatment completion. Receiving LTBI treatment via DOT can be viewed as unacceptable to clients who are completing therapy as a preventative measure and can be excessively costly to TB programs.[113] In our study, HCPs commented on the difficulties they encountered in reaching clients for their weekly dosing, remarking on the amount of resources and time required to do so, with clients reporting that competing priorities often interfered with their weekly appointment. This has been described in the literature as a barrier to using 3HP, and studies have demonstrated similar completion rates when 3HP is self-administered.[113,114] However, it is important to note that these studies are based around populations who may require less psychosocial supports for treatment completion than individuals who are unstably housed or experiencing homelessness. Furthermore, although recent changes to the CDC guidelines suggest 3HP can be administered by either DOT or SAT, in Canada, Rifapentine is only available through the Government of Canada's Special Access Programme and not yet licensed for sale.[115] As adverse events may be common and are not yet well understood, further evaluations on the safety profile of the regimen is needed, and support administration by DOPT.[54]

With regard to facilitators, our study revealed multiple factors that contribute to improved preventive therapy access, uptake, and adherence using a shortened treatment regimen, 3HP. Clients self-motivation and desire to be healthy, alongside education, health care outreach, relationships through DOPT, ease of treatment regimen, incentives and collaboration were described as supporting successful treatment outcomes. These results are aligned with existing literature on strategies to improve adherence to LTBI preventive therapy. Existing studies have

demonstrated the effects of incentives on increasing completion rates among LTBI patients with psychosocial barriers to treatment adherence, including a study by Tulsky et al which demonstrated an 18% increase in completion rates among adults who were homeless in the United States and a study by Chaisson et al which found that among persons who use drugs (PWUD) who received immediate incentives had higher LTBI preventive therapy completion rates than those who received deferred incentives (83% vs 75%).[78,116] As in the literature, our own findings indicate that educational outreach and nurse-led case management, including healthcare outreach, psychosocial support and linkages to medical and social services were found to support treatment uptake and adherence.[89,90,92,112,117] DOPT was identified as a way to facilitate this in our study, with clients referring to developing relationships with their care provider through the duration of their treatment at their weekly visit for observed dosing, and HCPs reporting the same, stating that the weekly DOPT appointment promoted relationship building and provided an opportunity to discuss and follow up on other health and social related matters in addition to ensuring the treatment was completed. The shorter treatment duration and less frequent dosing of the 3HP regimen were identified as facilitators to treatment uptake and adherence in our study by both clients and HCPs. Clients reported that they would be unlikely to complete both a longer daily regimen and preferred DOPT over SAT, and HCPs suggested that completion rates for standard LTBI preventive therapies would be lower among this population. This is supported by the literature, which has demonstrated that shorter treatment regimens with less frequent dosing are more likely to be adhered to than regimens of longer duration and more frequent dosing.[118]

Perceptions of stigma related to LTBI and TB were described by clients as well as feelings of shame or embarrassment related to their diagnosis. In other literature examining

beliefs and attitudes towards LTBI, studies have shown similar experiences of stigma. In a study by Joseph et al examining health care workers adherence to occupational TB screening and treatment, stigma was associated with TB disease and infection, with participants noting that they were treated differently by co-workers who may not have understood the difference between LTBI and TB disease.[90] Furthermore, perceived associations of TB with poverty, malnutrition, lifestyle choices and substance abuse, as well as negative stereotypes of individuals experiencing homelessness may contribute to the heightened sense of stigma expressed in our study population.[90,119] Among foreign-born individuals, immigrants, and refugees negative feelings and perceptions of TB including shame, secrecy, isolation and fear contributed to stigma experienced by those diagnosed with LTBI and hindered TB control.[89,120,121] We identified comparable findings in our study, as when asked about sharing their diagnosis with others, most clients reported that this was kept private and LTBI was not something they discussed among their peers. Further research examining how stigma impacts screening rates among underserved populations as well as the stigma experienced by those diagnosed with LTBI and its effect on preventive therapy uptake and adherence is needed.

Although not used to guide our analysis, findings from our study resonate with the Health Belief Model (HBM), which may be used to inform TB models of care and program delivery. As reviewed earlier in this thesis, the HBM focuses on individual level behaviour change including beliefs and perceptions, and has expanded to include the influence of demographic, structural, and psychosocial factors as mediators on individual perceptions and likelihood of health-related action.[94,95,97] Within this model, an individual engages in preventive health behaviours based on perceived susceptibility and severity of disease, and benefits and barriers of the recommended treatment or health intervention. Our results demonstrate that perceived susceptibility is

influenced by both knowledge and misunderstandings of TB and its transmission, as well as the risk of progression of LTBI to active disease. Perceived severity or threat of LTBI/TB was expressed through participants remarking about the progression, seriousness and ultimate risk of dying from the disease. Perceived benefits of preventive therapy were conveyed by clients who referred to how completing therapy would kill bacteria and eliminate the risk of transmission to friends or family, and also more broadly, how completing treatment was seen as a part of achieving wellness and improving health. Perceived barriers to preventive therapy uptake, adherence, and completion from a client's perspective included competing priorities and undesirable aspects of the regimen, including side effects and pill burden. These domains highlight areas for HCP practice implications, such as increasing education and awareness of TB/LTBI and modes of transmission, acknowledgement of perceptions and fears surrounding TB, and improving accessibility to preventive therapy. This is discussed further in the public health practice and policy implications section of this thesis.

From a socio-ecological perspective, our study demonstrates both individual and social level factors that may act as barriers and facilitators to preventive therapy access, uptake, and adherence using 3HP among individuals experiencing homelessness. In exploring our findings in the domains of the HBM, it is important to consider the impact of socioenvironmental factors on preventive therapy behaviours. Preventive therapy uptake and adherence behaviour can be viewed as a product of individual and environmental interactions. This further reveals the importance of responding to the interplay between both macro-level factors (e.g. logistical requirements, health care outreach) and micro-level factors (e.g. individual motivation, competing priorities) in treatment of LTBI among individuals experiencing homelessness and/or other psychosocial barriers to preventive therapy completion.

Public Health Practice and Policy Implications

The results of this study may inform the development of interventions and health policy to promote LTBI preventive therapy uptake and completion among underserved populations. As knowledge has been shown to be a facilitator of adherence, and lack of knowledge was identified in our study, targeted education on LTBI and TB may improve LTBI screening and preventive therapy uptake and completion among individuals experiencing homelessness. [90,112] This could be provided through health care outreach and routine educational sessions at shelters or inner-city locations where clients frequent, as well as through accessible educational brochures or infographics at outreach locations or during targeted screenings. Furthermore, the context of the risk or prevalence of TB in the community could also be included in education for both clients and providers. For example, as mentioned earlier in our study, Fort McMurray has been experiencing a smouldering outbreak of TB in their inner-city over the last decade, however this was not mentioned in interviews with clients. Increasing awareness of this outbreak among inner-city populations and health care providers may favourably influence the uptake of screening and preventive therapy if offered. Strategies to address barriers identified in our study may include providing incentives to clients throughout their treatment duration and once completed, such as food or transportation vouchers or cash incentives.[118] Continuing to provide mobile health care services, nursing outreach, and social support to individuals experiencing homelessness and/or other psychosocial barriers, can support preventive therapy success. This may include expanding services to treatment centres and also flexibility on who administers DOPT, such as a shelter support worker, community outreach worker or pharmacist which may also lessen the burden on the health care team of having to locate clients for weekly dosing. Our study also highlights the potential of more integrated models or approaches to care. In Fort

McMurray, care was provided to clients in the study through the "street connect" team- a multidisciplinary team which provides health care outreach and social support to underserved populations. Integrating biomedical or communicable disease systems care with social services, and ensuring services are accessible and reach target populations, while reducing the silo's in primary health care for individuals with complex health and social needs, can support TB care and adherence to treatment. This is an area of programmatic research which requires further exploration. In the 3HP regimen for adults, 900mg rifapentine (6 x150mg tablets) is taken with 900mg isoniazid (3 x 300mg tablets) alongside vitamin B6 for a total of 10 tablets per week. Lowering the pill burden by using a simpler fixed-dose combination (e.g. three tablets combined rifapentine 300mg and isoniazid 300mg) may improve treatment acceptance and adherence rates.[122] Further research and advocacy to pharmaceutical suppliers is needed. Additional advocacy to pharmaceuticals companies to apply for licensing of Rifapentine in Canada may lead to improved access. Furthermore, streamlining of pre-treatment requirements to reduce delays to treatment initiation may also improve uptake and adherence. This may be accomplished through mobile x-ray and/or lab collection. As identified in our study, clients who were self-motivated were likely to succeed with treatment completion, including motivational interviewing, adherence coaching and self-esteem counselling as well as peer-based interventions may also improve completion rates.[118]

Interventions and health policy should also address the stigma and shame associated with LTBI and TB and reduce their health impacts. Stigma and shame related to TB are often fuelled by misperceptions of transmission, disease severity, and a lack of understanding the difference between latency and active disease, however, these negative perceptions are attenuated by exposure to TB education.[89,120,123] Along with increasing educational outreach to facilitate

preventive therapy uptake and adherence, education may also be a way to diminish the social stigma surrounding TB. [90] HCPs and TB programs should also be cognizant of locations for DOPT to promote patient confidentiality and minimize perceptions of feelings of stigma among clients receiving treatment. Additionally, peer support and the development of "TB clubs" which meet, or are facilitated online, offer social and treatment adherence support which can empower individuals with TB and change broader community norms around negative attitudes and perceptions surrounding TB.[119] The introduction of a peer model that includes individuals diagnosed with TB for individuals experiencing homelessness or other psychosocial barriers to treatment adherence, may support preventive therapy uptake and completion.

Lastly, and arguably most importantly, is that interventions to support preventive therapy access, uptake, and completion do not occur in isolation from attention to and improvement of social determinants of health that confound TB elimination efforts. As mentioned earlier in this thesis, TB is a social disease as much as it is a biomedical condition and preventive therapy is an important part of a larger effort to prevent TB.[122] TB is a symptom of social inequity and requires socioeconomic interventions, including addressing poverty and homelessness. On a larger scale, national poverty reduction has been shown to reduce TB incidence.[122,124] Furthermore, prior to the discovery and use of antibiotic therapy to treat TB, reductions in TB incidence were made through improvements in socioeconomic conditions.[125] While our study identified ways to support and facilitate preventive therapy access, uptake and completion, we do not intend to draw attention away from the social conditions which foster TB transmission and incidence rates among at-risk populations. In examining TB adherence among an inner-city population in Edmonton, Peter De Vos[126] eloquently explains this dynamic:

> 'The insistence on treating the issue of adherence in isolation from the precipitating factors of poverty and powerlessness perpetuates a "blame the victim" mentality—that

> effectively deflects criticism from the inequalities inherent in the larger socio-political structure, of which medicine is a part' (p.134)

Advocacy efforts related to poverty reduction, housing first programming and addressing social determinants of health related to TB should be encompassed within TB programs. Due to the complexity of TB and the interaction of multiple social determinants of health, TB is a "wicked problem," and requires a collective, whole systems approach to care and in efforts to reduce rates and ultimately achieve elimination.

Limitations

This study faces a number of limitations. Firstly, the sample size was limited due to a variety of factors. A limited number of individuals were offered and either declined, discontinued, or completed 3HP during the study time frame due to restrictions imposed by both the timeline associated with degree completion, and the logistical constraints of access and use of the regimen within the Provincial TB program. In addition, the transient nature of the population and as mentioned in the discussion, competing priorities created challenges for client recruitment. Given the relatively small sample, the generalizability of findings may be limited. Another limitation includes the limited time spent by the researcher in the community, particularly in Fort McMurray, where the duration of stay was for a fixed period during data generation. As such, the researcher relied heavily on the relationships of the providers with the clients to facilitate recruitment. This reality has the potential to cast the researcher as an "outsider" to the community, which, in turn, may have impacted the interview process and data generation with clients, producing more superficial findings. Finally, due to logistical constraints, member checking was only completed with HCPs and the researcher was not able to review findings with the clients to ensure accurate interpretation of their interview data. However, completing member checking with HCPs who had extensive experience in TB

outreach and working with the population added to the rigor of the study and dependability of the results.

Strengths

Notwithstanding these limitations, this study also has a number of strengths. This is the first qualitative study to explore the use 3HP from both a client and provider perspective and adds to the rather limited existing literature exploring perceptions of LTBI and treatment adherence among individuals who are unstably housed or homeless and who face barriers to treatment completion. Through using qualitative methods, we captured the expressive and meaningful voices of those who are not often represented in TB research and who are at risk of developing active disease. By sharing their stories, this research can inform and support patient centered care for those diagnosed with LTBI or TB. The experience of the researcher in practice and care of clients and patients with communicable disease added strength to this study as well as the rigour of the analytic strategy. This insight gained from this study may be used to advise the provincial TB program in Alberta and improve TB control and LTBI preventive therapy access, uptake, and completion among underserved populations.

Knowledge Translation

Findings from this thesis will be disseminated using appropriate mediums to a variety of audiences. To reach inner-city populations, an infographic for TB/LTBI that could be advertised at shelters or other inner-city agencies will be developed and shared. To reach health care practitioners and/or policy makers, this study will be shared through an educational session offered to the Provincial TB Program and other TB working groups in Alberta and Canada. To reach a wider audience and researchers, this thesis will be developed into a manuscript for publication.

Conclusion

Individuals experiencing homelessness who have latent tuberculosis infection are less likely to complete preventive therapy. This study is the first in Canada to qualitatively explore the use of 3HP and adds to the small but growing body of literature on LTBI and use of this regimen. Our study used qualitative descriptive method to explore the understandings of LTBI and the barriers and facilitators to preventive therapy access, uptake, and adherence among individuals experiencing homelessness and their health care providers using a shortened treatment regimen, 3HP. Our study provides insight into the knowledge and understandings of LTBI and the multiple psychosocial factors which interact to influence preventive therapy access, uptake, and adherence. Removal of the LTBI reservoir, referred to as the "seedbeds" of tuberculosis, is key to TB elimination and a critical component of the World Health Organization's End TB strategy. Findings from our study can be used to inform health policy and TB programming aimed at removal of this reservoir and to address TB inequities among individuals experiencing homelessness.

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PARTICIPANT CONSENT FORM

Title of Study: *Management of LTBI among an inner-city population and those with psychosocial barriers to treatment*

Principal Investigator: Dr. Cam Wild and Dr. Richard Long

Research/Study Coordinator: Amber Lynn

Why am I being asked to take part in this research study?

You are being asked to participate in this study because you are a health care provider with programmatic and/or clinical experience in using 3HP for treatment of latent infection among individuals who are unstably housed or homeless.

Before you make a decision one of the researchers will go over this form with you. You are encouraged to ask questions if you feel anything needs to be made clearer. You will be given a copy of this form for your records.

What is the reason for doing the study?

The purpose of this research is to explore what latent or "sleeping" TB means among those living in the inner-city and to describe the treatment experiences, using 3HP, among persons who are unstably housed or homeless. To supplement this information, we are conducting interviews with health care providers who have programmatic and/or clinical experience using 3HP in the inner-city and in this population. We aim to increase understanding of treatment decisions and experiences to inform and improve TB prevention efforts.

What will I be asked to do?

- This study will take approximately 1 hour of your time and you will be asked to complete an interview to discuss your experiences and perceptions of using 3HP in this population

What are the risks and discomforts?

- There are no identified risks of participating

What are the benefits to me?

- Participating in interviews during this research study may be helpful to you and provides an opportunity for you to share your story
- This study may help other people with latent TB in the future
- However, you may not get any benefit from being in this research study

Do I have to take part in the study?

- Being in this study is your choice. If you decide to be in the study, you can change your mind and stop being in the study at any time, and it will in no way affect the medical care or treatment that you are entitled to
- During the interview process you do not have to answer any questions that you are uncomfortable with
- You will have 7 days after the interview is completed to reflect on the information shared and to withdraw from the study (including removal of the information you've shared) if you choose

Will I be paid to be in the research?

- A $10 gift care to Starbucks will be offered to for health care providers for participating in this study

Will my information be kept private?

- During the study we will be collecting data about you. We will do everything we can to make sure that this data is kept private. No data relating to this study that includes your name will be released outside of the researcher's office or published by the researchers. Sometimes, by law, we may have to release your information with your name so we cannot guarantee absolute privacy. However, we will make every legal effort to make sure that your information is kept private

By signing this consent form you are saying it is okay for the study team to collect, use and disclose information about you from your personal health records as described above.

After the study is done, we will still need to securely store your health data that was collected as part of the study. At the University of Alberta, we keep data stored for a minimum of 5 years after the end of the study.

If you leave the study, we will not collect new health information about you, but we may need to keep the data that we have already collected.

What if I have questions?

If you have any questions about the research now or later, please contact Amber Lynn at 403-829-6881
If you have any questions regarding your rights as a research participant, you may contact the Health Research Ethics Board at 780-492-2615. This office has no affiliation with the study investigators.

Appendix B: Participant Consent Forms and Information Sheets (Client and HCP)

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PARTICIPANT CONSENT FORM

Title of Study: *Management of LTBI among an inner-city population and those with psychosocial barriers to treatment*

Principal Investigator: Dr. Cam Wild and Dr. Richard Long

Research/Study Coordinator: Amber Lynn

Why am I being asked to take part in this research study?

You are being asked to participate in this study because you have been diagnosed with latent or "sleeping" tuberculosis and you are currently unstably housed and/or experiencing homelessness. You have also been offered treatment with "3HP", and may have declined, started, or completed your treatment.

Before you make a decision one of the researchers will go over this form with you. You are encouraged to ask questions if you feel anything needs to be made clearer. You will be given a copy of this form for your records.

What is the reason for doing the study?

The purpose of this research is to explore what latent or "sleeping" TB means among those living in the inner-city. We aim to increase understanding of treatment decisions and experiences to inform and improve TB prevention efforts.

What will I be asked to do?

- This study will take approximately 1 hour of your time and you will be asked to complete an interview to discuss latent or "sleeping" TB and any treatment experiences you have had
- With your consent, allow access to your medical records related to tuberculosis
- With your consent, allow storage of study information in a secure data repository to facilitate future research

What are the risks and discomforts?

- Risks to participating in this research are minimal, however, there is a possibility that the interview process may cause an emotional response or traumatic memory related to tuberculosis
- To lessen this risk, the TB outreach nurse is able to provide support and education to you and support services are available. It is not possible to know all of the risks that may happen in a study, but the researchers have taken all reasonable safeguards to minimize any known risks to a study participant

What are the benefits to me?

- Participating in interviews during this research study may be helpful to you and provides an opportunity for you to share your story
- This study may help other people with latent TB in the future
- However, you may not get any benefit from being in this research study

Do I have to take part in the study?

- Being in this study is your choice. If you decide to be in the study, you can change your mind and stop being in the study at any time, and it will in no way affect the medical care or treatment that you are entitled to
- During the interview process you do not have to answer any questions that you are uncomfortable with
- You will have 7 days after the interview is completed to reflect on the information shared and to withdraw from the study (including removal of the information you've shared) if you choose

Will I be paid to be in the research?

- A $20 gift card to 7/11 and a tobacco offering will be provided to you for your time and for sharing your story
- If you decide to withdraw from the study during or after the interview process, you will still be compensated

Will my information be kept private?

- During the study we will be collecting data about you. We will do everything we can to make sure that this data is kept private. No data relating to this study that includes your name will be released outside of the researcher's office or published by the researchers. Sometimes, by law, we may have to release your information with your name so we cannot guarantee absolute privacy. However, we will make every legal effort to make sure that your information is kept private
- The investigator or their study staff may need to look at your personal health records or at those kept by other health care providers that you may have seen in the past (i.e. your family doctor). Any personal health information that we get from these records will be only what is needed for the study

By signing this consent form you are saying it is okay for the study team to collect, use and disclose information about you from your personal health records as described above.

After the study is done, we will still need to securely store your health data that was collected as part of the study. At the University of Alberta, we keep data stored for a minimum of 5 years after the end of the study.

If you leave the study, we will not collect new health information about you, but we may need to keep the data that we have already collected.

What if I have questions?

If you have any questions about the research now or later, please contact Amber Lynn at 403-829-6881
If you have any questions regarding your rights as a research participant, you may contact the Health Research Ethics Board at 780-492-2615. This office has no affiliation with the study investigators.

TUBERCULOSIS PROGRAM EVALUATION AND RESEARCH UNIT
FACULTY OF MEDICINE AND DENTISTRY

3rd Floor, 8334A Aberhart Centre
11402 - University Avenue, NW
Edmonton, AB T6G 2J3
Tel: 780.407.1427
Fax: 780.407.1429
tbperu@ualberta.ca
www.ualberta.ca/department-of-medicine/divisions/pulmonary-medicine/tuberculosis-program-evaluation-and-research-unit

INFORMATION SHEET

Title of Study: Management of LTBI among an inner-city population and those with psychosocial barriers to treatment
Principal Investigator(s): Dr. Cam Wild and Dr. Richard Long **Phone Number(s):** 780.492.6752 or 780.407.1427
Study Coordinator: Amber Lynn **Phone Number(s):** 403.829.6881

	Yes	No
Do you understand that you have been asked to be in a research study?	☐	☐
Have you read and received a copy of the attached Information Sheet?	☐	☐
Do you understand the benefits and risks involved in taking part in this research study?	☐	☐
Have you had an opportunity to ask questions and discuss this study?	☐	☐
Do you understand that you are free to leave the study at any time, without having to give a reason and without affecting your future medical care?	☐	☐
Has the issue of confidentiality been explained to you?	☐	☐
Do you understand who will have access to your study records, including personally, identifiable health information?	☐	☐

Who explained this study to you? _____

I agree to take part in this study:

Signature of Research Participant _____

(Printed Name) _____

Date: _____

Signature of Witness _____

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.

Signature of Investigator or Designee _____ Date _____

THE INFORMATION SHEET MUST BE ATTACHED TO THIS CONSENT FORM AND A COPY GIVEN TO THE RESEARCH PARTICIPANT

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PARTICIPANT CONSENT FORM

Title of Study: *Management of LTBI among an inner-city population and those with psychosocial barriers to treatment*

Principal Investigator: Dr. Cam Wild and Dr. Richard Long

Research/Study Coordinator: Amber Lynn

Why am I being asked to take part in this research study?

You are being asked to participate in this study because you are a health care provider with programmatic and/or clinical experience in using 3HP for treatment of latent infection among individuals who are unstably housed or homeless.

Before you make a decision one of the researchers will go over this form with you. You are encouraged to ask questions if you feel anything needs to be made clearer. You will be given a copy of this form for your records.

What is the reason for doing the study?

The purpose of this research is to explore what latent or "sleeping" TB means among those living in the inner-city and to describe the treatment experiences, using 3HP, among persons who are unstably housed or homeless. To supplement this information, we are conducting interviews with health care providers who have programmatic and/or clinical experience using 3HP in the inner-city and in this population. We aim to increase understanding of treatment decisions and experiences to inform and improve TB prevention efforts.

What will I be asked to do?

- This study will take approximately 1 hour of your time and you will be asked to complete an interview to discuss your experiences and perceptions of using 3HP in this population

What are the risks and discomforts?

- There are no identified risks of participating

What are the benefits to me?

- Participating in interviews during this research study may be helpful to you and provides an opportunity for you to share your story
- This study may help other people with latent TB in the future
- However, you may not get any benefit from being in this research study

Do I have to take part in the study?

- Being in this study is your choice. If you decide to be in the study, you can change your mind and stop being in the study at any time, and it will in no way affect the medical care or treatment that you are entitled to
- During the interview process you do not have to answer any questions that you are uncomfortable with
- You will have 7 days after the interview is completed to reflect on the information shared and to withdraw from the study (including removal of the information you've shared) if you choose

Will I be paid to be in the research?

- A $10 gift care to Starbucks will be offered to for health care providers for participating in this study

Will my information be kept private?

- We will do everything we can to make sure that the information you provide is kept private. No data relating to this study that includes your name will be released outside of the researcher's office or published by the researchers. Sometimes, by law, we may have to release your information with your name so we cannot guarantee absolute privacy. However, we will make every legal effort to make sure that your information is kept private

What if I have questions?

If you have any questions about the research now or later, please contact Amber Lynn at 403-829-6881
If you have any questions regarding your rights as a research participant, you may contact the Health Research Ethics Board at 780-492-2615. This office has no affiliation with the study investigators.

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CONSENT FORM

Title of Study: Management of LTBI among an inner-city population and those with psychosocial barriers to treatment
Principal Investigator(s): Dr. Cam Wild and Dr. Richard Long **Phone Number(s):** 780.492.6752 or 780.407.1427
Study Coordinator: Amber Lynn **Phone Number(s):** 403.829.6881

	Yes	No
Do you understand that you have been asked to be in a research study?	☐	☐
Have you read and received a copy of the attached Information Sheet?	☐	☐
Do you understand the benefits and risks involved in taking part in this research study?	☐	☐
Have you had an opportunity to ask questions and discuss this study?	☐	☐
Do you understand that you are free to leave the study at any time, without having to give a reason?	☐	☐
Has the issue of confidentiality been explained to you?	☐	☐
Do you understand who will have access to your study records?	☐	☐

Who explained this study to you? _____

I agree to take part in this study:

Signature of Research Participant _____

(Printed Name) _____

Date: _____

Signature of Witness _____

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.

Signature of Investigator or Designee _____ Date _____

THE INFORMATION SHEET MUST BE ATTACHED TO THIS CONSENT FORM AND A COPY GIVEN TO THE RESEARCH PARTICIPANT

Appendix C: Interview Guide (Client)

Group 1: Offered, Accepted and Completed Treatment

1. Can you tell me about yourself? How long have you been in Edmonton (or Fort McMurray)?
2. Can you tell me what you know about TB?
3. Could you describe to me what latent or sleeping TB means to you?
4. Can you tell me what you know about the difference between latent TB and active TB?
5. Can you tell me about when you were first tested for LTBI?
6. Can you tell me about when you were first told that you had LTBI?
    a. What was that experience like?
    b. How did you feel?
    c. What did you say?
    d. What did you do?
7. When you were first diagnosed with LTBI and told that you were exposed to TB did you share this with anyone?
8. Is latent TB or TB something that you talk about with your friends or family?
9. Could you tell me if or how your diagnosis of LTBI affected your relationships?
10. Can you tell me about LTBI and your daily life?
    a. Does LTBI impact you? If so, how?
11. Can you tell me what you know about treatment for LTBI?
    a. Is this something that is important to you?
12. Have you ever been offered LTBI treatment before, not including this most recent time?
    a. Can you tell me a bit more about this experience? Did you accept or decline treatment?
13. What influenced your decision on whether to accept or decline treatment this time?
14. Could you tell me about the medication that you took most recently for treating your latent TB?
15. Could you describe to me what your treatment experience has been like?
    a. What made your treatment easier?
    b. What made your treatment difficult?
16. Can you tell me about your experience with directly observed treatment, where someone gives your medication to you?
    a. Is this something you felt comfortable with?
    b. Can you tell me about who provided your DOT? What was your relationship like with this person?
17. Could you tell me about any of the benefits that you received from completing treatment for latent TB?
    a. How and/or why are these benefits important?
18. Could you describe to me any negative effects that you experienced while completing treatment?
19. Is there anything that you would suggest to that would improve treatment completion?

These next questions focus on your living situation and experience of homelessness:

20. Could you tell me about your current living situation?
    a. Could you tell me about how long you have experienced homelessness or unstable living conditions?
21. Could you describe to me if or how homelessness or your current housing situation affected your decision to accept treatment for latent TB?
22. Thinking about the last few months, are there anyways that your housing situation or homelessness has impacted your ability to complete the treatment?

<u>Group Two: Offered, Accepted, did not complete treatment</u>

1. Can you tell me about yourself? How long have you been in Edmonton (or Fort McMurray)?
2. Can you tell me what you know about TB?
3. Could you describe to me what latent or sleeping TB means to you?
4. Can you tell me what you know about the difference between latent TB and active TB?
5. Can you tell me about when you were first tested for LTBI?
6. Can you tell me about when you were first told that you had LTBI?
    a. What was that experience like?
    b. How did you feel?
    c. What did you say?
    d. What did you do?
7. When you were first diagnosed with LTBI and told that you were exposed to TB did you share this with anyone?
8. Is latent TB or TB something that you talk about with your friends or family?
9. Could you tell me if or how your diagnosis of LTBI affected your relationships?
10. Can you tell me about LTBI and your daily life?
    a. Does LTBI impact you? If so, how?
11. Can you tell me what you know about treatment for LTBI?
    a. Is this something that is important to you?
12. Have you ever been offered LTBI treatment in the past, not including this most recent time?
    a. Can you tell me a bit more about this experience? Did you accept or decline treatment?
13. What influenced your decision on whether to accept or decline treatment this time?
14. Could you tell me about the medication that you took for treating your latent TB?
15. Could you describe to me what your treatment experience has been like?
    a. What made your treatment easier?
    b. What made your treatment difficult?
16. Can you tell me about your experience with directly observed therapy, where someone gives you your medication?
    a. Is this something you felt comfortable with?
    b. Can you tell me about how provided your DOT? What was your relationship like with this person?
17. Could you tell me about any of the benefits that you received from completing treatment for latent TB?

18. Could you describe to me any negative effects that you experienced while completing treatment?
19. Can you describe to me the factors that led to your decision to discontinue the treatment?
20. Is there anything that you would suggest to that would improve treatment completion?

These next questions focus on your living situation and experience of homelessness:

21. Could you tell me about your current living situation?
    a. Could you tell me about how long you have experienced homelessness or unstable living conditions?
22. Could you describe to me if or how homelessness or your current housing situation affected your decision to accept treatment for latent TB?
23. Thinking about the last few months, are there anyways that your housing situation or homelessness has impacted your ability to complete the treatment?

<u>Group 3: Offered, declined treatment</u>

1. Can you tell me about yourself? How long have you been in Edmonton (or Fort McMurray)?
2. Can you tell me what you know about TB?
3. Could you describe to me what latent or sleeping TB means to you?
4. Can you tell me what you know about the difference between latent TB and active TB?
5. Can you tell me about when you were first tested for LTBI?
6. Can you tell me about when you were first told that you had LTBI?
    a. What was that experience like?
    b. How did you feel?
    c. What did you say?
    d. What did you do?
7. When you were first diagnosed with LTBI and told that you were exposed to TB did you share this with anyone?
8. Is latent TB or TB something that you talk about with your friends or family?
9. Could you tell me if or how your diagnosis of LTBI affected your relationships?
10. Can you tell me about LTBI and your daily life?
    a. Does LTBI impact you? If so, how?
11. Can you tell me what you know about treatment for LTBI?
    a. Is this something that is important to you?
12. Have you ever been offered LTBI treatment in the past, not including this most recent time?
    a. Can you tell me a bit more about this experience? Did you accept or decline treatment?
13. What influenced your decision on whether to accept or decline treatment this time?
14. Can you tell me if you would be interested in the future of taking treatment for latent TB?
    a. What are some of the reasons or factors that change your decision to accept treatment in the future?

These next questions focus on your living situation and experience of homelessness:

15. Could you tell me about your current living situation?
    a. Could you tell me about how long you have experienced homelessness or unstable living conditions?
16. Could you describe to me if or how homelessness or your current housing situation affected your decision to accept treatment for latent TB?
17. Is there anything that you would suggest to that would improve treatment acceptance and completion rates among individuals like yourself, who may be experiencing homelessness to treatment?

Appendix D: Interview Guide (HCP)

Health Care Provider Interview Guide

1. Can you tell me about yourself? How long have you been working in the inner-city (or as part of the TB outreach team)?
2. When did your program start using 3HP for LTBI treatment?
3. Was the use of 3HP targeted at a specific population, if so, which ones?
4. Did your program initially plan on treating individuals who are homeless or unstably housed?
5. What were the required resources to provide 3HP to individuals who are unstably housed or homeless?
6. Were than any additional cost implications of using 3HP among this population?
7. What resources did you find helpful in communicating effectively with patients about taking 3HP?
8. Are there any other resources or tools that you think would be useful for health care providers using 3HP in this population?
9. What are your eligibility criteria for treating a patient for LTBI with 3HP?
10. Can you describe the overall process of targeting LTBI screening and 3HP implementation?
11. What were the perceptions and expectations of using 3HP before your program started using it?
12. Was treatment directly-observed?
    a. If yes, can you describe the setting where this occurred? E.g. clinical setting, pharmacy, home
13. How were side effects monitored and addressed? Was this done any differently than how it is for other self-administered LTBI treatment regimens?
14. What do you find challenging about using 3HP in persons experiencing homelessness?
15. What were the experiences patients expressed about 3HP?
16. Would you say there is a difference in using 3HP among those experiencing homeless in comparison to individuals who are stably housed or institutionally housed?
17. What do you like best about using 3HP in comparison to other treatment regimens for LTBI among persons experiencing homelessness?
18. Are there any challenges you faced while using 3HP among this population?
    a. Are there any additional challenges you think other health care providers or facilities might face in adopting the use of 3HP?
19. Overall, based on your experiences, do you feel that 3HP should or should not be used in patients who are unstably housed or experiencing homelessness?