Tuberculosis screening in a cohort of individuals diagnosed with HIV in Ontario during 2001 to 2009

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ABSTRACT

Tuberculosis (TB) is a preventable and a treatable disease yet it is considered to be one of the most common infections seen in HIV. People who are infected with HIV are 20 times more likely to develop TB than those without HIV. Globally, there are nearly 40 million people living with HIV and at least one-third of them are infected with TB. Ontario accounts for the highest number of TB cases in Canada yet HIV-TB co-infection in Ontario is not well described. Despite the close relationship between TB and HIV and increasing efforts to fight both concurrently, TB continues to create economic and social burden in HIV infections.

Our study estimates the prevalence of active and latent TB and identifies risk factors associated with TB in a cohort of individuals living with HIV in Ontario. Cases diagnosed with HIV during 2001 to 2009 were extracted from the Ontario HIV Treatment Network Cohort Study (OCS). Reviewing Mantoux test results, diagnoses and medication history, identified active and latent TB cases. Period prevalence was estimated by proportion with TB and multivariate analyses were performed to identify associated factors.

One thousand two hundred and ninety-three cases (1293) met our selection criteria. Three hundred and eighty four (384; 29.7%) were 29 years or younger, 805 (62.3%) aged between 30 years and 50 years and 104 (8.0%) aged 50 years or older. One thousand and nine (1009; 78.0%) were males. Four hundred and sixty six (466; 36.0%) had at least one record of a Mantoux skin test. The prevalence of active TB was 76/1293 = 0.0587 or 5.87% (95% CI 4.6% to 7.0%)

whereas the prevalence of latent TB varied from 5.26% (68/1293 = 0.0526) 95% (CI 4.0% - 6.5%) to 11.37% (53/466 = 0.1137) 95% CI (8.2% to 13.7%) depending on the methodology.

In the multivariate analysis, factors associated with active TB were age and birthplace. Individuals 50 years and older were more likely to have active TB than individuals 30 years and younger (OR 4.3 CI (1.7-12.7), $p < 0.01$). Individuals born in Africa were more likely to have active TB than Canadian born (OR 14; 95% CI (5.9 – 32.8) $p < 0.001$). Factors associated with latent TB were sex and birthplace. Females were more likely to have latent TB than males (OR 2.4; 95% CI (1.1 – 5.2) $p < 0.05$). Individuals born in Africa were more likely to have latent TB than Canadian born (OR 12.3; 95% CI (4.7 – 32.1) $p < 0.001$).

TB remains a major problem in persons infected with HIV with rates disproportionally high among the foreign born population. Low rates of Mantoux tests in OCS present a missed opportunity for active TB prevention among individuals with HIV. To identify individuals with higher risk of having TB after HIV diagnosis, better screening tools to identify latent TB are needed. Consideration should be given to data capture systems that would ideally be linked between Public Health and HIV clinics.

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GLOSSARY OF ABBREVIATIONS

TB	Tuberculosis
HIV	Human Immunodeficiency Virus
MDR	Multiple drug resistance
BCG	Bacille Calmette-Guerin
DOTS	Directly Observed Therapy Short Course
INH	Isoniazid
RIF	Rifampicin
PZA	Pyrazinamide
ETH	Ethambutol
OHTN	Ontario HIV Treatment Network
OCS	OHTN Cohort Study
PHAC	Public Health Agency of Canada
LTBI	Latent Tuberculosis Infection

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CHAPTER 1 OVERVIEW OF TB/HIV CO-INFECTION

1.1 Overview

Tuberculosis (TB) is a preventable and a treatable disease, yet it is the leading cause of death in people with HIV in most parts of the world, particularly in Africa (1). While the overall occurrence of TB is on the decline, there has been an increase in the number of reported cases of TB in people with HIV. This may be due to people with HIV having a weakened immune system (2). Ninety percent (90%) of people with HIV can die within a year of diagnosis of TB unless properly treated. In 2008, there were an estimated 1.4 million HIV positive TB patients, of which 500,000 people died of HIV-associated TB in that same year (1). Globally, there are nearly 39 million people living with HIV and at least one-third of them are infected with TB (2). The majority of HIV and TB co-infections occur in sub-Saharan Africa, where up to 80 percent of TB patients may be co-infected with HIV (2).

In 2009 in Canada, the Public Health Agency of Canada (PHAC) reported 1600 new and relapsed cases of TB (3). While TB is on an overall decline in Canada, specific population groups continue to account for high number of cases reported (3). Foreign-born individuals and Canadian born Aboriginals accounted for nearly 63% and 21% of all the reported TB cases in 2009, respectively (3). Ontario continued to have the most number of TB cases with 654 cases in 2007 (4).

HIV prevalence has been steadily increasing in Canada due to steady incidence rate and also because more Canadians are now living with HIV infection due to Highly Active Antiretroviral

Therapy (HAART). An estimated 65,000 Canadians were living with HIV at the end of 2008 (5). In terms of new cases, 2,300 to 4,300 HIV infections occurred in 2008 (5). The majority of the new HIV positive tests came from three provinces with Ontario having 42.7%, Quebec 24.7% and British Columbia 13.6% of all the cases (5).

Many of the factors associated with increasing HIV prevalence such as poverty, social inequities, weak public physical and social infrastructures, are also core determinants of TB (6). Co-infection with HIV and TB complicates patient management with potential complications of treatment and medication interactions (7). People with HIV have an increased risk of developing active TB whereas active TB can have a complex effect on HIV treatment (7).

Although HAART has dramatically reduced mortality and AIDS related morbidity among HIV patients, TB remains a major opportunistic infection. Canadian Tuberculosis Standards recommended that all HIV-infected individuals should be screened for TB using tuberculin skin test (TST) (8). However, several studies have shown significantly low adherence to such recommendations (9-14). Results in a Swiss cohort study have underlined the need for improvements in TB screening among HIV-infected patients (15). To our knowledge, no studies have been conducted in Ontario to assess the adherence rates of TB screening in HIV-infected patients. Furthermore, 26% of all the HIV prevalent cases in Canada are not aware of their HIV infection (16), which puts them at a higher risk of developing active TB. As many individuals with HIV are not tested for TB, the proportion of HIV/TB co-infection is not well described.

1.2 Rationale

This study supports Canada's role in the Global Plan to Stop TB, which aims to reduce the burden of the disease by 50 % compared to the mid 1990 levels (17). It also aims to eliminate TB as a public health problem by 2050. The main objectives of the Global Plan to Stop TB are to achieve universal access to high-quality care for all people with TB and protect vulnerable populations from TB, TB/HIV and drug-resistant TB (18).

We believe that this study will provide benefits to people living with HIV in Ontario as well as to the Ontario Cohort Study (OCS) participants, who are a vulnerable group at much higher risk of developing TB. Such benefits may include access to improved tools for TB screening, better linkages between Public Health and HIV clinics, vigilant monitoring for drug-resistant TB and finally prevention of TB occurrence in HIV infected persons. Results of this study will help researchers estimate the burden of HIV related TB in Ontario. The results of this study will also help to engage communities and researchers in working together to generate the knowledge that is needed for better care for those living with HIV in Ontario.

LITERATURE REVIEW

CHAPTER 2 TUBERCULOSIS

2.1 Historical Context

Tuberculosis was once thought to be a disease of the past yet one-third of the world's population is infected with TB (19). Each year, an estimated eight million people worldwide develop active TB and two to three million die from it (20).

The TB epidemic in Europe, later known as the “great White Plague” started at the beginning of the 17th century, and continued for the next 200 years (21). Death from TB was thought to be inevitable and TB was the leading cause of mortality by 1650. The necessary environment for the spread of this disease was provided by high population density and poor sanitary conditions in the enlarging cities of Europe and North America at that time (21). In the 1900s, general improvements in public health and the introduction of anti-tuberculosis drugs led to greater control of TB, but it never quite disappeared. Around 1985, TB cases started to rise again in industrialized countries. Several factors such as homelessness, injection drug use, crowded housing, immigration, and increase in prison populations drove the resurgence of TB. Above all, HIV further fuelled the re-emergence of TB. Also, TB program activities were less intense because the disease was regarded as close to elimination (21).

In the early 1990s, the World Health Organization (WHO) started to prioritize activities to globally combat TB. The World Health Assembly of 2000 supported the establishment of a

Global partnership to stop TB and to reduce the global burden of TB by 50% by 2015 in relation to the 1990 levels (17). In spite of such global efforts, TB remains a threat, in part because of its synergistic relationship with the HIV pandemic (21).

2.2 Epidemiology of Tuberculosis

2.2.1 Global Burden

Despite the known characteristics and treatment, TB still remains a major cause of morbidity and mortality worldwide, especially in Asia and Africa. Globally, TB has infected about one-third of the world's 5 billion people (22). The World Health Organization (WHO) has estimated that 9.27 million new cases of TB occurred in 2007. The global prevalence of TB has been in decline since 1990s. This decline can be explained by two factors: 1) a decrease in the average duration of disease as number of cases treated in the Directly Observed Treatment Short (DOTS) programs has increased and 2) a relatively short duration of TB mainly because of marked reduction in life expectancy among people with advanced HIV infection (23). Despite the overall decline in global prevalence, regions in Africa and Europe continued to have prevalence rates that were increasing during the 1990s (23). Furthermore, in terms of mortality, an estimated 1.77 million people died of TB in 2007. Of these 1.77 million, 1.32 million were HIV negative and 456,000 were among HIV-positive people (24). Mortality attributable to TB in HIV infected people accounted for 23% of the estimated 2 million HIV deaths that occurred in 2007 (24).

2.2.2 Canada

TB was a major cause of morbidity and mortality during the first half of the 20th century. Thereafter, rates declined rapidly as a result of improvements in the living conditions and public health measures to control disease transmission (8). Over the past two decades, reported TB cases have continued to decrease. In 2006, members of a National Consensus Conference on Tuberculosis decided to set the Canadian goal to reduce the incidence rate of TB in Canada to 3.6 per 100,000 by 2015 (8).

According to the PHAC TB report of 2009, 1600 new and relapsed TB cases (rate of 4.8 per 100,000 population) were reported in 2008. The data suggests an increase of 1.5% from 1,577 cases in 2007 to 1600 cases in 2008 (8). Individuals who were visitors or were born outside of Canada account for over two third of all reported TB cases in Canada (25). The Canadian tuberculosis committee and its Immigration subcommittee recommended that all immigrants to Canada undergo TB screening using chest radiography, which is mainly used to detect active TB and may miss opportunities to detect latent TB (25). People from countries where TB rates are high and in whom previous TB reactivation is likely, arrive in Canada each year with 250 000 as landed immigrants and another 2 million as visitors (22). Of the 250,000 immigrants and refugees coming to Canada each year, 80% of them originate from TB endemic countries (8). The proportions of TB cases that are foreign born persons have increased significantly, rising from 18% of all cases in 1970 to 67% in 2004 (8). In 2008, foreign born individuals accounted for 63% of all reported TB cases in Canada whereas Canadian-born non-Aboriginal accounted for 15% and Canadian-born Aboriginal accounted for 21% of all reported cases (3).

The Canadian Aboriginal population includes Status and non-Status Indians, Inuit and Metis. In 2004, these groups together constituted 3.5% of the overall Canadian population but accounted for 17% of the TB burden (8). While the TB cases in Aboriginal populations is generally higher than among Canadian born non-Aboriginal peoples, there is broad variation in the levels of disease among these communities and regions. For example, the status Indians have a TB incident rates ranging from 0 per 100,000 in Atlantic Regions to 72.7 per 100,000 in Manitoba (8). Similarly, the Inuit people have an incident rate of 95 per 100,000 in Quebec but 102.2 per 100,000 in the Northern territories (Yukon, Nunavut, and Northwest Territories) (8).

2.2.3 Ontario

Ontario continues to have more TB cases than any of other Canadian provinces (4). One third of Canadian TB cases are in the Greater Toronto Area (GTA). The majority of Ontario cases are foreign-born individuals (4). In 2007, Ontario reported 654 new TB cases, a rate of 5.1 per 100,000 (4). In Canada, drug-resistant [1]TB is most commonly reported in foreign-born individuals. In Ontario, particularly in GTA, the rate of drug resistant TB is much higher than that of other regions of Canada (4). Furthermore, HIV epidemic has had a dramatic impact on TB rates and on TB control in populations where both infections are prevalent (26).

[1] Drug-resistance is further described in Section 2.9.

2.3 Cause of TB

TB is caused by a bacillus called *Mycobacterium tuberculosis*. *M.tuberculosis* multiplies relatively slowly compared to most other bacteria. It is also a strictly aerobic bacterium and multiplies efficiently in pulmonary tissue where the oxygen concentration is high (27). Primary TB infection almost always occurs in the lung because of inhalation of droplets carrying the TB bacillus. Therefore, it usually infects the lungs (pulmonary TB or PTB) but can also occur in other parts of the body (extra-pulmonary TB) including the kidneys, spine and brain. Major symptoms of TB are cough, fever, weight loss and weakness (27).

2.4 Transmission

TB is transmitted from person to person by the airborne route (20). A person with active TB disease has the potential to infect a large number of individuals (4). The source of infection is most often a person with cavitary pulmonary TB who expectorates bacilli by coughing or sneezing. During this process, the person produces tiny infectious droplets, which are then inhaled by another person in the vicinity (27). Infectivity of a person is related to the quantity of bacilli contained in his/her sputum. The most contagious person is the one with sputum smear-positive microscopy (M+). Those with only culture-positive results (M-, C+) are less contagious and person whose sputum smear microscopy and culture are negative (M-, C-) is generally not contagious (25). Transmission normally requires close, frequent and prolonged exposure to a source case (27). In order to fully transmit the disease, certain factors must be met. These factors include 1) viable presence of bacilli in the sputum or larynx of the source case; 2) aerosolization of sputum by cough or other mechanisms; 3) adequate concentration of bacilli in the air; 4) a susceptible host and 5) a sufficient duration of time during which the host is exposed (4).

2.5 Latent TB

The lung is the primary entrance point of the tuberculosis bacillus, which causes a localized infection in the lung (21). The infection spreads to local lymph nodes and through the blood stream to other body sites. The bacilli pathogens are taken up by macrophages at many sites in the body and may remain dormant for years. This is referred to as latent TB. Most TB disease in adults is reactivation of TB at one of these sites, most often the lung. Direct progression to active TB is more likely when infection occurs in young children (4). In most individuals, latent TB infection clinically results in no apparent symptoms and the infection may stay latent for life or until reactivation (4). The individual with latent TB is also not contagious. A weakened cellular immune system such as in those with HIV may allow multiplication of previously dormant bacilli and activation of the disease (4). The development of active TB disease will take place in 5%-10% of latent TB infected persons at some point in their lives. Approximately 5% of persons who have been infected with TB will develop active TB disease within two years of exposure to the disease and the other 5% will develop active TB disease sometime later in their lifetime depending on the risk factors (21).

2.5.1. Risk Factors for Latent TB

Factors that increase the risk of acquiring latent TB infection (LTBI) in Canada involve 1) Close contacts of an infectious case of TB; 2) Immigrants and visitors from countries of high TB incidence; 3) Persons who are homeless; 4) Elderly persons who lived through an era when TB was common; 5) Aboriginal communities with high rates of LTBI or TB disease; 6) Healthcare

workers or persons at risk due to occupational exposure and 7) Residents of long-term care facilities and correctional facilities (4).

2.6 Active TB

For the 5-10% who will acquire active TB disease, development and further multiplication of bacilli will continue. With active TB disease, the tubercle bacilli will replicate in the lungs, and due to the interaction of the bacillus and the cellular immune system, and area of tissue necrosis develops and hence a cavity. This active replication may result in more than 10^8 (10 to the power of eight) bacilli per cavity with a diameter of less than 2 cm (21). The development of tubercle cavities in the lung builds a platform for the infectious material to spread further through bronchi (21). The individual may start to have TB symptoms like coughing, chest pain, fever and weakness. At this point, the individual is contagious and can spread *M.tuberculosis* bacillus to other persons in the surroundings (21).

The disease progression may be different in persons with HIV, depending on the status of their immune system. If the immune system is severely compromised, the classic cavity may not form, and although there may be large numbers of bacilli in the sputum, lack of a cavity may complicate the diagnosis of active tuberculosis (21).

2.6.1. Risk Factors of active TB

Factors that carry a high risk of developing active TB among persons with latent TB infection are 1) Acquired immunodeficiency syndrome (AIDS) or HIV infection; 2) Organ transplantation-linked to immunosuppressant therapy; 3) Silicosis; 4) Chronic renal failure requiring hemodialysis; 5) TB infection within the past two years; 6) Abnormal chest X-ray and 7) Children less than 12 months of age (5).

2.7 Diagnosis

This section is further divided into two categories: 1) Diagnosis of Tuberculosis Infection and 2) Diagnosis of active Tuberculosis Disease. According to the Ontario's TB Best Practices guidelines, a TB case is defined as an individual: 1) with positive culture of *Mycobacterium tuberculosis* from sputum, body fluids or tissues or 2) without bacteriological evidence but with clinical signs and symptoms, radiological or pathological evidence of active pulmonary or non-pulmonary disease (28). The primary instrument to diagnose TB infection is the tuberculin skin test (TST) whereas diagnosing active tuberculosis disease usually consists of three aspects: a) symptoms, b) radiographic presentation and, c) evidence of mycobacterium (i.e. specimen collection for acid fast bacilli smear and culture) (28).

2.7.1 Diagnosis of latent TB

The tuberculin skin test (TST) is a useful method of diagnosing TB infection, however it is not as helpful in the diagnosis of active TB disease. Over the past few years, a significant advancement

has been the development of T-cell based interferon-gamma release assays (IGRAs), another test designed to identify individuals with LTBI (29).

Tuberculin Skin Test (TST)

Tuberculin Skin Test (TST) is comprised of the intradermal injection of a small amount of purified protein derived from *Mycobacterium tuberculosis* bacteria. In a person with cell mediated immunity to tuberculin antigens, a hypersensitivity reaction will occur within 48 to 72 hours (30).

In general, testing for latent TB is recommended when the risk of developing active TB disease is increased (8). There are many common situations when the risk of developing active disease is increased: 1) recent TB infection, most commonly contacts of a person with a recent diagnosis of active, contagious respiratory TB, 2) foreign born coming from countries of high TB incidence. 3) increased risk of reactivation due to impaired immunity including HIV infection and other immunosuppressed conditions, diabetes, renal failure, immunosuppressant medication and pulmonary silicosis. 4) radiographic evidence of previous, healed inactive TB with no prior TB treatment (8).

There is a possibility of false negative TST results, particularly in people with HIV. At least 20% of patients with active TB may have a negative TB skin test. A higher number of false negative results, close to 50% are observed in persons with HIV infection, depending on their immune

status (30). Therefore, a negative TB skin test never rules out TB whereas a positive skin test alone is not enough to establish the diagnosis of active TB (30).

A positive skin test is defined by the size of the swelling. A skin reaction size of 0-4 mm in a person with a compromised immune system due to HIV infection and with a high likelihood of TB infection is usually considered positive (4). A skin reaction of 5-9 mm in a person with HIV infection, close contact of active contagious TB case, abnormal chest X-ray or other immune suppression is considered positive. All the other persons with a skin reaction size greater than 10 mm are also considered positive (4). Other factors to evaluate with the TST results include non-tuberculosis mycobacteria (NTM) and Bacille Calmette-Guerin (BCG) vaccination (4).

NTM are species of mycobacteria and may present as opportunistic infection in the immune compromised individuals. Common clinical symptoms linked with NTM are lymphadenopathy, chronic pulmonary disease and skin or soft tissue infections (4).

The appropriate interpretation of TST result needs prior knowledge of the possible confounding factors such as previous Bacille Calmette Guerin (BCG) vaccination. Although many countries have stopped the usage of BCG vaccination, it is still offered in high TB prevalence populations and in high-risk groups such as newborn Canadian Aboriginals living on reserve (31). Immunization with BCG significantly increases the possibility of a positive TB skin test and therefore the interpretation of the skin test should be done in the individual clinical context and

evaluation of other risk factors for infection (31). BCG vaccination provides protective effect against TB. In a meta-analysis study on efficacy of BCG in the prevention of TB, the risk of TB was significantly reduced by 50% on average with the use of BCG vaccine (32).

BCG vaccine is mainly used in TB control and prevention programs to prevent complications in undiagnosed TB persons who do not have access to early identification and treatment of TB (33). BCG is thought to reduce hematogenous spread of Mycobacterium tuberculosis from the site of primary infection (33). In Canada, BCG immunization programs exist in some First nations and Inuit communities, targeting newborns and individuals in certain high-risk settings (33). BCG vaccination is contraindicated for people with a compromised immune system or people with immune deficiency disease including HIV infection (33). A previous administration of BCG vaccine has the potential to make interference with surveillance efforts of investigating active TB cases (31).

Interferon Gamma Release Assays *(*IGRAs)

Until recently, the only diagnostic test available to diagnose latent TB was TST. However, as previously mentioned, TST has its limitations since a false-positive result can occur among individuals with a BCG vaccination or who have been exposed to NTM. A false-negative result can occur in individuals with a compromised immune system (34). As a result, Interferon-gamma release assays (IGRAs) were recently developed to address many of these limitations (34). IGRAs are whole blood tests that can help in diagnosing latent TB (29). IGRAs works on the principle that T cells of a person sensitised with tuberculosis antigens produce interferon

when they reencounter mycobacterial antigens. Therefore, a high level of interferon is indicative of latent TB (35).

Previous systematic reviews (35-37) have shown that IGRAs have a higher specificity in low TB incidence settings however such reviews were not able to assess the diagnostic ability of IGRAs in HIV-infected persons. A recent study in 2011 performed a systematic review to determine whether IGRAs should replace TST as a screening tool for latent TB in HIV-infected persons. The study found insufficient evidence to conclude that either test was superior to the other (34).

Two IGRAs that are currently approved in Canada are the QuantiFERON-TB Gold (QFT) assay and the T-SPOT.TB assay (29). The TST is still recommended to be the initial test used to detect latent TB, however due to a possibility of false negative TST result in an immune compromised person, a clinician concerned about the possibility of latent TB with a negative initial TST result may perform an IGRA test (29).

2.7.2 Diagnosis of active TB Disease

Symptom Presentation

Depending on the duration and site of TB disease, the symptom presentation can be highly variable. The primary symptoms for pulmonary tuberculosis include chronic cough for three or more weeks, fever, and night sweats. When the TB disease gets to an advanced stage, other symptoms such as hemoptysis (coughing of blood), anorexia, weight loss and chest pain also

appear (4). The symptoms of extra-pulmonary TB are often site specific such as lymph node swelling, neurological changes (i.e. headache or neck stiffness), bone pain/joint swelling, lower back pain, urinary tract infections in renal TB disease, or abdominal pain or infertility. Pulmonary and Extra-pulmonary TB can occur at the same time (4).

Radiographic Presentation

Chest X-rays with both posterior-anterior and lateral views are mechanisms towards diagnosing pulmonary tuberculosis. A typical radiographic presentation of tuberculosis includes infiltrates, nodules, and cavities in the upper lobes of the lungs or superior segment of the lower lobes (4). Other abnormalities may include fibrosis, scarring, granulomas, or volume loss (due to destruction of lung tissue or lung contraction by the tuberculosis bacillus) (4).

Mycobacterial Evidence

Mycobacterium tuberculosis (MTB) is a slow growing mycobacterium, which usually takes up to seven weeks to grow in order to acquire a final culture result (4).

Acid Fast Bacilli (AFB) Smears

Acid Fast Bacilli (AFB) is a laboratory rapid test used to analyze specimen for the presence of TB bacilli (20). The specimen is smeared onto a microscope slide, stained and then examined (4). If the TB bacilli are found in the specimen, it is referred as smear positive TB. It is graded according to the amount of bacilli per field with No AFB (negative), Few (weakly positive), 1+

(moderately positive), 2+ (moderately positive), 3+ (strongly positive), 4+ (strongly positive). Although AFB smears test is rapid, specific for bacteria and with not many types of equipment needed, it is less sensitive than culture. It can detect only concentrations of at least 10^{-5} bacilli per ml of specimen. A single sputum smear has sensitivity between 22% and 80% (20) depending on the bacterial load. Therefore, multiple (usually three) sputum smears are used to increase sensitivity. The specificity of smear method also varies with different population groups. It is quite high in developing countries but much lower in developed countries due to the frequent presence of atypical mycobacteria (i.e. bacteria other than those causing TB) (20). Both mycobacterium tuberculosis and non-tuberculosis mycobacteria will result in AFB smear positive. It is important to determine whether a positive AFB smear is caused by MTB or NTM (4).

Mycobacterial Culture

In Ontario, every specimen that is sent for AFB smear testing is also cultured for mycobacteria (4) at the Public Health central laboratory. The culture for *M.tuberculosis* is considered the gold standard of diagnosing TB. Cultures are usually associated with higher detection rates, because sensitivity is higher than that of AFB smears (20). Although six cultures are required to achieve 100% sensitivity, three cultures are recommended in Canada because the sensitivity of three exceeds 90% and create a balance between high sensitivity and efficiency (30). Nevertheless, cultures occasionally can be false negative, mainly because of cross-contamination inside the laboratory (30).

2.8 TB Treatment

Patients diagnosed with active disease of Tuberculosis take oral drug treatments for duration without even hospitalization unless it is a severe case or MDR-TB, and can easily return to their daily life routine (38). TB treatment is classified as first-line or second line drug treatments. First-line drugs are the drugs of choice administered to patients after their diagnosis of TB. These drugs are generally more effective, less toxic, cheaper and easier to administer than the second line agents. The most common first-line drugs are isoniazid (INH), rifampicin, streptomycin, ethambutol, and pyrazinamide (38). The primary purpose of TB treatment is to eliminate the infection in the body, prevent resistant strains and control transmission of the disease. If TB remains untreated, 50% of the cases with active TB disease would die within 2 years (20).

2.9 Drug Resistant TB

Drug resistant TB is a form of TB in which the bacteria have become resistant to the first-line TB medicines. Resistance to TB drugs occurs when these drugs are misused or mismanaged. Multidrug-resistant (MDR) TB is when TB bacteria are those that are resistant to the two most common TB medications, isoniazid and rifampin (39). The most dangerous form is Extensively Drug-Resistant (XDR) TB where the bacteria is resistant to many common TB medicines such as, isoniazid, rifampin, fluoroquinolone, and at least one of three injectable medicines (capreomycin, kanamycin, and amikacin) (39).

CHAPTER 3 HUMAN IMMUNODEFICIENCY VIRUS (HIV)

3.1 Background

The human immunodeficiency virus (HIV) is a virus that infects cells of the immune system, notably CD4 T cells (a type of white blood cell vital to fight off infections), destroying or impairing their functions (40). As the immune system becomes more damaged, the individual may develop severe opportunistic infections and cancers, resulting eventually to Acquired Immunodeficiency Syndrome (AIDS). According to WHO, the critical criteria used to diagnose the progression to AIDS is when any condition listed in the clinical stage IV of WHO's clinical stages[2] is diagnosed and/or the CD4 count is less than 200 cell/mm^3 (40).

3.2 Clinical Background

Once the HIV enters the body, it is widely spread, mainly to lymphoid tissues (41). As time progresses, the quantity of HIV increases in the blood while the number of CD4 T cells decline (42). Antiretroviral Therapy (ART) is a potent combination of medications that inhibits viral replication and reduces the amount of virus present in the body, allowing CD4 T cells to increase in numbers, and improvement in function of the immune system (42). People who are HIV negative and generally are in good health have approximately 800 to 1200 CD4 T cells per cubic millimetre (mm3) of blood. However, with the HIV infection, the CD4 T count drops dramatically (42).

[2] WHO's clinical stages are listed in Appendix A

3.2.1 Symptoms and Diagnosis

Most people will experience very few, if any, symptoms in the early stages of HIV infection. Some individuals may have flu like symptoms including fever, headache, tiredness and enlarged lymph nodes in the neck and groin area (43). However, these symptoms usually disappear within a week to a month and are often mistaken for influenza or another viral infection (43). Individuals during this period are highly infectious as the amount of HIV present in the body is in large quantities. Symptoms vary from person to person and some may experience severe symptoms initially, while others may not experience any symptoms at all for 10 years or more (43). As HIV progresses to the late stages, the virus severely compromises the immune system and individuals may develop symptoms including 1) weight loss; 2) recurring fever or profuse night sweats; 3) extreme and unexplained fatigue; 4) prolonged swelling of the lymph glands in the axilla, groin or neck; 5) diarrhoea that lasts for more than a week; 6) sores of the mouth, anus or genitals; 7) pneumonia; 8) red, brown, pink or purplish blotches on or under the skin or inside the mouth, nose or eyelids and 9) memory loss, depression and other neurological disorders (43).

3.3 Epidemiology of HIV

HIV is a worldwide pandemic that has killed more than 25 million people to date (44). According to the WHO, nearly 33.4 million were living with HIV in 2008. During the same year, 2.7 million people were newly infected and 2.0 million died of AIDS (45). Two thirds of HIV infections are found to be in sub-Saharan Africa (45).

3.3.1 HIV Prevalence in Canada

The first reported case of HIV was reported in 1982 in Canada. Since then, it is estimated that a total of 65,000 people were living with HIV in Canada at the end of 2008, which is an increase of approximately 14% from the estimated 57,000 in 2005 (46).

Due to advances in HIV treatment, many people are living longer with HIV infection, contributing to the rising prevalence of Canadians living with HIV (47). The majority of the reported HIV cases in 2008 came from three provinces: 42.7% from Ontario, 24.7% from Quebec and 13.6% from British Columbia (5). However, trends in the newly diagnosed cases differ among the provinces/territories with Saskatchewan having the highest rate (20.8%), twice those of Ontario (10.3%), while the lowest rates were reported in Newfoundland and Labrador (0.7%) and the territories (0.0%) (5).

In terms of infection, men having sex with men (MSM) is the highest prevalence group with 31,330 (48%) individuals, 11,180 (17%) Intravenous Drug Users (IDUs), 10,710 (17%) heterosexual/non-endemic, 9,250 (14%) heterosexual/endemic, 2,030 (3%) MSM-IDU and 500 (1%) other exposures (46). The public health agency of Canada categorizes HIV exposure through a hierarchical system with Men having sex with men (MSM) being the highest in the hierarchy. For example, if a MSM from a HIV endemic country were HIV positive then he would be placed in the MSM category and not in the HIV endemic country category.

3.3.2 HIV Incidence in Canada[3]

The number of newly diagnosed HIV cases in 2008 ranged from 2,300 to 4,300, which is around the same as the estimated range of 2,200 to 4,200 in 2005 (46). In terms of infection, MSM accounted for the highest proportion of new infections (44%) whereas the infections among IDUs increased to 350-750 (17%) in 2008 (46). Foreign-born Canadians and Immigrants from HIV endemic countries continue to be over represented in Canada's HIV epidemic. 360 to 670 (16%) of heterosexual/endemic cases were attributed in the new HIV infections in 2008. Individuals from HIV endemic countries account for 2.2% of the Canadian population but the estimated HIV incident rate among individuals from HIV-endemic countries is at least 8.5 times higher than among other Canadians (46).

3.3.3 Undiagnosed HIV infections in Canada

As mentioned earlier, an estimated total of 65,000 people were living with HIV by the end of 2008 in Canada (46). Of this estimate, 16,900 (26%) of prevalent cases were unaware of their HIV infection (16). In terms of exposure category, the estimate percentage varies. It is estimated that 19% of MSM and 26% of IDU were unaware of their HIV infection while the heterosexual individuals who were unaware of their infection had a much greater proportion (35%) (16).

3.4 Vulnerable Communities in Canada

There are many different vulnerable populations living with HIV in Canada. Such populations include: 1) Gay, Bisexual and MSM; 2) people from HIV endemic countries; 3) Aboriginal

[3] Incidence implies new HIV infections within a specific time period.

People ; 4) Injection Drug Users ; 5) Mother to Child HIV Transmission vulnerability ; 6) Older Canadians and 7) Youth in Canada (48). The following information is the latest set of data available and as current as up to 2008 in most cases, except for the section of HIV endemic countries where the data is updated up to 2005.

3.4.1 HIV among Youth in Canada

Youth in Canada between the ages of 15 and 29 years have accounted for 26.5% of all positive HIV test reports since the beginning of HIV reporting (49). Canadian Youth in general are vulnerable to HIV infection due to many factors. Such factors include risky sexual behaviour, substance use that includes injection drug use, and lack of accurate information and awareness on HIV transmission (49). In terms of gender, males accounted for around 95.8% of the HIV test reports when reporting began in 1985. In 2008, proportion of females in the age group of 15-29 was reported to be highest among all female HIV test reports and represented 33.5% of all positive HIV test reports among youth (49). Data from various studies show that street-involved youth, youth who are injection drug users, and youth men who have sex with men are at a higher risk of having HIV infection (50-53).

3.4.2 HIV among Women in Canada

According to the PHAC report in 2012, the proportion of HIV infection that represents women has been increasing over the last 10 years. In 2008, women accounted for 17% of people living with HIV and 26% of all new HIV infections in Canada (54). Also in the same year, three

quarters of newly diagnosed cases occurring among women are attributed to heterosexual sex exposure and more than one third can be attributed to exposure through injection drug use (54).

There are certain groups of women who are more likely to be over-represented and disproportionately affected in the HIV endemic. Such groups are Aboriginal women, women from countries where HIV is endemic, injection drug users, and women in prison. For example, women from HIV endemic countries represent more than half of the positive HIV tests attributed to women (54).

While biological differences in women increase their susceptibility to HIV than men, many factors, known as social determinants of health, also have an impact on women's vulnerability to HIV (54). Factors such as gender, income, education, unemployment, access to stable housing, access to health services, social support services, racism, and early childhood development are social determinants will have an impact on women's vulnerability to HIV (55-58). There are also other factors such as sexual violence, culture, HIV/AIDS related stigma, and discrimination that can make women more vulnerable to HIV (59-61).

3.4.3 HIV among Older Canadians

HIV and AIDS has generally been perceived as a disease that mainly occurs in younger people however, it is quite clear that older[4] Canadians are not only affected but are also at risk of

[4] Older Canadians were defined as 50 years of age and older.

acquiring HIV infection (62). It is possible that older Canadians could have acquired the HIV virus after the age of 50 years or could have acquired it at a younger age and survived it into an older age, particularly due to the advances of highly active retroviral therapy (HAART) (62). 9.6% of the cases that have been reported positive for HIV test since the beginning of HIV reporting up to 1985 accounted for older Canadians aged 50 years and above. 84% of this proportion was male and 48% of them were MSM (62).

3.4.4 Perinatal HIV Transmission

PHAC estimates that 25% of untreated HIV pregnant women will transmit the virus to their infant either during pregnancy or at birth (63). The percentage can further increase to 35% if the mother decides to breastfeed her baby. Overall, the situation of perinatal HIV transmission in Canada has significantly improved over the last decade (63). Although the number of infants perinatally exposed to HIV has increased as there are now more people living with HIV, the number of these infants who were subsequently infected with HIV has had a dramatic decline (63). In 2001, out of the 168 infants born to HIV infected women, 10.01% were infected whereas in 2008, only 1.7% infants out of the 238 exposed to HIV were confirmed as infected. Highly active anti-retroviral therapy has played a major role in the decrease of HIV infected infants (63).

3.4.5 HIV among Aboriginal People in Canada

Aboriginal people represent 3.8% of the Canadian population yet they continue to be over represented in the HIV epidemic in Canada (64). It is estimated that in 2008, there were 4,300 to 6,100 Aboriginal people who were living with HIV, which is 8.0% of the HIV prevalent

infections (64). In terms of new infections, there were 300 to 520 new HIV infections that occurred in Aboriginal population in 2008 only (64). According to the PHAC HIV related surveillance report (64), injection drug users (IDUs) in the Aboriginal population account for 66% of the new infections, a rate much higher than among all other Canadians (17%). Aboriginal communities are disproportionately affected by many conditions termed social determinants of health such as, poverty, substance/drug use, and limited access to health care services. All these factors increase their vulnerability to HIV infection (65-67).

3.4.6 HIV among Gay, Bisexual and Other Men Who Have Sex with Men in Canada

The HIV epidemic continues to have a disproportionate effect on gay, bisexual and other men who have sex with men (MSM). This population accounts for the largest proportion of positive HIV tests among adults, representing 56.1% of total HIV positive test reports since the introduction of HIV reporting in 1985 (68). MSM also accounts for the largest proportion of cases with a representation of 48% (31,330) of all the estimated prevalence in 2008 (68). Further, MSM continues to account for the largest proportion of estimated incident cases with an estimated proportion of 45% in 2008 (68). According to PHAC, recent data suggests that certain subgroups within MSM continue to be at high risk of HIV infection by engaging in unprotected sex with serodiscordant[5] partners or partners of unknown HIV status (68).

[5] A term used to describe in which one partner is HIV positive and the other is HIV negative.

3.4.7 HIV among people who inject drugs in Canada

Injection drug users constitute 17.7% of cumulative positive HIV reported cases up to 2008 (69). While there has been a decreasing trend noted in positive HIV cases attributable to injection drug use among men, an increasing trend has been observed among women since 2003. Of the proportion, for which age and exposure category was provided, the highest proportion among the injection drug use was accounted by individuals aged 30 to 30 years (33.5%) and 40 to 49 years (32.3%) (69). In the national estimates for 2008, IDU represented 17% (11,180) of all the prevalent cases where as the proportion for incident cases was estimated to be 17% (390-750) as well (69). It is further estimated that roughly 25% of this proportion (prevalent cases) were unaware of their infection. It was also observed that Aboriginal people represented 66% of the newly diagnosed cases in 2008 (69).

3.4.8 People from Countries where HIV is Endemic

The term "people from countries where HIV is endemic" refers to population that is mainly comprised of Black people of African and Caribbean descent (70). Although a number of Black Canadians are able to trace their roots in Canada all the way to the early 1600s and 1700s, this group largely came to Canada through immigration during the last five decades (70).

According to the estimates by PHAC in 2012, people from HIV endemic countries represent 14% of people living in Canada while they only represent 2.2% of the population (71). HIV endemic has a significant impact on women who come from HIV endemic counties. Females 15

years of age or older accounted for 55.3% of HIV positive test reports between 1998 and 2009 and also represented 40.7% of AIDS cases during the same time period (70).

Of the total prevalence of HIV cases in Canada (65,000 at the end of 2008), an estimated 9,250 (14%) were people infected through heterosexual contact and were born in an HIV-endemic country (71). People from HIV endemic countries were also over-represented among new HIV infections. The estimated new infection rate among individuals born in HIV-endemic countries is approximately 8.5 times higher than among other Canadians (71).

Many factors such as those described in social determinants of health have been observed to increase the Black population's vulnerability to HIV. Such factors include income, education, unemployment, housing, early childhood development (e.g. history of child abuse), physical and social environments, access to health services, racism, support networks, gender inequalities and sexual violence (72-74).

3.5 Smoking, HIV and TB

While the rates of opportunistic infections such as TB, in individuals with HIV, have declined due to HAART medications, studies have shown that smokers are more likely to acquire opportunistic infections than non-smokers (75). While many previous studies related to smoking and TB have not considered the role of HIV infection in the past (75). Some studies also show that individuals with HIV are more likely to smoke than those without HIV. Individuals with

HIV who smoke cigarettes also have shown to develop AIDS faster than non-smokers (75). Smoking cigarettes and tobacco affect individuals with HIV in several ways. Smoking cigarette in individuals with latent TB also increases the risk of development of active TB by two to three times, compared to non-smokers (76).

3.6 HIV Testing and Treatment

Routine HIV testing is recommended for adults, adolescents, and pregnant women during routine medical care (77). HIV testing is performed by testing a blood sample to detect the presence of HIV specific antibodies (77). Since 1985, blood tests for HIV antibodies have been available in Canada. Standard HIV testing includes pre-test counselling. In the laboratory if the screening test is positive, the laboratory continues to do a confirmatory test called Western blot to rule out a false-positive result before sending the result back (77). The results are returned to the clinic after two weeks and the patient receives a post-test counselling (77).

It is estimated that at least 26% of HIV-positive people are unaware of their HIV status (16). Therefore, it is imperative to improve access and ease of HIV testing across Canada. Many community based organizations and health service providers are increasingly using rapid point of care (POC) HIV testing, which may help to increase testing rates in the communities (77). This type of testing allows health service providers to deliver immediate HIV test results (77). In comparison with the standard HIV antibody test, during the use of POC test, patients are provided with pre-test counselling, and informed of the need for confirmatory blood work if the

POC test is reactive (77). The test itself is performed on a drop of blood from the finger, in a separate room out of the sight of the patient and the result is available within approximately two minutes (77). The individual is provided with post- testing counselling right after the test results are examined and again when they return to receive their confirmatory results one to two weeks later (77).

There are many benefits associated with the use of POC HIV testing. It is much more portable than the standard HIV antibody blood test, which allows it to be performed in any kind of community settings (77). It also provides a better counselling experience since pre and initial post-test counselling is provided by the same person, which is often not possible to ensure with the two – week waiting period during the standard HIV testing (77)

At present, there is no cure for HIV infection, however, there is HAART treatment available for HIV patients that can suppress the HIV viral replication and the progression of HIV infection. HAART consists of three or more anti-HIV drugs (78). Use of a single drug results in selection of resistance mutations. However, the chances of HIV mutation or replication are low if the patient receives three anti-HIV drugs at once (78).

CHAPTER 4 COINFECTION OF HIV AND TB

4.1 Epidemiology of HIV/TB co-infection

4.1.1 Globally

Globally, there are nearly 39 million people living with HIV and at least one-third of them are infected with TB (2). People who are infected with HIV are 20 times more likely to develop TB than those without HIV (79). Ninety percent of people with HIV can die within months of contracting TB unless properly treated. In people with HIV and latent TB, the chance of developing active TB increases by 6 times in the first year after HIV infection, and continues to increase over the years (22). In the absence of antiretroviral therapy, the likelihood of progressing to AIDS increases by 100 times when people with HIV develop active TB (80-81). In 2008, there were an estimated 1.4 million HIV positive TB patients, out of which 500,000 people died of HIV-associated TB in the same year (82). The majority of HIV and TB co-infections occur in sub-Saharan Africa, where up to 80 percent of TB patients may be co-infected with HIV (83).

4.1.2 Canada

While there is no national surveillance system that tracks TB and HIV co-infection rates, several Canadian studies have been conducted to determine the overlap of TB and HIV or even TB and AIDS. These studies mainly determined the burden of HIV among the TB population, particularly HIV testing in this population (83). However, not many examined the TB rates in HIV population and the burden of HIV disease in TB.

A study by Geduld and Archibald (2005) reported 5.6% TB cases among all the AIDS cases reported to PHAC from 1994 to 2003 (84). Two thirds of TB and AIDS infected cases were foreign born. The study concluded that at least one in twenty AIDS cases were also infected with TB and a large proportion of these cases are among foreign born population (84).

In a study of HIV related TB in British Columbia, Blenkush et al. (1996) found that there were 44 people identified with HIV infection and TB during the period of 1990 and 1994 (85). Although the study identified the number of individuals rather than estimating the TB rate, the general over-lap of HIV and TB related cases in British Columbia was 3.8% (85). The mean age was 38 years among 37 men and 7 women. 70% of the participants were Canadian born and 18% came from countries where TB was highly prevalent. 52% (22/40) were Intravenous users and 31% (14/44) were Aboriginal Canadians. The study also compared these proportions with the proportions of patients diagnosed with TB and HIV during the years of 1984 to 1990. The study concluded that there were significantly more intravenous drug users, Aboriginal Canadians and women with HIV-related TB than in the previous years of 1984 to 1990 in British Columbia (85).

In a Quebec study on HIV related TB, Brassard and Remis (1999) reported 4,684 people with HIV, of which 5.2% had active TB at some point during their course of illness (86). The majority of people co-infected with HIV and TB were male (75.2%) and manual workers (40.1%). Montreal had the highest TB rate of 9.6% among those with HIV, possibly due to its urban setting (86). People with HIV who were born in an HIV-endemic countries in the Caribbean and

sub-Saharan Africa were 21.8 and 17.9 times more likely to have TB respectively than those born in Canada. Manual workers and unemployed people with HIV were 1.6 and 2.0 times more likely to have TB than professional workers with HIV. HIV was concluded to be a significant factor in the contribution of TB cases (86).

A recent study conducted by Brassard et al. (2009) explored the proportion of TB screening among the HIV-infected patients (87). Out of the 2121 HIV patients observed in a Canadian clinic in a tertiary setting, 22.4% patients were treated by TST within 90 days of first clinic visit (87). 17 patients developed active TB, of which 9 (53%) had no documented TST prior to the diagnosis of TB. The study found inconsistencies in the administration of TSTs to newly diagnosed HIV patients and recommended that all patients should be screened for TB at the time of HIV diagnosis (87).

A retrospective cohort study by Creatore et al. (2005) studied patterns of TB risk over time among recent immigrants to Ontario (88). 92% of TB cases in Toronto were accounted for people born outside of Canada (88). Although this study examined all the immigrants rather than only HIV positive population, conclusions made in this study were coherent with the study by Brassard et al. People from sub-Saharan Africa had the highest TB incidence, with a 96 times more risk than of the non-Aboriginal Canadian population (88). Overall, recent immigrants had a risk 23 times higher than non-Aboriginal Canadians. Region of birth, particularly countries where TB is highly endemic was a significantly higher risk of getting TB in people born outside of Canada (88).

4.2 Pathology, Clinical Picture and Diagnosis of HIV/TB Co-infection

Individuals with HIV are vulnerable to reactivation of TB due to their weakened immune systems (89). CD4 T cells play a vital role providing protection from reactivation of *M.tuberculosis* (90). HIV infection is a major known risk factor for reactivation of LTBI-HIV infection. As the HIV infection progresses, the count of CD4 cell count declines. Therefore, the risk of active TB disease significantly increases as the HIV infection progresses and concentration of CD4 cells decline in count and function (91). A research study has estimated that the incidence of TB increases by a factor of 2.1 for each reduction of 200/ul in the CD4 count (91). Although TB is an easily treated opportunistic infection taking place in HIV positive people, its clinical picture is often atypical which in many cases can lead to a delay in diagnosis. Latent and active TB can occur at any CD4 count. The nature and clinical features of TB depends on the immunosupression related to HIV (91).

In HIV patients with early diagnosis of TB and a normal count of CD4 cells, the clinical symptoms (cough, fever and weight loss) are similar to that in HIV negative patients (91). As the level of immunosuppression increases, the clinical symptoms start to become non-specific and atypical. One of the challenges is that the fever and weight loss (classic symptoms of TB) can be common symptoms of HIV disease alone (91). A significant association has been explored between low CD4 count and an increased extra-pulmonary TB frequency (91).

Furthermore, the immunosuppression also has a negative impact on the sputum smear microscopy and TB culture as it reduces the sensitivity of such diagnostic tests. As the immunosuppression increases, the results of sputum smear and culture are often negative in late HIV disease (91). Similarly, the radiological findings are also different for HIV-positive person. The classical common changes associated with pulmonary TB are upper lobe infiltration, cavitation and fibrosis, but as HIV disease progresses, diffuse shadowing and miliary infiltrates are more common radiological findings (91).

Tuberculin skin testing (TST) also has its limitations when it comes to testing for TB in people with HIV. The sensitivity of this test is significantly reduced in HIV-positive people, particularly those with advanced HIV disease (92). Individuals with AIDS may not show a positive skin test result despite TB infection or disease. (92).

4.3 Prevention and Treatment of TB in people with HIV

Treatment for latent TB also called TB prophylaxis is used to prevent active TB diseases. It is suggested to health care providers that they consider treatment for individuals with a positive TB skin test and where the presence of active TB has been ruled out (4). Isoniazid (INH) is one of the medications used to treat latent TB since its first effectiveness was reported in 1957. As the drug has been proven to be safe, cheap and easy to take, its effectiveness depends on adherence to treatment with adequate duration. Patients who took 80% or more of the recommended doses of daily INH for at least one year achieved a 93% protection against activation of TB disease (4).

In HIV positive individuals, the Lung Association of Canada suggests that prophylaxis treatment for latent TB should be offered regardless of TB skin test. The recommended dosage of INH for latent TB in adults is 5 mg/kg/day (max.300 mg daily) (4). However, compliance remains a significant barrier to an effective prophylaxis. In various settings, compliance rates were only 50% to 75% through one year of preventive therapy (93). In one study involving Canadian Aboriginals, a program of daily-observed prophylaxis and education improved compliance rates but were not sustained after the observation was discontinued (94).

Despite the close relationships between the two diseases (TB and HIV) and increasing efforts to fight both concurrently, uptake of policies linking HIV and TB has been slow (83). As many individuals with HIV are not tested for TB, the prevalence of HIV-TB co-infection is not well described. Further, adults with TB infection have about a 10 % chance of developing TB disease in their lifetime while those co-infected with HIV have a 10 % risk of developing TB disease every year. TB infection also makes HIV infection progress to AIDS faster (95).

5.0 ONTARIO HIV TREATMENT NETWORK (OHTN)

The datasets were provided by Ontario HIV Treatment Network (OHTN), which is an independently incorporated, not-for-profit organization funded by the AIDS Bureau and Ontario Ministry of Health and Long-Term Care (96). OHTN works towards better HIV treatment, research, and education in Ontario. It is a collaborative network of researchers, health service providers, policy makers, community members, volunteers and people with HIV (96). The OHTN owns and houses a clinical and epidemiological database on people with HIV in the province. This database is called OHTN Cohort Study (OCS). It has been used as the basis of data analysis for the thesis study. OCS has its roots in AIDS activism and the demands for research that would improve the quality of life of people living with HIV (97). OCS is unique in comparison with other HIV cohorts because it is community driven and involves all the stakeholders including people living with HIV, dedicated HIV care physicians, researchers and policy makers (97).

6.0 RESEARCH OBJECTIVES

The overall objective of this study is to estimate the prevalence of TB in the OCS database and to identify risk factors associated with TB among people living with HIV. The specific research objectives are as follows:

1.) To determine the period prevalence of active and latent cases of TB among HIV positive individuals in the OCS database during the period of January 2001 to Dec 2009.

2.) To identify risk factors associated with active TB in the OCS database.

3.) To identify risk factors associated with latent TB in the OCS database.

4.) To identify the factors associated with having a Mantoux test in the OCS database.

CHAPTER 7.0 METHODOLOGY

7.1 Study Design

Our study of TB will be based on observational data that is already collected and currently stored in OCS database. Our group of interest was participants diagnosed with HIV during the period of January 2001 to Dec 2009. This time period was selected so it would provide rich demographic and clinical data on most recent HIV diagnosis since the OCS has undergone changes in adding social and psychological data in addition to the clinical data. .

7.1.1 Inclusion Criteria

1) Participants in OCS diagnosed with HIV during the time period January 2001 to Dec 2009.

7.1.1 Ethics and Data Confidentiality

This study was approved by the Research Ethics Board (REB) of University of Ontario Institute of Technology (UOIT). The OCS data are governed by the REB of University of Toronto. A data confidentiality agreement was signed between OHTN and the researchers (see Appendix D).

7.1.2 OCS Database

The source of data is OHTN's Cohort Study (OCS) database. OCS is a multi site research study that collects clinical and socio-behavioural information voluntarily from people with HIV across Ontario (98). There were eleven HIV sites across Ontario that provided data to OHTN on

regular intervals (98). Five of the sites were located in the GTA, and one site was located in Sudbury, Ottawa, Kingston, Windsor, and London. Other sites in Ottawa and Hamilton were not actively recruiting participants as of date (98). Once a person is diagnosed with HIV, sites may wait up to a year before they approach HIV positive individuals to participate in the OCS. Individuals who were diagnosed with HIV prior to the site opening were immediately recruited after the site opening (98). Participation in the study is voluntary and patients are assured that the provision of treatment and clinical services will continue at the same standards regardless of their participation in the OCS. They can refuse to participate in the study or withdraw from the study at any time. Participants must be consented before participating (98).

Personal data such as name, address, health care number, etc., is used at the recruiting site to generate a complex encrypted unique identifier, which allows the person's data to be accurately tracked at OHTN while keeping it confidential. The process is strictly anonymous and one-way encryption cannot be decrypted to reveal the original information that was used to create the unique identifier (99). No personal identifier information is stored in the database. The HIV clinics mainly use a computer-based systems or chart abstraction tools to collect clinical data (100). Data is loaded onto the OHTN database using secure methods. For sites using chart abstraction, an electronic data abstraction tool is used to collect clinical data elements (100). OHTN provides funding to HIV clinics so that they can hire qualified staff to perform chart abstraction and or extract data from electronic medical records (100).

Access to the data in the OCS database is approved by the OCS Governance committee who can allow specific subsets of the data to be accessed by researchers according to the purpose of the study (101). The committee is governed by people living with HIV as well as other stakeholders in the HIV community to ensure that it's intended use is appropriate and meets community's ethical requirements (101).

OCS is the only HIV cohort study in Ontario that collects a combination of different data elements for each individual. It is unique in a way that it gathers socio-behavioural information as well clinical information. OCS collects social behavioural information through an annual in person interview (101). The social behavioural questionnaire includes data elements such as demographics, employment, substance use, smoking, immigration, mental health, housing, stigma, stress, social support, medication and adherence (101). Data retrieved from clinical charts include, diagnosis, medications, adverse events, medical charts, viral load and CD4 count and other medical tests (101). Additional data including viral load and genotypic test is obtained from Public Health Laboratories (PHL) (101).

After the recruitment process, data for each individual is collected retrospectively (i.e. clinical history, infection date) as well as prospectively (i.e. annual interviews and ongoing clinical data capture) (101).

There are over 5,600 participants who have enrolled in the OCS. It is a diverse group of people living with HIV in Ontario. Although, most OCS participants are MSM (Men having sex with Men), a significant number are also females or individuals infected by a different mode of transmission (98). The average age at enrolment is 41 years and over one third of participants reported a race other than white (98). As of 2010, 63% of the participants enrolled in the study were still actively participating. The remaining participants were lost to follow up either because they were deceased (14.6%) or were recruited in sites that are no longer collecting data (3.2%) (98).

A quick snapshot of the OCS data sample in 2008 provides some characteristics of OCS participants (n = 1,406). The mean age of the participants is 47 (SD 10.0) with 85% of them being male. 70% of the participants are either gay, lesbians, or bisexual and 73% of them are white (101). In terms of other demographic factors, 85% of them have more than high school education and 44% of them were employed. The proportion of participants earning a personal income greater than $30,000 a year was 44% (101). From a clinical perspective, 47% of the participants have had their recent CD4 count to be greater than 500 cells/ml and 74% of the participants have had their recent viral load to be undetectable. 21% of the participants present in the OCS database had an AIDS-defining condition whereas the mean years since HIV diagnosis were 11 (SD 7.0) (101).

Data Elements Extracted from OCS

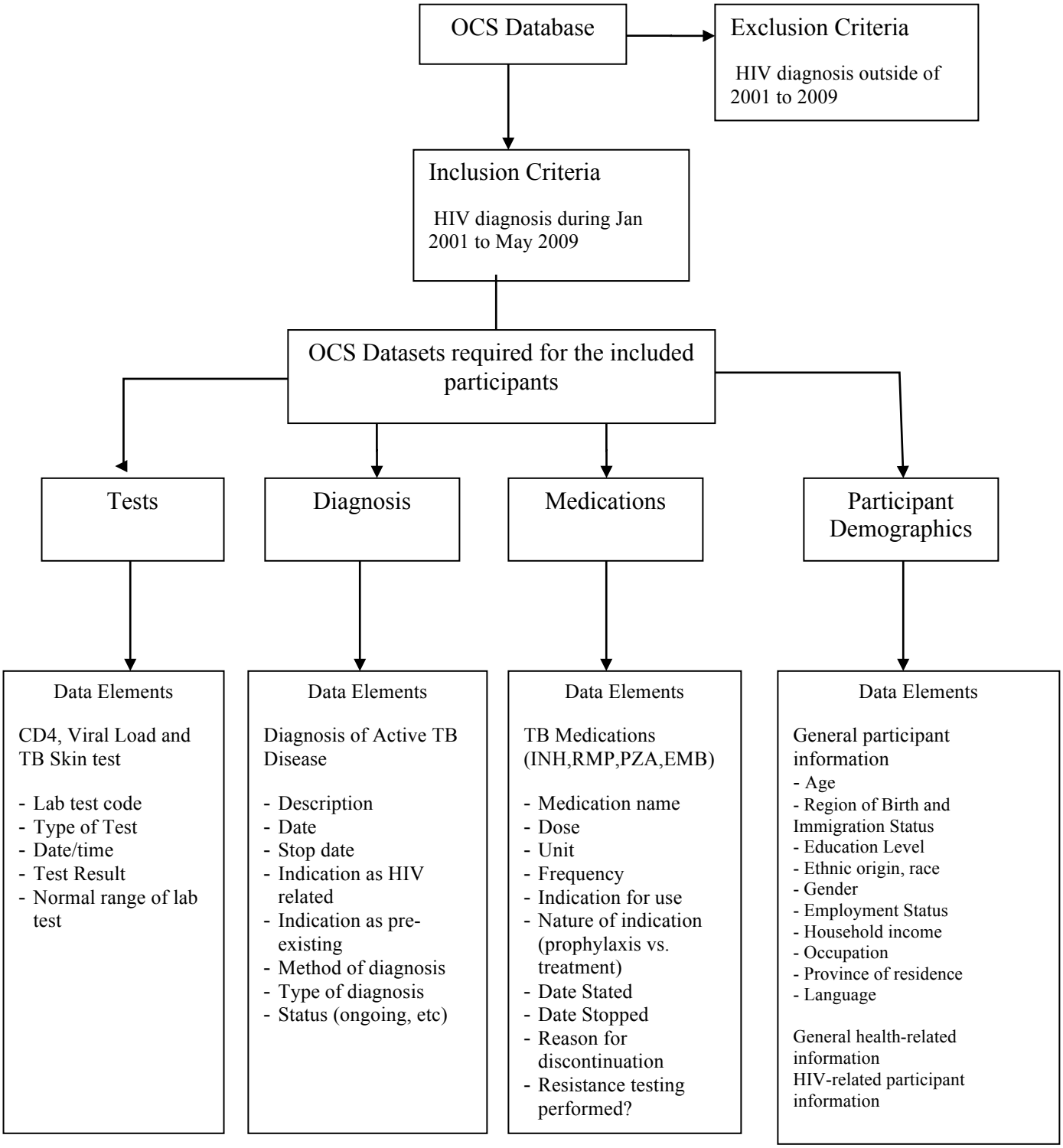

Figure 7.1 Data extraction process from the OCS Database

7.2 Data Request to OHTN

A formal proposal was drafted for the OCS review committee, requesting the data needed in order to achieve the study's research objectives (see Appendix E). The figure in the previous page includes a detailed list of data elements required from the OHTN to proceed with this study. The list of variables that were required included sex, age, race/ethnicity, HIV transmission risk, smoking status, rural/urban residence, recency of HIV infection, recency of immigration, TB skin test record, CD4 count, Viral load count, co-morbid conditions, TB and HIV treatment and duration and dates of death if applicable.

7.2.1. Datasets provided by OHTN

Upon approval by the OCS committee, data was provided on an encrypted USB drive. The research laptop that was used was also protected using the encryption software (True Crypt). All participants matching the inclusion criteria were part of the data analysis. Individuals who withdrew from the study due to loss of follow up or due to death were still included in the sample, as they had previously provided demographic and clinical data to OCS.

The data consisted of nine datasets and was provided in both SAS and SPSS versions. Most of the data analysis was performed using SPSS version 19. The nine datasets included were: 1) demographics, 2) TB mantoux records, 3) TB diagnosis, 4) adverse events, 5) AIDS Defining Conditions, 6) TB medications, 7) CD4 count, 8) Viral load, 9) HIV medications.

Demographics Dataset

The dataset was originally named "main" and it contained 1293 unique records with 17 variables that were associated with demographic characteristics of these individuals. The variables were organized in the following order: cohort IDs (cohort_id) date of HIV diagnosis (min_hivposdate), Gender (sex), region of birth (countryrgn), HIV risk transmission category(hivriskcat), Area of residence (urban_rural), Mortality (death), Age at the time of HIV diagnosis (hivpostestage2), year of death if the person is not alive (deathyear), participants for which the death year is unknown (deathyear_unknown), date of interview with the OCS staff (interviewdt), History of Smoking (cigaretteHistory), smoking frequency (perWeekDay & howMany), age at the start of smoking (age), smoking duration in years (Years) and how long have they been living in Canada if they were foreign born Canadians (yearsinCanada).

Mantoux Skin Test Dataset

The dataset was named “tb_mantoux” and it contained 732 records and 9 variables. The variables were in the following order: Cohort IDs of participants (cohort_id), grouping of type of test (group 1), subgrouping (sub_group1), name of the OCS test (OCS_TEST_NAME), date of the lab test, result (Result_Value), details of the result (TEST_RESULT_DETAILS) and description of the test (TEST_DESC). Of the 732 records, 172 (23.5%) had more than one Mantoux test records.

Diagnosis Dataset

The dataset was named “tb_dx” and it contained 11 records and 4 variables. The variables were in the following order : Cohort IDs (cohort_id), diagnosis description (dxdescription), date of the diagnosis (DXDATE), and diagnosis date flag (DXDATE_FLAG).

Adverse Events Dataset

The dataset was named “tb_ae” and it contained 26 unique records and 5 variables. The variables were in the following order: Cohort IDs (cohort_id), result of the adverse event (RESULT_VALUE), description of the event (test_desc), lab test date (labtestdate), and lab test date flag (labtestdate_flag).

AIDS Defining Condition (ADC) Dataset

The dataset was named “tb_adc” and it contained 30 unique records and 4 variables. The variables were in the following order: Cohort IDs (cohort_id), description of the diagnosis (dxdescription), date of the diagnosis (DXDATE), and diagnosis date flag (DXDATEFLAG).

TB Medications Dataset

The dataset was named “tb_meds” and it contained 149 records and 12 variables. The variables were cohort IDs (cohort_id), treatment and prophlyaxis (T_VS_P), ATC Code (ATC_Code), first stop reason (stop_reason_1), second stop reason (stop_reason_2), third stop reason (stop_reason_3), generic drug name (generic_name), brand drug name (brand_name), medication

start date (medstartdate), start date flag (medstartdate_flag), stop date (medstopdate), stop date flag (medstopdate_flag). 149 records belonged to 75 unique cohort IDs as each unique ID had more than one TB medication listed in the medication history.

Antiretroviral Medication Dataset

The dataset was named "arv" and it contained 5694 records and 13 variables. The variables were cohort IDs (cohort_id), generic drug name (generic_name), brand drug name (brand_name), drug class (drug_class), ATC coding (ATC_code), start date of medications (medstartdate), start date flag (medstartdate_flag), drug dosage (dose), drug dosage unit (unit), frequency of prescribed drug (frequency), method of intake (route), stop date (medstopdate), stop date flag (medstopdate_flag). 5,694 records were of the 1033 unique cohort IDs as each unique ID was on several different medications.

CD4 count Dataset

The dataset was named "cd4" and it contained 19065 records and 11 variables. The variables were cohort IDs (cohort_id), CD4 Test Date (CD4TestDate), CD4 Test Date Flag (CD4TestDate_Flag), CD4 Numeric Result-Standard (RESULT_NUMERIC), CD4 Character Result Standard (RESULT_CHAR), Laboratory Result Qualifier (lab_qual), Flag for converted CD4 results (result_flag), Units - Standard International (result_unit), First CD4 Test Date Flag (fcd4date_flag), Last CD4 Test Date Flag (lcd4date_flag) and minimum CD4 Result Test Date Flag (mcd4date_flag). 19,065 records were of the 1237 unique cohort IDs as each unique ID had several CD4 test results.

Viral Load Dataset

The dataset was named "vl" and 1284 individuals had 22,227 records and 7 variables. They variables were cohort IDs (cohort_id), Viral Load test date (vltestdate), Undetectable Viral Load (undetectable), Viral Load (vl), Viral Load test date flag (vltestdate_flag), first Viral Load test flag (fvldate_flag), and last Viral Load test flag (lvldate_lag).

7.3 Data Manipulation and Descriptive Statistics

Demographic Variables

An initial frequency analysis of all the datasets was performed to examine any missing values and to ensure it was coded appropriately. In the demographics dataset, the age variable (hivpostestage2) contained ages of participants at the time of their HIV diagnosis. This variable was provided in a continuous variable format. Two new categorical variables were created so the data can be categorized in different age groups. Other HIV-TB related studies were followed as a guide to organize the data. Initially, only one age categorical variable (ageatHIVdiagnosis_var4) was created which categorized the data into five different age group (years): 15 to 19, 20 to 24, 25 to 44, 45 to 64 and 65 and above. However, another age variable (ageatHIVdiagnosis_var1) with only three different age groups was created so there is less variation in the regression analysis. This variable categorized the data in the age groups (years) of: 29 and less, between 30 and 49, and 50 and above. Frequency results of both variables were organized and recorded in table 8.1, which is shown in the results section.

The birthplace data (countryrgn) originally provided were grouped into thirteen different birthplace regions. To create broader categories and to minimize the risk of identifying OCS participants, several regions were grouped together. A new variable for birthplace regions (countryregion_var2) was created and regions of Middle East, South Asia, Europe, Pacific Ocean, Atlantic Ocean, Russia, Central and South America, which had cell frequencies less than five, were merged according to geographical relevance. Asia and Pacific Ocean were merged into a new category called Asia and Pacific regions. Europe, Atlantic Ocean and Russian Republic were merged into a new category called Europe and Central Asia. South America and Central America were merged into another new category called South and Central America. Aboriginal Canadians were excluded from the Canadian category and were placed into a new category due to clinical relevance (Health inequalities in Aboriginal's Canadians). In order to identify Canadian and foreign born individuals, a new demographic variable (CdnbornvsForeignborn) was created to categorize the participants either into Canadian born or foreign born based on their birth region. While a new variable (birth_region) was created and several birthplace groups were further merged together to reduce variations in the analysis. Caribbean was merged with South and Central America. Africa, Aboriginals and Canada were left as is whereas all the remaining categories were merged into "Others".

Frequency analysis was performed to describe the characteristics of the data. Variables related to enrolment in OCS used in the frequency analysis were 1) Follow up Status, 2) Follow-up duration, 3) Duration between HIV diagnosis and OCS enrolment. Follow-up status variable was already provided in the demographic dataset. Follow-up duration was measured by subtracting the HIV diagnosis year from the last interview year of each individual. The values were grouped

in three categories of < 12 months, 12-24 months, and > 24 months. Duration between HIV diagnosis and OCS enrolment was measured by subtracting the HIV diagnosis date from the OCS enrolment date. The values were grouped in four categories of < 1 year, 1-2 year, 2-5 years and > 5 years. The frequency and the percentage of each category of the variables were described. If an individual was missing data for a required variable, that individual was censored from the analysis. Missing data was handled by either removing it from the analysis when certain analysis.

Clinical Variables

CD4 cells are white blood cells that maintain the function of the human immune system. As the presence of HIV increases in the blood, the number of CD4 cells decline (36). For purposes of the study, the CD4 count nearest to the time of enrolment as well as nearest to the time of person's HIV diagnosis was selected from the CD4 dataset. In order to identify the CD4 test nearest to the time of enrolment, a calculation in SPSS was performed which calculated the period differences between the time of enrolment and the time of CD4 test. SPSS computed the differences in seconds, which were converted into days by dividing by 86,400 (24x 60 x 60) and then dividing it again by 30, or 365.25 to get duration in months or years. The difference with the lowest monthly duration was selected as the CD4 test at the time of enrolment. Similarly, CD4 test at HIV diagnosis was measured by subtracting the CD4 test dates from the HIV diagnosis dates. The CD4 count measured the CD4 cells per millilitre. Other HIV-related studies were used as a model to classify the CD4 count (cell/ml).

Viral load test measures the amount of HIV virus in the blood. The average viral load count at the time of enrolment as well as at the time of HIV diagnosis was selected from the viral load dataset. In order to identify the viral load test nearest to the time of enrolment, a similar computation like the one described earlier for CD4 test, was performed in SPSS. The computation calculated the period differences between the time of enrolment and the time of viral load tests. The difference was calculated in seconds by SPSS, which was further divided by 86,400 to convert into days and then further by 30 or 365.25 to convert into months or years. The difference with the lowest monthly duration was selected as the viral load test at the time of enrolment. Once the viral load test at the time of enrolment and at the time of diagnosis was selected, the log was taken to display the results in the form of log 10 copies per milliliter. Other HIV-related studies were used as a model to classify the viral load count (log copies/ml).

The year of HIV diagnosis for each participant was provided in the demographic dataset. Years were clustered in three different periods to see if the proportion of HIV diagnosis was consistent throughout the years. The three different calendar time period groups were 1) 2001 – 2003, 2) 2004-2006 and 3) 2007 – 2009.

7.4 Identifying latent TB cases

Mantoux test records were extracted from the Mantoux dataset. Mantoux test records were collected retrospectively as well as prospectively for the participant as part of the OCS. Mantoux test record was not available for everyone. Result values for each participant were coded as negative, positive or missing.

To identify the proportion of participants diagnosed with latent TB, Mantoux test records, TB medications and diagnosis datasets were examined. Participants who were coded "positive" for Mantoux test were deemed positive for latent TB. For those participants with multiple Mantoux test records, the most recent test was selected. Participants who were on TB medications for the latent TB treatment were also deemed positive for latent TB. Participants with 'negative' or 'missing' Mantoux test value were coded as positive if they were on treatment for latent TB. Other datasets of adverse events, Aids Defining Conditions and diagnosis were also searched to identify if there were any latent TB cases there. If any of these datasets indicated a participant with "positive for Mantoux test" or "latent TB", then they were added into the positive category.

7.5 Identifying active TB cases

Active TB cases were identified from datasets of Diagnosis, Adverse events, AIDS defining conditions and TB medications. Participants with active TB were already coded positive in the datasets. TB medication dataset indicated whether TB medications were prescribed for treatment or prophylactic reasons. Cases receiving medication for the treatment of TB were coded positive for active TB whereas cases receiving medication for TB prophylaxis were coded positive for latent TB.

7.5.1 MDR-TB Cases

The identification of drug resistant cases, particularly MDR-TB cases was based on the TB medications and the length of TB treatment for each case. MDR-TB cases were defined as cases

that were at least resistant to Isoniazid (INH) as well as Rifampin (RMP). Cases that were resistant to other combinations of anti-TB medications but not to INH and RMP were not selected as MDR-TB cases.

In order to calculate the length of treatment for each person, a new variable was created that computed a subtraction between the start and the stop date of TB medications. The result values were calculated in seconds by SPSS and which were further divided by 86,400, and then 30 to convert the values from seconds days and months respectively. Another variable was created that categorized these values in four different durations; 1) Less than 6 months, 6 months to 12 months, 12 months to 18 months, and 18 months and above. These categories were created based on the fact that the minimum length of treatment for a MDR-TB case is between 18 months to 24 months. Next step was to select the cases that were on TB medications for at least 18 months. After identifying such cases, the anti-TB medications were checked to see whether or not they received INH and RMP. Cases that were on treatment for at least 18 months, received alternative anti-TB drugs instead of INH and RMP were categorized as MDR-TB cases.

It is possible for someone with HIV who is enrolled in the OCS study to be previously infected and diagnosed with active TB. Analysis was performed to identify the proportion of active TB cases that were diagnosed before or after their HIV diagnosis. After the active TB cases were identified, they were further categorized in terms of the period in which they were diagnosed with active TB. The start date of the TB treatment or the date of the diagnosis was used as an indicator of their diagnosis. This date was stored in a ‘TB diagnosis date’ variable and was

subtracted from the HIV diagnosis date variable. An SPSS computation was performed that produced the output values in seconds which were further divided by 86,400 and then 365.25 to convert into days and years respectively.

Proportions of cases with TB and without TB were entered in tables displaying results for bivariate and multivariate analysis. Particular attention was paid to any table columns with a frequency cell of zero or less than 5. Cells with a frequency of 5 or less had the categories collapsed in an appropriate way to eliminate those cells.

7.6 Estimating active and latent TB prevalence

Period prevalence of active TB was calculated by dividing the number of persons infected with active TB by the number of persons examined in the sample. For example, in a study where 6000 individuals completed the questionnaire (or were examined) and of these 6000 people, 200 suffered with a condition A, the prevalence of condition A in the cohort will be 200/6000 = 0.033. Prevalence of active TB was expressed as a percentage, calculated by multiplying the ratio by 100.

Similarly, period prevalence of latent TB was also calculated by dividing the number of persons infected with latent TB by the number of individuals in the cohort. The denominator was chosen to be all persons examined in the sample because latent TB cases were identified from more than one source. If we identified latent cases by only examining the Mantoux test records, then the

denominator would simply be the number of Mantoux test records. Latent cases were also identified via medication history (medication history data was captured of the whole sample) and the diagnosis data (also extracted from the entire dataset). By expanding our sources of identifying latent cases, the risk exposure is not just limited to cases with Mantoux test records, but the entire data sample. This method assumes that a missing would be negative for TB.

Another method was also performed in which, latent TB prevalence was estimated by taking the positive Mantoux test records and dividing them by the total number of Mantoux test records found in the OCS. Results that estimated the prevalence of latent TB were shown using both methods.

7.7 Data Merging

Once the data manipulation was processed, key variables from all the datasets were combined and merged into one dataset named "main_mantoux_adc_ae". The common variable across all the datasets was "cohort_id" which was used to merge the variables. The key variables from the demographic dataset were cohort IDs, sex, age, birthplace, area of residence, HIV transmission risk factor, recency in Canada, smoking status, date of HIV diagnosis, interview date, and follow-up status. Variables such as diagnosis and diagnosis date from "diagnosis", "adverse events" and "AIDS defining conditions" datasets were also merged. Drug name, medication start date and medication stop date from TB medication dataset were also merged. Clinical variables such as CD4 count and viral load results were also merged.

7.8 Bivariate and multivariate Analysis

The risk factors that were associated with active TB and HIV in the OCS were identified using bivariate and multivariate analysis. HIV infected persons in OCS who had active TB based on clinical diagnosis and medication history were compared with HIV infected persons who did not have active TB. Since reoccurrence of TB is a possibility even after the treatment of TB, cases that developed TB prior to their HIV diagnosis were also included.

Based on the objectives of this study, the outcome variables were active TB, latent TB and Mantoux test record in OCS with a dichotomous outcome. For example, active TB had an outcome of 1 = with TB and 0 = without TB. Bivariate and multivariate analyses were performed to identify factors associated with the outcome variables. Demographic and clinical variables provided in the OCS datasets were selected to be included in the analysis. Several previous studies (84-88) were used as a guide to identify variables as risk factors associated with outcome variables. The independent variables or the covariates were age, sex, birthplace, HIV transmission risk factors, area of residence, smoking status, follow-up duration in the OCS, and the results for viral load and CD4 count at the time of HIV diagnosis and at the time of enrolment in OCS. All the variables were coded as categorical. For continuous covariates such as age, the values were categorized into different age groups.

Bivariate analysis was performed by comparing the outcome variables with the rest of the individuals in the sample. Pearson Chi Square test was used to identify any level of association. The Odds Ratio (OR), is defined as the ratio of the odds for x = 1to the odds for x = 0, and is

given by the following equation where π is the probability of having TB given x = 1. Unadjusted Odds Ratios (OR), 95% Confidence Intervals (CI) were computed using bivariate logistic regression analysis.

$$OR = \frac{\pi(0)/[1-\pi(0)]}{\pi(1)/[1-\pi(1)]}$$

Multivariate logistic regression analysis for each outcome variable was performed to adjust for any confounding factors in the covariates. The significance of each variable was measured using a Wald Statistic with chi-square distribution. Upon finishing the bivariate analysis, an independent variable with a p-value < 0.25 was a candidate for the multivariate model along with other variables known for clinical importance (i.e. gender and age). The recommendation of choosing 0.25 level as a criterion for variable selection is based on the literature work of Mickey and Greenland (1989) on logistic regression, found in the book by Hosmer and Lemeshow (75). Their algorithm, in effect, retains candidate variables for which the bivariate test statistic (equivalent to a chi-square value) ≥ 1.32. Use of an alpha level higher than 0.25 has a disadvantage of including variables that are of questionable importance, whereas use of an alpha level lower than 0.25 may not include variables that were weakly associated in bivariate analysis but become important predictors of dependent outcome when taken together with all other variables. Area of Residency, CD4 count both at diagnosis and enrolment, and viral load both at diagnosis and enrolment were excluded since they did not show a significant association in the bivariate analysis as the p-value was greater than 0.25. Since the cumulative risk of TB depended on the duration of follow-up, this variable was also adjusted for by including it in the multivariate model. The final covariates included in the multivariate models were sex, age, birthplace region, HIV transmission risk, follow up duration and smoking status.

Once the models representing the main effects were refined, the next step was to check for interactions among the variables in the model. However, the final decision whether the interaction effect should be included in a model were decided based on practical as well as statistical considerations as per the recommendations of Hosmer and Lemeshow (102). Computing the arithmetic product of variables that may have significant association created interaction variables. Comparing the standard errors and confidence intervals to bivariate models assessed collinearity in multivariate models. If there was evidence of highly inflated standard errors and confidence intervals in the multivariate model, then suspected collinear variables were compared using chi-squared tests during our analysis. Multivariate models with and without collinear covariates were also compared.

Adjusted Odds Ratios (OR) and 95% CI were computed as part of the multivariate regression analysis. For each covariate, a reference group was used to compare the Odds Ratio proportions within each subcategory. For example, Canadian born category was the reference group for the birthplace variable. Values for Odds Ratios, 95% Confidence Intervals and p-values of each variable were entered and organized in tables.

CHAPTER 8 RESULTS

8.1 Descriptive Statistics

Our group of interest had 1293 individuals in the cohort that matched the inclusion criteria of being diagnosed with HIV during the period of January 2001 to Dec 2009. One hundred and ninety nine 199 (15.4%) of the 1293 in the cohort were enrolled in OCS within a year of HIV diagnosis, 194 (15.0%) were enrolled between 1 to 2 years after HIV diagnosis, 479 (37.0%) between 2 to 5 years and 421 (32.6%) were enrolled after 5 years of HIV diagnosis. Figure 8.1a shows a graphical representation of time interval between HIV diagnosis and enrolment to OCS.

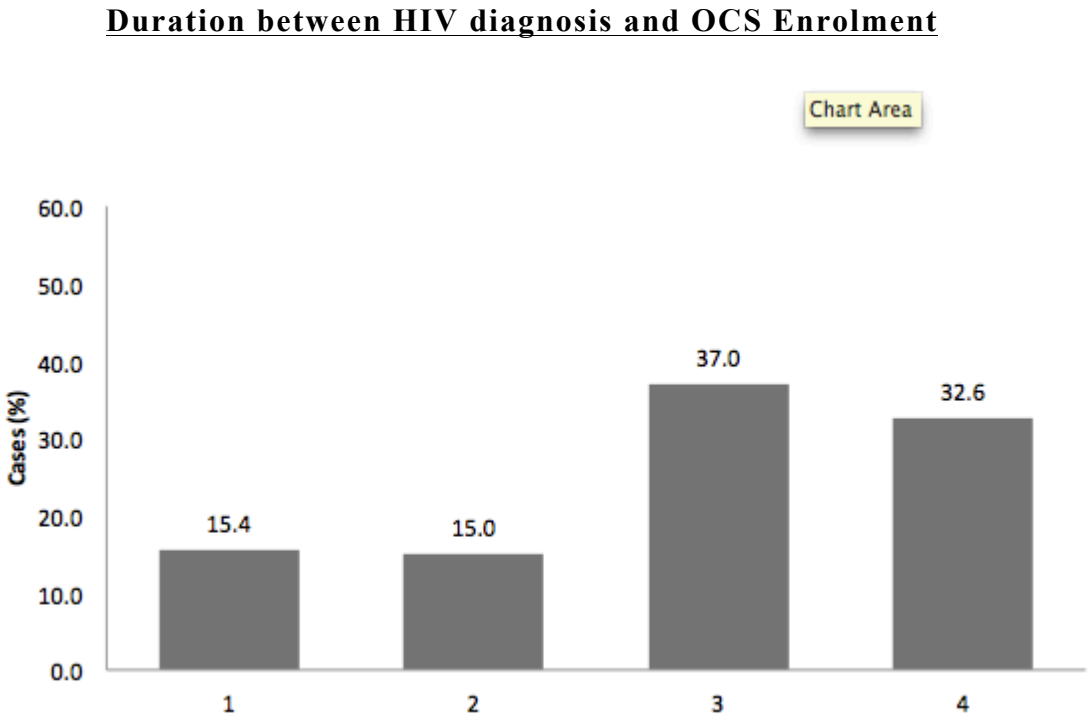

Figure 8.1a – Time duration between HIV diagnosis and enrolment in OCS. 1 = Less than 1 Year, 2= 1 Year and Less than 2 Years, 3 = 2 Years and Less than 5 Years, 4 = More than 5 Years

Of 1293, 1225 (94.7%) cases that had information on follow up duration in the database, of whom 422 (34.4%) were followed up for less than 12 months, 646 (52.7%) were followed up for

12 to 24 months and 157 (12.1%) were followed up for more than 24 months. Figure 8.1b shows a graphical representation of the follow-up of participants in the study.

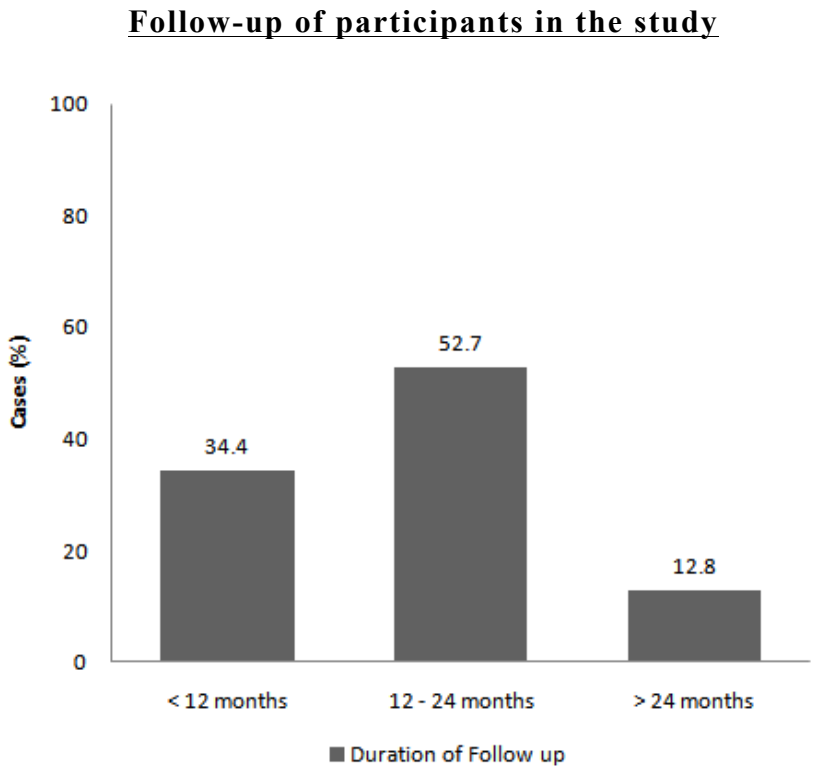

Figure 8.1b – Duration of follow up in OCS (n = 1225)

Demographic Characteristics[6]

The majority of the individuals were males 1009 (78.0%) and 274 (21.2%) females. The remaining 10 (0.8%) had no information about gender in the database. The mean age of the group was 36.5 (SD 10.0) years at the time of their diagnosis with HIV. The youngest person in the cohort diagnosed with HIV was 15 years old whereas the oldest person diagnosed with HIV was 81 years old. 384 (29.7%) were aged less than 30, 805 (62.3%) were aged between 30 and 50, and 104 (8.0%) were aged 50 and above at the time of their HIV diagnosis.

[6] Frequency tables of demographic characteristics computed in SPSS are provided in Appendix B

536 (41.5%) of the individuals were diagnosed with HIV during the years 2001 and 2003, 463 (35.8%) were diagnosed during 2004 and 2006 and 294 (22.7%) were diagnosed between 2007 and 2009. A graph illustrating this data is shown in Figure 8.1c whereas a graph illustrating HIV diagnosis per year is shown in Figure 8.1d.

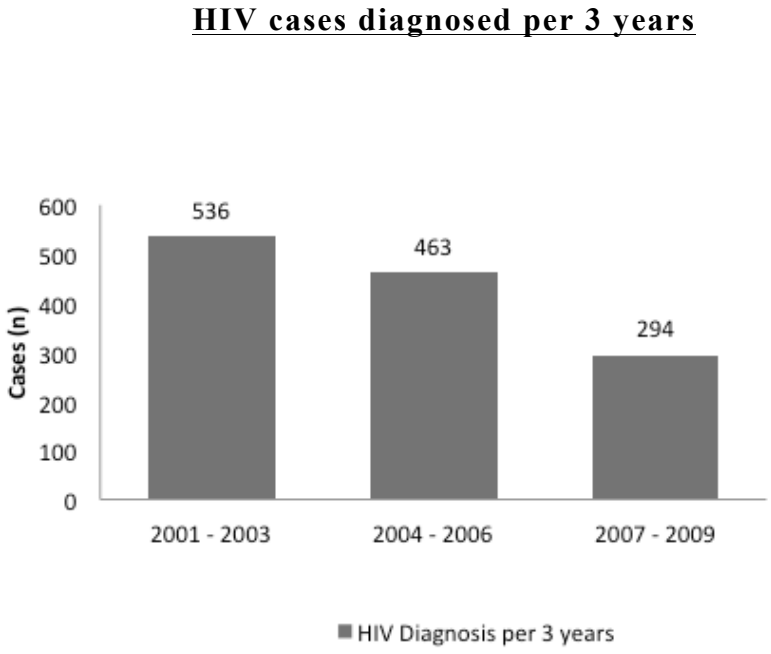

Figure 8.1c – Number of cases diagnosed with HIV per 3 years

HIV cases diagnosed per year (2001 – 2009)

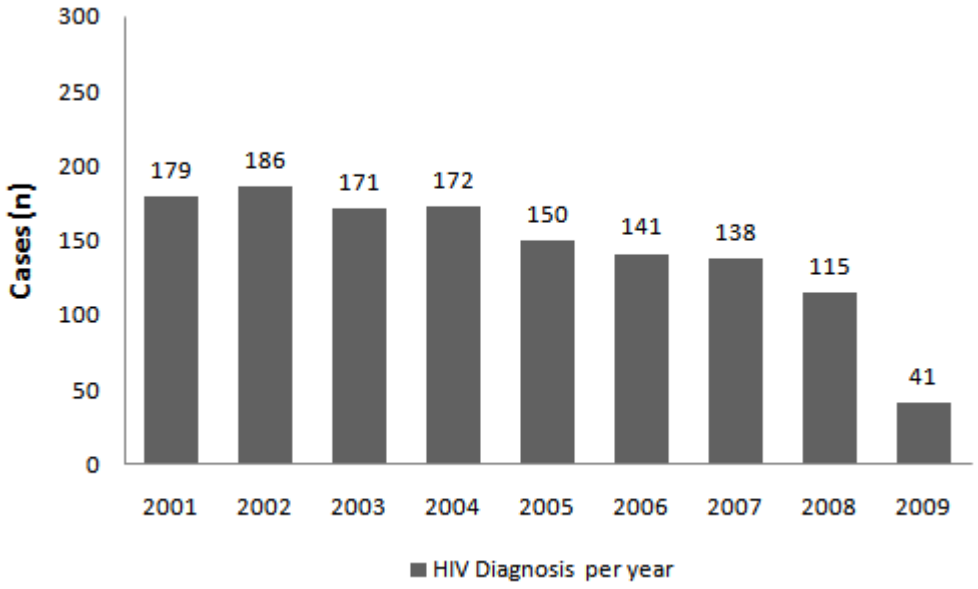

Figure 8.1d – Number of cases diagnosed with HIV per year. Columns represent year and rows represent number of cases

639 (49.4%) of the 1293 individuals were non-Aboriginals born in Canada, 110 (8.5%) were Canadian born Aboriginals, 168 (13.0%) were born in Africa, 65 (5.0%) in Caribbean, and 61 (4.7%) were born in Europe and Central Asia. A complete proportion of birthplace regions can be found in table 8.1.

Of the 396 individuals who were recent to Canada, 294 (74.2%) had been living in Canada for more than 5 years whereas 102 (25.7%) have been living in Canada for less than 5 years. In terms of residency for the entire group, 1086 (84.0%) resided in an urban area where as 50 (3.9%) were living in a rural area.

In terms of HIV risk exposure category, men having sex with men (MSM) were most frequently represented with 684 (52.9%) individuals, 202 (15.6%) were in the people from HIV-endemic countries category, 149 (11.5%) were in the heterosexual category and 94 (7.3%) were in the Intravenous Drug Users (IDUs) category.

Clinical Characteristics

466 (36.0%) had at least one record of Mantoux skin test result in the database whereas (827; 64.0%) had no record of any Mantoux test result. Medication history indicated 75 people to be on TB treatment medications, out of which 56 (74.7%) received medication for the treatment of active TB and 17 (22.7%) received medication for treating latent TB. 1033 (79.9%) of all cases were on HAART medications and 260 (20.1%) did not have a record of HAART medications in the database, possibly due to a recent HIV diagnosis at the time.

Baseline Characteristics of individuals matching the inclusion criteria			
Baseline Characteristics (n)		**Sample n= 1293**	
		Percent (%)	Frequency (n)
Gender	Male	78	1009
	Female	21.2	274
	Missing	0.8	10
Age Category 1	< 30	29.7	384
	30 - 50	62.3	805
	>50	8.0	104
Age Category 2	15-19	2.6	34
	20-24	8.9	115
	25-44	68.7	888
	45-64	19.3	249
	65 and above	0.5	7
Canadian or Foreign Born	Canadian Born	57.9	749
	Foreign Born	34.4	445
	Missing	7.7	99
Birthplace Region	Canada (non-Aboriginals)	49.4	639
	Canada (Aboriginal)	8.5	110
	Africa	13	168
	Caribbean	5	65
	Middle East	0.8	10
	South Asia	0.6	8
	Asia or Pacific Regions	3.6	47
	Europe or Central Asia	4.7	61
	North America (excluding Canada)	2.9	37
	Central and South America	3.8	49
	Missing	7.7	99
Years in Canada[7]- (n = 396)	< 5 Years	25.8	102
	5-10 Years	24.5	97
	> 10 Years	49.7	197

Continued...

[7] This category is for those who reported to be born outside of Canada

Baseline Characteristics of individuals matching the inclusion criteria (cont'd..)			
Baseline Characteristics (n)		**Entire Cohort n= 1293**	
		Percent (%)	Frequency (n)
HIV Risk Categories -1293	MSM	52.9	684
	HIV- endemic	15.6	202
	Heterosexual	11.5	149
	IDU	7.3	94
	MSM- IDU both	4.4	57
	Clotting Factor/Transfusion	1.2	15
	Others/NIR	7.1	92
Living Area	Urban	84	1086
	Rural	3.9	50
	Missing	12.1	157
Clinical (at the time of Registration)	Baseline Mean CD4 count (cells/mL)	0-1440*	376.9**
	Baseline Viral Load Count (log copies/ml)	1.59-6.04*	2.64**
Mantoux Test Record	Yes	36.0	466
	No	64.0	827
Follow up Duration (in OCS Study)	<12 months	32.6	422
	> 12 months	62.1	803
Smoking Status	Never Smoked	34.6	448
	Currently Smoke	33.8	437
	Former Smoker	16.2	209
	Missing	15.4	199
Year of HIV Diagnosis	2001 – 2003	41.5	536
	2004 – 2006	35.8	463
	2007 - 2009	22.7	294

Table 8.1 Baseline Characteristics of Individuals diagnosed with HIV from 2001 to 2009

*indicates a range between the lowest and the highest value, rather than a percentage.

**indicates a mean value instead of a frequency value.

Clinical data showed the mean CD4 count at the time of registration to the OCS study was 376.9 cells/ml. 466 (36.0%) of the cohort had a CD4 count greater than 500 cells/ml, 632 (48.9%) had a CD4 count between 200 to 500 cells/ml and 139 (10.8%) had a CD4 count less than 200. There were 56 (4.3%) individuals who did not have a record of CD4 count at the time of registration. In terms of viral load, the baseline viral load count at the time of registration was 2.64 $\log^{10}$ copies per ml.

1094 (84.6%) individuals had data on smoking status in the database, 448 (34.6%) of them never smoked, 437 (33.8%) currently smoke, and 209 (16.2%) were former smokers.

In terms of interview dates of participants in OCS, 1098 (84.9%) of the 1293 cases had a record of an interview date in the database.

8.2 Prevalence of active TB in the cohort

Of the 1293 individuals in the cohort, 76 had active TB. The period prevalence of active TB in the individuals diagnosed with HIV during 2001 to 2009 was 76/1293 = 0.0587 or 5.87% (95% CI 4.6% to 7.0%). Sixty-six (66) of 76 cases had the TB diagnosis date in the database. 52 (78.8%) of the cases were diagnosed with TB after their diagnosis of HIV and 14 (21.2%) were diagnosed with TB before their HIV diagnosis. The occurrence of active TB relative to the time of HIV diagnosis is presented in Figure 8.2b. When examined for a Mantoux test record in cases that were identified as having active TB, 37 (48.7%) of 76 TB cases had no record of a previous Mantoux test in the database.

There were 30 active TB cases present in AIDS defining conditions (ADC) dataset, out of which 9 were identified as pulmonary and 11 as extra-pulmonary. The other 10 cases were only labelled as active TB cases. In the adverse event dataset, 7 were identified as active TB cases. When medication history data was explored, 56 cases received treatment for active TB. 17 out of the 56 cases were excluded as they were already identified in adverse events and ADC. The remaining 39 were added to the list of active TB cases. Based on the treatment regimen and duration of treatment, there were no MDR-TB cases identified in the database. A complete flow chart of TB cases is presented in Figure 8.2.a.

To examine an association between active TB and a previous negative Mantoux test, cross tab analysis between the two variables was performed. There were 4 (10.0%) cases that had a previous negative Mantoux test result but were identified as active TB cases in the database.

Flow Chart to identify TB Cases

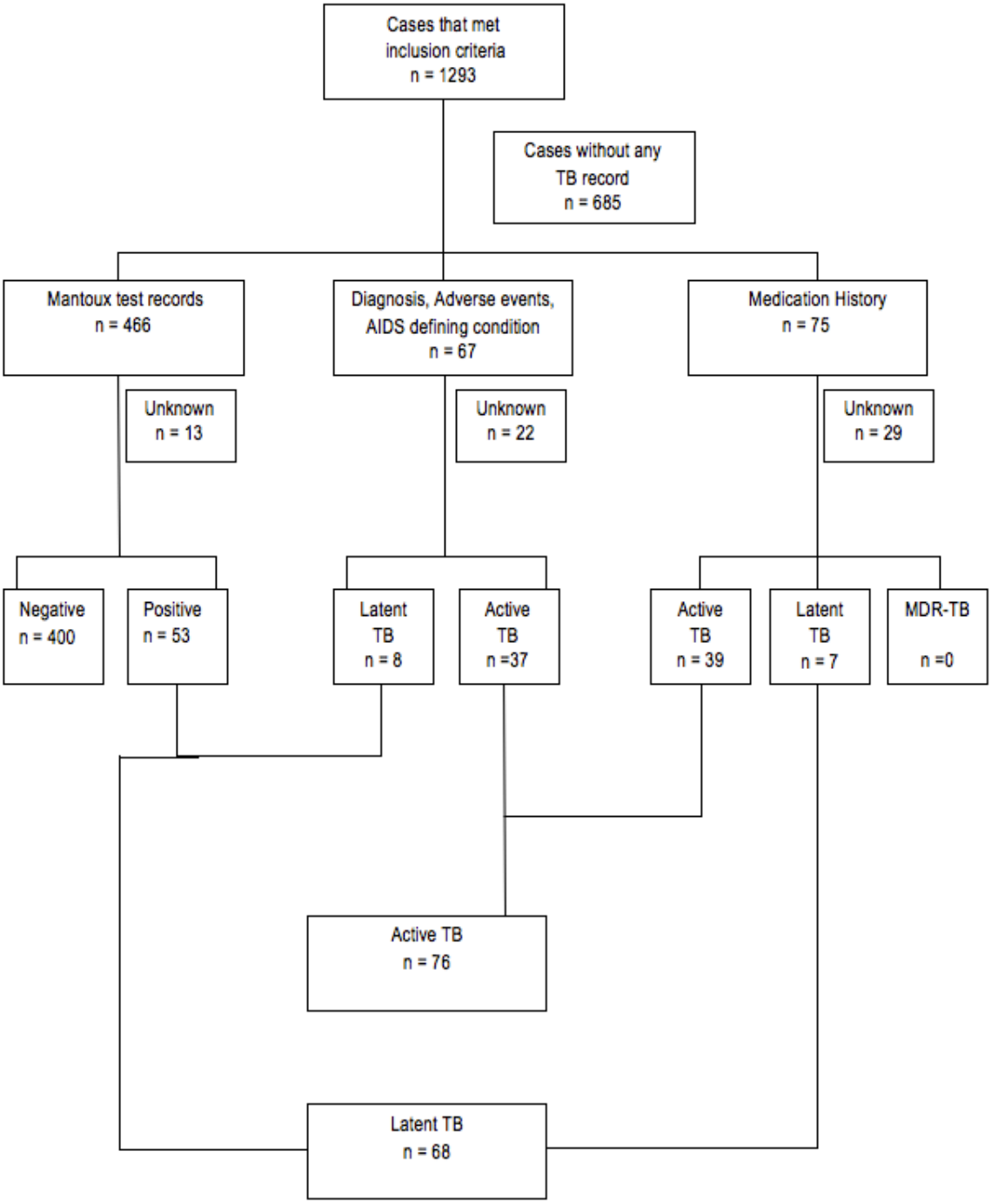

Figure 8.2a –Active and Latent TB cases in the datasets provided. Mantoux tests, adverse events, AIDS defining conditions, diagnosis and medication history in the OHTN Cohort Study.

Time duration between HIV Diagnosis and active TB

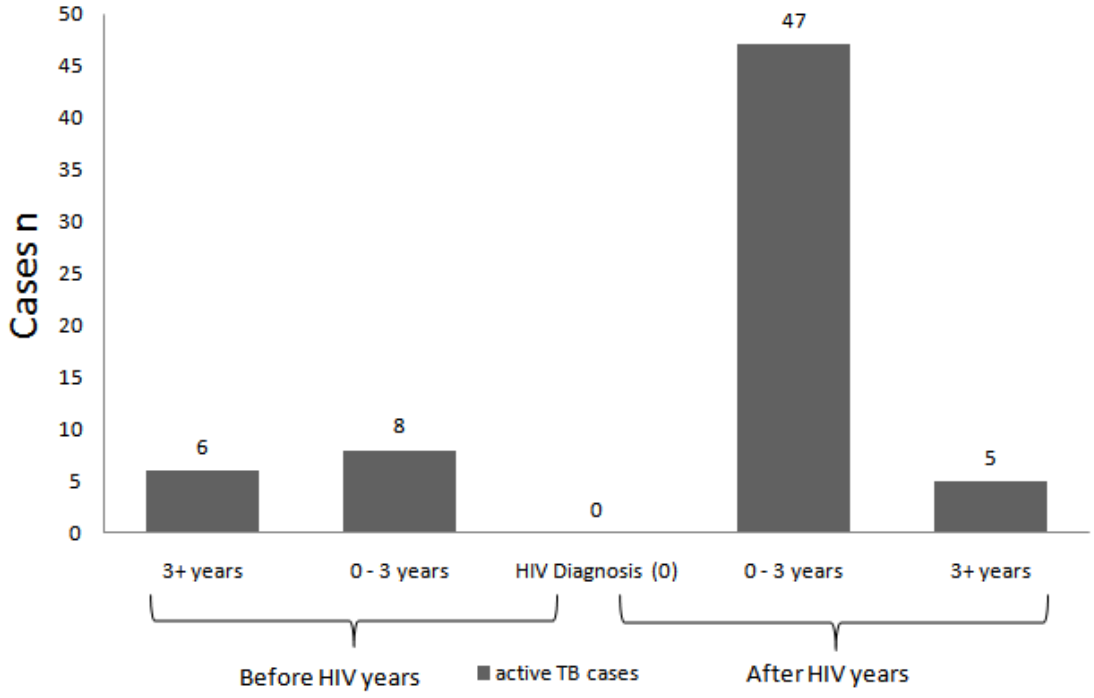

Figure 8.2b – Time interval between HIV diagnosis and active TB diagnosis. The interval labelled HIV diagnosis (0) represents patients diagnosed with tuberculosis at the time of HIV diagnosis.

73 of 76 active TB cases were still actively participating in OCS. Two (2) were lost to follow up and one (1) person died. In terms of the duration of the follow-up, 70 of 76 cases had a record of last follow up date, out of which 57 (81.4%) were followed up for more than 12 months whereas 13 (18.6%) were followed up for less than 12 months.

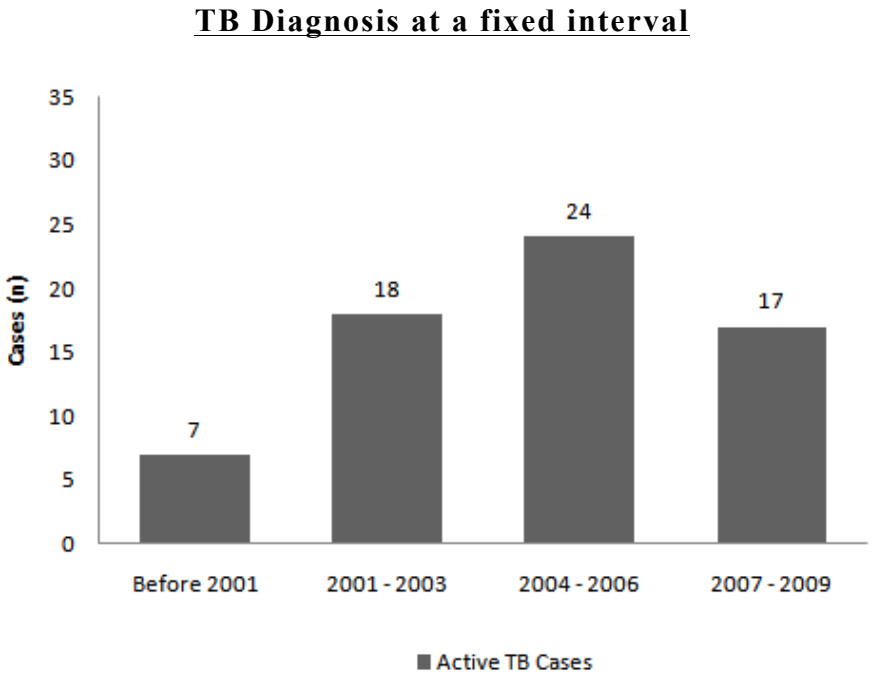

Figure 8.2c – Diagnosis of active TB at a fixed interval.

8.2.1 Characteristics of cases with active TB

Of the 76 cases diagnosed with TB, 40 (52.6%) were males and 35 (46.1%) were females. 20 (26.3%) were aged 29 years and less, 38 (63.2%) were aged between the years of 30 and 50, and 8 (10.5%) were aged 50 and 81

53 (69.7%) of these individuals were foreign-born Canadians whereas 13 (17.1%) were born in Canada, out of which 2 were aboriginal Canadians. Of the 53 foreign-born Canadians, 39 (51.3%) were African and 6 (7.9%) were born in Caribbean or Latin America. A detailed list of birthplace regions is displayed in Table 8.2.

48 individuals with active TB who were born outside of Canada provided data on how long they have lived in Canada. 19 (25.0%) of these individuals had lived in Canada for less than 5 years and 29 (60.4%) had lived in Canada for more than 5 years.

In terms of HIV exposure category, 39 (51.3%) individuals with TB were from HIV-endemic countries, 11 (14.5%) were MSM, and 4 (5.3%) were IDUs. 59 (77.6%) individuals with active TB were living in urban areas in Ontario and 3 (3.9%) were living in rural Ontario.

72 out of 76 TB cases had data on CD4 count at the time of registration. 26 (34.2%) had a CD4 count more than 500 cells/ml, 40 (52.6%) between 200 and 500 cells/ml, and 6 (7.9%) had a CD4 count less than 200 cells/ml.

Characteristics of individuals with active TB and HIV			
		Frequency (n)	Percent (%)
Gender	Male	40	52.6
	Female	35	46.1
	Missing	-	1.3
Age	< 30	20	26.3
	30 – 50	48	63.2
	> 50	8	10.5
Birthplace Region	Canada (non-Aboriginals)	11	14.4
	Canada (Aboriginal)	-	2.6
	Africa	39	51.3
	Caribbean	-	5.3
	South Asia	-	1.3
	Asia and Pacific Regions	4	5.3
	North America (excluding Canada)	-	3.9
	Central and South America	-	2.6
	Missing	10	13.2
Follow up Duration	< 12 months	13	7.1
	12 – 24 months	45	59.2
	>24 months	12	15.8
	Missing	6	7.9
HIV Risk	MSM	11	14.5
	HIV-endemic	39	51.3
	Heterosexual	8	10.5
	IDU	-	6.6
	Others	13	17.1
Smoking Status	Never	38	50.0
	Former	8	10.5
	Smoke	15	19.7
	Missing	-	5.3

Table 8.2 Characteristics of individuals with active TB and HIV
(Frequency of 5 or less are removed to minimize identification risk)

8.3 Prevalence of latent TB in the cohort

Of the 1293 cases examined, 68 had latent TB. The period prevalence of latent TB cases in individuals diagnosed with HIV during 2001 to 2009 was 5.26% (68/1293 = 0.0526) 95% (CI 4.0% - 6.5%). 50 of the 68 cases (73.5%) were followed up for more than 12 months, 13 (19.1%) were followed up for less than 12 months and 5 (7.4%) had no data on the duration of follow-up.

The prevalence of latent TB is estimated to be much higher if only Mantoux test records are used as per the other method described on page 68. Of the 466 Mantoux test records with a definite result, 53 were positive. Therefore, the period prevalence of latent TB according to this method was to 11.37% (53/466 = 0.1137) 95% CI (8.2% to 13.7%)

8.3.1 Characteristics of latent TB cases

Of the 68 latent TB cases, 35 (51.5%) were females, 32 (47.1%) were males and 1 (1.5%) did not provide information on gender. Distribution of gender proportion between HIV only and HIV/Latent TB groups is provided in Figure 8.3a.

22 (32.4%) individuals were aged 29 years and less, 39 (57.4%) aged between 30 and 49 years and 7 (10.3%) aged between 50 and 81 years.

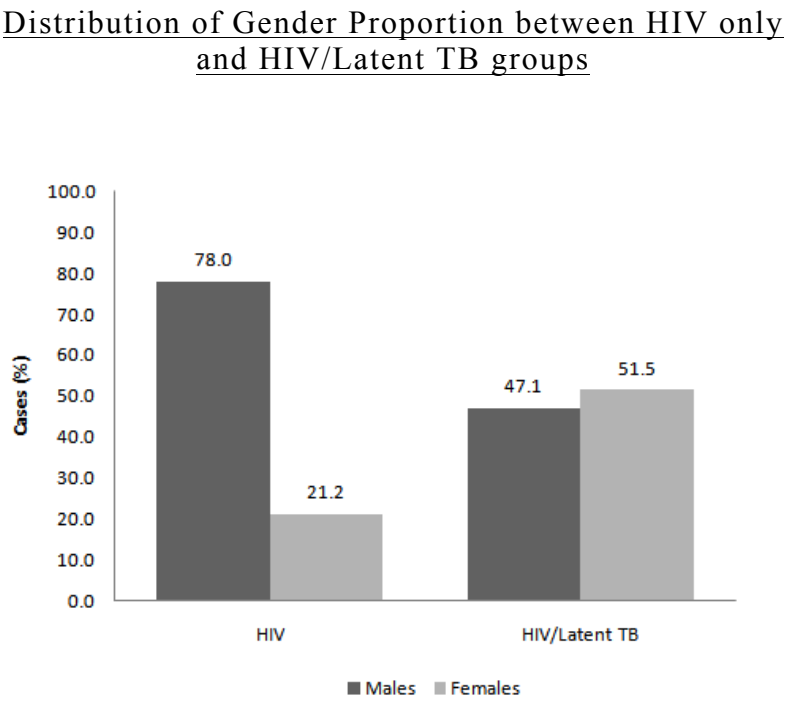

Figure 8.3a – Gender proportions distribution for Latent TB/HIV and HIV only cases. HIV n = 1283 and HIV/Latent TB n = 68.

57 (83.8%) of 68 latent TB individuals had birth-place information in the database, of whom, 8 (14.0%) were born in Canada (non-Aboriginals), 31 (54.4%) were born in Africa, 5 (8.8%) were born in Caribbean or Latin America, 4 (5.9%) were born in Asia or Pacific Regions, 3 (4.4%) in Europe or Central Asia and 2 (2.9%) in South Asia.

43 (63.2%) of latent TB individuals born outside of Canada provided information on the length of stay in Canada, of whom 18 (26.5%) lived for less than 5 years and 25 (36.8%) lived for more than 5 years in Canada.

In terms of HIV transmission risk, the highest proportion were of people from HIV endemic countries (32; 47.1%), 17 (25.0%) were MSM, 5 (7.4%) were heterosexual, 2 (2.9%) were IDUs and 12 (17.6%) were categorized under the others category.

Of the 68 latent TB, 63 (92.6%) had a record of Mantoux skin test in the database and were identified as latent TB cases based on the Mantoux results. Five (7.4%) had no previous record of Mantoux skin test but were identified as latent TB cases based on the medication history.

8.4 Bivariate and Multivariate Analysis[8]

Proportions of cases with outcome variable (active TB, latent TB, Mantoux test record) and HIV, were compared with proportions of HIV only. Bivariate analyses were performed to calculate the unadjusted odds ratio. Multivariate analyses were performed to calculate the adjusted odds ratio. The final variables included in the multivariate analysis were sex, age, birthplace region, HIV transmission risk, follow-up duration, and smoking status. There was evidence of collinearity between the birthplace region and HIV transmission risk variable as individuals born in Africa (birthplace variable) and individuals from HIV endemic countries (HIV transmission risk variable) would have assessed the same cases. Results from models with and without the inclusion of HIV transmission variable are shown below.

8.4.1 Factors associated with active TB

Results of the logistic regression analysis that identifies factors associated with active TB and HIV are provided in table 8.4a (1) and 8.4a (2). Although there was no significant interaction among the variables, collinearity was found in the HIV transmission risk variable as one of its categories (HIV endemic country) in the variable had an overlap with one of the categories (Africa) of the birthplace region variable. Table 8.4a (1) shows results of bivariate and multivariate analysis including the HIV transmission risk variable whereas table 8.4a (2) shows results after excluding this variable.

[8] Multivariate analysis results computed in SPSS are shown in Appendix C.

Results indicate that females with HIV were 3.5 times (95% CI 2.2 – 5.7, $p < 0.001$) more likely to have active TB than males with HIV but when adjusted for age, birthplace region, HIV exposure, follow-up duration and smoking status, the risk was reduced to 1.2 times (95 % CI 0.6 – 2.5, $p = 0.56$) and was not statistically significant.

The age analysis showed that before adjusting, individuals with HIV aged 30 to 50 were 1.1 times (95% CI 0.7 – 1.9, $p = 0.601$) and individuals with HIV aged greater than 50 were 1.5 times (95% CI 0.6 – 3.5, $p = 0.337$) more likely to have TB than individuals aged less than 30. This risk, however, was not significant. After adjusting for sex, birthplace region, HIV exposure, follow-up duration and smoking status, a significant risk was found in individuals aged 50 and over as they were 3.7 times (95% CI 1.2 – 10.9, $p = 0.01$) more likely to have active TB.

In terms of birthplace region, bivariate and multivariate analysis compared individuals who were born in Canada (non-aboriginals) with Aboriginal Canadians, individuals born in Africa, Caribbean and Latin America. Aboriginal Canadians had a slightly increased risk (OR 1.05 95% CI 0.2 – 4.8, $p = 0.94$) of having TB than non-Aboriginal Canadians but when adjusted for age, sex, HIV exposure, follow-up duration and smoking status, the risk of TB decreased (OR 0.7 95% CI 0.1-3.5, $p = 0.70$). Both risks were statistically not significant.

Individuals with HIV who were born in Africa were at a much higher risk as they were 17.2 times (95% CI 8.4 – 34.6, $p <0.001$) more likely to have active TB than non-aboriginal

Canadians. After adjusting for age, sex, HIV exposure, follow-up duration and smoking status, the risk of TB decreased to 7.6 times (95% CI 1.9 – 39.1, p = 0.004) but was still statistically significant.

Similarly, individuals with HIV who were born in Caribbean or Latin America were 3.1 times (95% CI 1.1 – 8.4, p = 0.02) more likely to have active TB than non-aboriginal Canadians. However, after adjusting for age, sex, HIV exposure, follow-up duration and smoking status, the risk of TB not only decreased to 2.2 times (95% CI 0.6 – 8.2, p = 0.2) but also was not significant.

Individuals who were in the HIV endemic category of the HIV exposure variable were 14.6 times (95% CI 7.3 – 29.2, p <0.001) more likely to have active TB than those in the MSM category. After adjusting for age, sex, birthplace region, follow-up duration and smoking status, the risk reduced to 3.2 times (95% CI 0.8 – 12.7, p = 0.09) and was not statistically significant.

Individuals who were in the heterosexual category were 3.4 times (95% CI 1.3 – 8.7) more likely to have active TB than those in the MSM category. After adjusting for age, sex, birthplace region, follow-up duration and smoking status, the risk was slightly reduced to 3.0 times (95% CI 1.0 – 8.9, p = 0.039) but was still significant.

Individuals who acquired HIV infection through IDU contact were 2.1 times (95% CI 0.7 – 6.1, p = 0.176) more likely to have active TB than those in the MSM category but this was not statistically significant. When adjusted for age, sex, birthplace region, follow-up duration and smoking status, the risk slightly increased to 2.2 times (95% CI 0.7 – 7.2, p = 0.171) and remained not significant.

In terms of duration of follow up, individuals who were followed up in the study for more than 12 months were 2.4 times (95% CI 1.3 – 4.4, p <0.01) more likely to have TB than individuals who were followed up for less than 12 months. After adjusting for age, sex, birthplace region, HIV exposure, and smoking status, the risk decreased to 1.5 times (95% CI 0.7 – 2.9, p = 0.26) and was not significant.

Before adjusting for age, sex, birthplace region, and HIV exposure, individuals with HIV who never smoked had a higher chance (OR 2.6; 95% CI 1.4 – 4.8, p <0.05) of acquiring TB than individuals who smoked frequently, however, after adjusting, individuals who never smoked had less risk (OR 0.9; 95% CI 0.4 – 2.0, p < 0.85) than individuals who smoked but was not significant.

After removing the HIV transmission variable from the multivariate analysis, significant factors associated with active TB were age and birthplace region. Individuals with HIV aged 50 and older were 4.3 times (95% CI 1.5 – 12.7, p = 0.006) more likely to have active TB than

individuals aged 30 and younger. Similarly, individuals born in Africa were 14 times (95% CI 5.9 – 32.8, $p < 0.0001$) more likely to have active TB than those born in Canada. Individuals born in Caribbean & Latin America were also more likely to have active TB than those born in Canada (OR 3.3, 95% CI 1.1-9.3, $p = 0.028$). Results are shown in Table 8.4 a (2).

Active TB Cases (n =76)	Cases with TB/HIV		Cases with HIV only		Unadjusted OR	95% CI	p-value	Adjusted OR	95 % CI	p-value
	n	%	n	%						
Sex										
Male	40	4.0	969	96.0	1			1		
Female	35	12.8	239	87.2	3.5	2.2-5.7	<0.001	1.2	0.6 – 2.5	0.56
Age										
<30	20	5.2	364	94.8	1			1		
30-50	48	6.0	757	94.0	1.1	0.7-1.9	0.601	1.7	0.9 – 3.5	0.099
>50	8	7.7	96	92.3	1.5	0.6-3.5	0.337	3.7	1.2 – 10.9	0.016
Birthplace Region										
Canada (non-Aboriginals)	11	1.7	628	98.3	1			1		
Aboriginal Canadians	2	1.8	108	98.2	1.05	0.2 – 4.8	0.943	0.7	0.1 - 3.5	0.708
Africa	39	23.2	129	76.8	17.2	8.6-34.6	<0.001	7.6	1.9 – 30.1	0.004
Caribbean & Latin America	6	5.3	108	94.7	3.1	1.1-8.4	0.026	2.2	0.6 – 8.2	0.210
Others	8	4.9	155	95.1	2.9	1.2-7.1	0.022	3.1	1.2 – 8.2	0.019
HIV transmission mode										
MSM	11	1.6	673	98.4	1			1		
HIV Endemic	39	19.3	163	80.7	14.6	7.3 – 29.2	<0.0001	3.2	0.8-12.7	0.094
IDU	5	3.3	146	96.7	2.1	0.7 – 6.1	0.176	2.2	0.7-7.2	0.171
Heterosexual	8	5.4	141	94.6	3.4	1.3 – 8.7	0.009	3.0	1.0 – 8.9	0.039
Others	13	12.1	94	87.9	8.4	3.6 – 19.4	<0.001	3.7	0.7 – 20.2	0.122
Duration of Follow-up										
<12 months	13	3.1	409	96.9	1			1		
>12 months	57	7.1	746	92.9	2.4	1.3 – 4.4	0.005	1.5	0.7 – 2.9	0.262
Smoking Status										
Smoke	15	3.4	422	96.6	1			1		
Never	38	8.5	410	91.5	2.6	1.4 - 4.8	0.002	0.9	0.43 – 2.0	0.856
Former Smoker	8	3.8	201	96.2	1.1	0.4 – 2.6	0.8	0.8	0.30 – 2.0	0.649

Table 8.4.a(1) – Factors associated with active TB

Active TB Cases (n =76)	Cases with TB/HIV		Cases with HIV only		Unadjusted OR	95% CI	p-value	Adjusted OR	95 % CI	p-value
	n	%	n	%						
Sex										
Male	40	4.0	969	96.0	1			1		
Female	35	12.8	239	87.2	3.5	2.2-5.7	<0.001	1.8	0.9-3.5	0.077
Age										
<30	20	5.2	364	94.8	1			1		
30-50	48	6.0	757	94.0	1.1	0.7-1.9	0.601	1.7	0.9 – 3.5	0.094
>50	8	7.7	96	92.3	1.5	0.6-3.5	0.337	4.3	1.5 – 12.7	0.006
Birthplace Region										
Canada (non-Aboriginals)	11	1.7	628	98.3	1			1		
Aboriginal Canadians	2	1.8	108	98.2	1.05	0.2 – 4.8	0.943	0.9	0.1 - 4.2	0.708
Africa	39	23.2	129	76.8	17.2	8.6-34.6	<0.001	14.0	5.9 - 32.8	0.0001
Caribbean & Latin America	6	5.3	108	94.7	3.1	1.1-8.4	0.026	3.3	1.1 – 9.3	0.028
Others	8	4.9	155	95.1	2.9	1.2-7.1	0.022	3.2	1.2 – 8.2	0.015
Duration of Follow-up										
<12 months	13	3.1	409	96.9	1			1		
>12 months	57	7.1	746	92.9	2.4	1.3 – 4.4	0.005	1.5	0.7 – 2.9	0.262
Smoking Status										
Smoke	15	3.4	422	96.6	1			1		
Never	38	8.5	410	91.5	2.6	1.4 - 4.8	0.002	0.9	0.43 – 2.0	0.856
Former Smoker	8	3.8	201	96.2	1.1	0.4 – 2.6	0.8	0.8	0.30 – 2.0	0.649

Table 8.4.a (2) – Factors associated with active TB (excluding HIV transmission variable)

8.4.2 Factors associated with Latent TB

Results of the logistic regression analysis that identifies factors associated with latent TB and HIV are provided in table 8.4b (1). Proportions of cases with latent TB and HIV were compared with proportions of cases with HIV only. Bivariate analysis was performed to calculate the unadjusted odds ratio. Multivariate analysis was performed to calculate the adjusted odds ratio.

Females with HIV were 4.4 times (95% CI 2.7 - 7.3, $p < 0.001$) more likely to acquire latent TB than males. After adjusting for age, birthplace region, HIV exposure risk, follow-up duration, and smoking status, the risk of acquiring latent TB for females was 2.5 times (95% CI 1.0 – 6.02, $p < 0.05$) more than males.

Individuals with HIV aged 30 to 50 years had similar risk (OR 0.8; 95% CI 0.4 - 1.4, $p = 0.83$) of being with latent TB than individuals aged 30 and less. After adjusting, the latent TB risk increased as the individuals aged 30 to 50 years were 1.2 times (95% CI 0.6 – 2.4, $p = 0.57$) more likely to be infected with latent TB than individuals aged 30 and less. Both risks were statistically not significant. Similarly, individuals with HIV aged 50 years and over had slightly increased risk (OR 1.2; 95% CI 0.4 – 1.4, $p = 1.1$) of acquiring latent TB than individuals aged 30 and less. After adjusting for sex, birthplace region, HIV exposure risk, follow-up duration, and smoking status, the risk further increased to 1.9 times (95% CI 0.5 – 6.6, $p = 0.33$) but remained statistically not significant.

There were no Aboriginal Canadians found to be infected with latent TB in the database. Individuals with HIV who were born in Africa were 20.9 times (95% CI 9.4 – 46.5, $p < 0.001$) more likely to have latent TB than non-Aboriginal Canadians. After adjusting for age, sex, HIV exposure risk, follow-up duration, and smoking status, the risk dropped to 11. 9 times (95% CI 2.4 – 58.1, $p < 0.002$) but remained statistically significant. Individuals with HIV who were born in Caribbean or Latin America were 4.2 times (95% CI 1.3 – 13.2, $p < 0.05$) more likely to have latent TB than non-Aboriginal Canadians. After adjusting, the risk dropped to 1.9 times (95% CI 0.4 – 9.3, $p < 0.40$) and was statistically not significant.

Individuals who were in the HIV endemic country category of the HIV transmission risk variable were 7.3 times (95% CI 4.0 – 13.6, $p < 0.0001$) more likely to have latent TB than those in the MSM category. After adjusting for age, sex, birthplace region, follow-up duration, and smoking status, individuals who acquired HIV infection through HIV endemic country were less likely (OR 0.9; 95% CI 0.2 – 4.7, $p = 0.98$) to be infected with latent TB than those in the MSM category. There was no statistical significance difference in the risk between the two groups.

Individuals who were in the heterosexual category were 1.3 times (95% CI 0.4 – 3.7, $p = 0.5$) more likely to have latent TB than those in the MSM category. After adjusting, individuals in the heterosexual category were less likely (OR 0.9; 95% CI 0.2 – 3.3, $p = 0.89$) to be infected with latent TB than those in the MSM category. The difference also however, was not statistically significant in the two groups.

Individuals in the IDU contact category were less likely (OR 0.5; 95% CI 0.1 – 2.3, p = 0.39) to be infected with latent TB than those in the MSM category. The risk difference was not significant. The risk was not significant even after adjusting for age, sex, birthplace region, follow-up duration, and smoking status (OR 0.3; 95% CI 0.04 – 2.8, p = 0.32).

In terms of duration of follow-up, participants who were followed up in the study for more than 12 months provided more exposure in the database and were 2.1 times (95% CI 1.1 – 3.9, p < 0.05) more likely to have latent TB than individuals who were followed up for less than 12 months. After adjusting for age, sex, birthplace region, HIV exposure risk, and smoking status, the risk decreased to 1.7 times (95% CI 0.7 – 3.7, p = 0.18) but was not significant.

Before adjusting for potential confounding factors, individuals with HIV who never smoked had a higher odds (OR 3.4; 95% CI 1.6 – 6.9, p < 0.01) of acquiring TB than individuals who smoked frequently, however, after adjusting for age, sex, birthplace region, HIV exposure risk, and follow-up duration, individuals who never smoked had less risk (OR 0.8; 95% CI 0.3 – 2.0, p < 0.75) than individuals who smoked but was not significant.

After removing the HIV transmission variable from the multivariate analysis, significant factors associated with latent TB were sex and birthplace region. Females were 2.4 times more likely (95% CI 1.1 – 5.2, p = 0.017) to have latent TB than males. Individuals born in Africa were 12

times (95% CI 4.7 – 32.1, $p < 0.0001$) more likely to have latent TB than those born in Canada. Results are shown in Table 8.4 b (2).

Latent TB Cases (n = 68)	Cases with TB		Cases without TB		Unadjusted OR	95% CI	p-value	Adjusted OR	95 % CI	p-value
	n	%	n	%						
Sex										
Male	32	3.2	977	96.8	1			1		
Female	35	12.8	239	87.2	4.4	2.7 – 7.3	<0.001	2.5	1.0 – 6.02	0.046
Age										
<30	22	5.7	362	94.3	1			1		
30-50	39	4.8	766	95.2	0.8	0.4 – 1.4	0.838	1.2	0.6 – 2.4	0.575
>50	7	6.7	97	93.3	1.2	0.4 – 2.8	1.187	1.9	0.5 – 6.5	0.328
Birthplace Region										
Canada (non-Aboriginals)	8	1.3	631	98.7	1			1		
Aboriginals Canadians	0	0	110	100				-	-	-
Africa	31	18.5	137	81.5	20.9	9.4 – 46.5	<0.001	11.9	2.4 – 58.1	0.002
Caribbean & Latin America	5	4.4	109	95.6	4.2	1.3 – 13.2	<0.05	1.9	0.4 – 9.3	0.406
Others	13	8.0	150	92.0	8.0	3.2 – 19.7	<0.001	4.9	2.1 – 15.1	0.001
HIV Transmission										
MSM	17	2.5	667	97.5	1			1		
HIV Endemic	32	15.8	170	84.2	7.3	4.0 -13.6	<0.0001	0.9	0.2 – 4.7	0.98
IDU	2	1.3	149	98.7	0.5	0.1 – 2.3	0.39	0.3	0.04 – 2.8	0.32
Heterosexual	5	3.4	144	96.6	1.3	0.4 – 3.7	0.5	0.9	0.2 – 3.3	0.89
Others	12	11.2	95	88.8	4.9	2.2 – 10.7	<0.001	1.9	0.3 – 11.3	0.47
Duration of Follow-up										
<12 months	50	6.2	753	93.8	1			1		
>12 months	13	3.1	409	96.9	2.1	1.1 – 3.9	0.02	1.7	0.7 – 3.7	0.18
Smoking Status										
Smoke	10	2.3	427	97.7	1			1		
Never	33	7.4	415	92.6	3.4	1.6 – 6.9	<0.01	0.8	0.3 – 2.06	0.75
Former Smoker	8	3.8	201	96.2	1.7	0.6 – 4.3	0.27	1.2	0.4 – 3.2	0.74

Table 8.4b (1) – Factors associated with latent TB

Latent TB Cases (n = 68)	Cases with TB		Cases without TB		Unadjusted OR	95% CI	p-value	Adjusted OR	95 % CI	p-value
	n	%	n	%						
Sex										
Male	32	3.2	977	96.8	1			1		
Female	35	12.8	239	87.2	4.4	2.7 – 7.3	<0.001	2.4	1.1 – 5.2	0.017
Age										
<30	22	5.7	362	94.3	1			1		
30-50	39	4.8	766	95.2	0.8	0.4 – 1.4	0.838	1.2	0.6 – 2.3	0.593
>50	7	6.7	97	93.3	1.2	0.4 – 2.8	1.187	1.7	0.5 – 6.2	0.360
Birthplace Region										
Canada (non-Aboriginals)	8	1.3	631	98.7	1			1		
Aboriginals Canadians	0	0	110	100				-	-	-
Africa	31	18.5	137	81.5	20.9	9.4 – 46.5	<0.001	12.3	4.7 – 32.1	0.0001
Caribbean & Latin America	5	4.4	109	95.6	4.2	1.3 – 13.2	<0.05	1.7	0.4 – 7.06	0.418
Others	13	8.0	150	92.0	8.0	3.2 – 19.7	<0.001	5.4	2.0 – 14.1	0.001
Duration of Follow-up										
<12 months	50	6.2	753	93.8	1			1		
>12 months	13	3.1	409	96.9	2.1	1.1 – 3.9	0.02	1.7	0.7 – 3.7	0.178
Smoking Status										
Smoke	10	2.3	427	97.7	1			1		
Never	33	7.4	415	92.6	3.4	1.6 – 6.9	<0.01	0.9	0.4 – 2.1	0.661
Former Smoker	8	3.8	201	96.2	1.7	0.6 – 4.3	0.27	1.2	0.4 – 3.37	0.668

Table 8.4b (2) – Factors associated with latent TB (excluding HIV transmission variable)

8.4.3 Factors associated with having a Mantoux test in the OCS database

Results of the logistic regression analysis that identifies factors associated with having a Mantoux test in the OCS database provided in table 8.4c. Proportions of cases with a record of Mantoux test were compared with proportions of cases without a record of Mantoux test. Bivariate analysis was performed to calculate the unadjusted odds ratio. Multivariate analysis was performed to calculate the adjusted odds ratio by adjusting for potential confounding variables. Such variables were sex, age, birthplace region, HIV exposure risk, follow-up duration, and smoking status.

Females were less likely (OR 0.6; 95% CI 0.4 - 0.8, $p < 0.001$) to receive a Mantoux test than males. After adjusting for age, birthplace region, HIV exposure risk, follow-up duration, and smoking status, the risk remained significant (OR 0.5; 95% CI 0.3 - 0.8, $p = 0.003$).

Age was not found to be a significant factor that is associated with receiving a Mantoux test. HIV infected persons aged 30 years and under did not have a significantly different proportion of Mantoux test records than persons aged 30 – 50 years and 50 and over years. The proportion remained insignificant after adjusting (<30 vs. 30-50, OR 0.8; 95% CI 0.6 - 1.1, $p = 0.17$) and (<30 vs. >50, OR 0.9; 95% CI 0.5 - 1.5, $p = 0.75$).

Aboriginal Canadians were slightly less likely (OR 0.6 ; 95% CI 0.4 - 0.9, $p = 0.03$) to receive a Mantoux test than non-Aboriginal Canadians , however this difference became insignificant after adjusting for sex, age, HIV exposure risk, follow-up duration, and smoking status (OR 0.7, 95%

CI 0.4 - 1.1, p = 0.176). HIV infected persons born in Africa were less likely (OR 0.6; 95% CI, 0.5 - 0.9, p = 0.02) to receive a Mantoux test than non-Aboriginal Canadians. This association remained significant after adjusting for sex, age, HIV exposure risk, follow-up duration, and smoking status (OR 0.4; 95% CI 0.1 - 0.8, p = 0.0019).

In terms of HIV exposure risk, individuals in the heterosexual category were more likely (OR 0.6; 95% CI 0.4 - 0.9, p = 0.04) to receive a Mantoux test than the individuals in the MSM category, but after adjusting for sex, age, birthplace region, follow-up duration, and smoking status, individuals in the HIV endemic countries category (OR 2.4; 95% CI 1.1 - 5.2, p = 0.02) and IDUs category (OR 1.8; 95% CI 1.1 - 2.8, p = 0.01) were the only groups associated with receiving a Mantoux test.

Duration of follow up in the OCS study was not associated with receiving a Mantoux test (<12 months vs. > 12 months, OR 1.1; 95% CI 0.8 - 1.4, p = 0.579). The results remained the same after adjusting for sex, age, birthplace region, HIV exposure, and smoking status (<12 months vs. > 12 months, OR 1.1; 95% CI 0.8 - 1.4, p = 0.733).

After removing the HIV transmission variable from the multivariate analysis, significant factors associated with having a Mantoux test record in OCS were sex and smoking status. Females were less likely (OR 0.6; 95% CI 0.4 – 0.9, p < 0.01) to have a Mantoux test record in OCS than males. Individuals with HIV who were former smokers were more likely (OR 1.4; 95% CI 1.0 – 2.1, p = 0.039) to have a Mantoux test record in OCS than individuals who currently smoked. Results are shown in Table 8.4 c (2).

Cases with a Mantoux Test record (n = 466)	Cases with Mantoux test		Cases without Mantoux test		Unadjusted OR	95% CI	p-value	Adjusted OR	95 % CI	p-value
	n	%	n	%						
Sex										
Male	338	33.5	671	66.5	1			1		
Female	126	46.0	148	54.0	0.6	0.4 – 0.8	<0.001	0.5	0.3 – 0.8	0.003
Age										
<30	143	37.2	241	62.8	1			1		
30-50	289	35.9	516	64.1	1.05	0.8 – 1.3	0.654	0.8	0.6 – 1.1	0.275
>50	34	32.7	70	67.3	1.2	0.7 – 1.9	0.393	0.9	0.5 – 1.5	0.756
Birthplace Region										
Canada (non-Aboriginals)	212	33.2	427	66.8	1			1		
Aboriginals Canadians	48	43.6	62	56.4	0.6	0.4 – 0.9	0.03	0.7	0.4 – 1.1	0.176
Africa	72	42.9	96	57.1	0.6	0.5 – 0.9	0.02	0.4	0.1 – 0.8	0.019
Caribbean & Latin America	39	34.2	75	65.8	0.9	0.6 – 1.4	0.82	0.9	0.5 – 1.5	0.756
Others	63	38.7	100	61.3	0.8	0.5 – 1.1	0.18	0.8	0.5 – 1.3	0.513
HIV Transmission										
MSM	237	34.6	447	65.4	1			1		
HIV Endemic	79	39.1	123	60.9	0.8	0.6 – 1.1	0.245	2.4	1.1 – 5.2	0.028
IDU	47	31.1	104	68.9	1.1	0.8 – 1.7	0.408	1.8	1.1 – 2.8	0.010
Heterosexual	65	43.6	84	56.4	0.6	0.4 – 0.9	0.040	1.1	0.6 – 1.7	0.779
Others	38	35.5	69	64.5	0.9	0.6 – 1.4	0.861	0.8	0.3 – 2.2	0.714
Duration of Follow-up										
<12 months	156	37.0	266	63.0	1			1		
>12 months	284	35.4	519	64.6	1.1	0.8- 1.4	0.579	1.1	0.8 – 1.4	0.733
Smoking Status										
Smoke	171	39.1	266	60.9	1			1		
Never	159	35.5	289	64.5	1.1	0.8 – 1.5	0.263	1.4	1.0 – 1.9	0.036
Former Smoker	62	29.7	147	70.3	1.5	1.0 – 2.1	0.019	1.6	1.1 – 2.3	0.013

Figure 8.4c (1) Factors associated with having a Mantoux test record in the OCS database

Cases with a Mantoux Test record (n = 466)	Cases with Mantoux test		Cases without Mantoux test		Unadjusted OR	95% CI	p-value	Adjusted OR	95 % CI	p-value
	n	%	n	%						
Sex										
Male	338	33.5	671	66.5	1			1		
Female	126	46.0	148	54.0	0.6	0.4 – 0.8	<0.001	0.6	0.4 – 0.9	0.01
Age										
<30	143	37.2	241	62.8	1			1		
30-50	289	35.9	516	64.1	1.05	0.8 – 1.3	0.654	0.8	0.6 – 1.1	0.421
>50	34	32.7	70	67.3	1.2	0.7 – 1.9	0.393	0.9	0.5 – 1.6	0.880
Birthplace Region										
Canada (non-Aboriginals)	212	33.2	427	66.8	1			1		
Aboriginals Canadians	48	43.6	62	56.4	0.6	0.4 – 0.9	0.03	0.8	0.5 – 1.2	0.328
Africa	72	42.9	96	57.1	0.6	0.5 – 0.9	0.02	0.7	0.1 – 0.8	0.256
Caribbean & Latin America	39	34.2	75	65.8	0.9	0.6 – 1.4	0.82	1.2	0.7 – 1.9	0.450
Others	63	38.7	100	61.3	0.8	0.5 – 1.1	0.18	0.8	0.5 – 1.2	0.405
Duration of Follow-up										
<12 months	156	37.0	266	63.0	1			1		
>12 months	284	35.4	519	64.6	1.1	0.8- 1.4	0.579	1.1	0.7 – 1.4	0.758
Smoking Status										
Smoke	171	39.1	266	60.9	1			1		
Never	159	35.5	289	64.5	1.1	0.8 – 1.5	0.263	1.2	0.9 – 1.7	0.128
Former Smoker	62	29.7	147	70.3	1.5	1.0 – 2.1	0.019	1.5	1.0 – 2.1	0.039

Figure 8.4c (2) Factors associated with having a Mantoux test record in the OCS database (excluding HIV transmission variable)

CHAPTER 9 DISCUSSION

9.1 Active TB among individuals with HIV

To our knowledge, the present study is the only study that estimates active TB and latent TB rates in people infected with HIV in Ontario. While there has been no national or provincial surveillance system that tracks TB cases in people with HIV, several Canadian studies with varied methodology have estimated the burden of TB and HIV in the past (84-88).

Results in our study have estimated active TB rate to be 5.9% among the HIV infected persons in the OCS. Brassard and Remis (1999) reported that 5.2% had active TB in 4684 AIDS-infected people in Quebec (86). Similarly, in another study by Geduld and Archibald (2005), 5.6% of all the AIDS reported to PHAC during 1994 to 2003 were co-infected with active TB cases (84). In contrast, studies that examined TB-HIV co-infection by estimating HIV infection among active TB cases, have reported much higher co-infection rates. Studies by Blenkush et al (1996) (85) and Kim et al (2008) (103) have reported the co-infection rate to be as high as 13.8% and 24.5%, respectively. Although, the TB rate reported by Geduld and Archibald (84) and Brassard and Remis (86) is similar to the rate of this study, they reported the TB rate only among the AIDS cases.

Our TB-HIV cases are likely to underestimate the true numbers of HIV-TB cases in the OCS cohort. While the OCS cohort represents a diverse group of people living with HIV in Ontario, it

does not capture all the HIV infections. One reason could be because it does not gather data from all the HIV clinics in Ontario. Further, groups such as Infants and temporary immigrants who may not permanently reside in Ontario are not likely to participate in OCS.

Secondly, it can be seen from figure 8.1a that majority of the participants in the OCS are recruited during 2 to 5 years (37%) or even after 5 years (32.6%) of their HIV diagnosis. This increases the possibility that many individuals who are diagnosed with HIV between the years of 2007 and 2010 with active TB would not have been recruited for the OCS until later in 2012 or 2013.

9.1.1 MDR-TB among individuals with HIV

There were no MDR-TB cases found in the OCS database. The attempt to identify drug resistant TB cases was based on TB medication history and duration of treatment. However, none of the cases matched the criteria for having MDR-TB. Although HIV infection is associated with MDR-TB in institutional settings such as hospitals and prisons, it is unclear if there is any association between MDR-TB and HIV in a community setting (104). Several studies have shown HIV infection to be highly correlated with MDR-TB (104-106). However, the association could be confounded by shared risk factors such as injection drug use, imprisonment, socioeconomic status, alcohol use and hospitalization (104).

There are several reasons why MDR-TB cases could not have been identified or were not present in the database. Firstly, any OCS participants infected with MDR-TB would most likely be seeking treatment under the Directs Observed Therapy Short-Course (DOTS) program by Public Health, which means that medication history may not have been captured in the OCS. Secondly, the proportion of MDR-TB cases in Canada is much lower than the global average estimated by WHO (1.1% vs. 4.8%) (107). In the period of 10 years from 1998 to 2008, only 181 cases have been classified as MDR-TB (107). Thirdly, MDR-TB and HIV creates an extremely complex clinical scenario, which may lead to severe illness or even death. A study in Peru explored that more than 50% of HIV-infected MDR-TB patients died within two months of diagnosis (108). Other studies with longer follow up had a mortality rate of 72 to 89% (109). A UK study estimated that immune-compromised MDR-TB patients are nine times more likely to die than those non immune-compromised with MDR-TB (110). Due to the severity of the illness and the nature of MDR-TB, any individual infected with HIV and MDR-TB could have been too ill to participate in the OCS study. Fourthly, access to Public Health drug resistant TB culture results in the OCS database would have confirmed the presence of MDR-TB cases, however they were not available at the time this study was conducted.

9.2 Latent TB among individuals with HIV

While there were no studies that reviewed the latent TB rates all across Ontario, several Canadian studies have measured the number of positive Mantoux test rates (positive Mantoux test constitutes as a latent TB case) and have shown the rates to range from 10.2% to 35.6% (111 - 114). The estimated prevalence of latent TB in our current study varies from 5.3% to 11.3% depending on the methodology. The prevalence rate of 5.3% for latent TB is certainly questioned

as the latent TB/HIV rate was expected to be quite higher than the active TB rate (5.8%). Therefore, the prevalence rate of 11.3% appears closer to the true prevalence of latent TB. It is still likely that the latent TB cases were under estimated. Possible explanations in the underestimation of latent TB include poor completion rates[9] of Mantoux test and lack of sensitivity of this test in people with HIV may be another reason why physicians may not always use this test. Furthermore, limited data capture ability of medications used for treatment of latent TB could also account for low latent TB estimate. Anti-TB medications are often provided by Public Health and may not always be captured in the patient's records at the HIV clinic sites.

Studies (115-116) have examined the usage of TB skin testing for the screening of NTM in children. They have found TB skin testing as a valuable first step in screening for NTM in children without a history of TB exposure or BCG vaccination. In the study by Farhat et al. has conducted an extensive literature review and meta-analysis to determine the effect of NTM infection and a positive TST reaction (116). The study found that false-positive TB skin tests due to NTM were very uncommon and were only important in populations with a low prevalence of TB infection (116). Since our data mostly consists on adults with a high risk of TB, we believe that a positive TB skin test is indicative of a TB infection and therefore believe NTM has not had an impact on the results of our study.

[9] Further explained in section 9.3 (second paragraph) on the next page

9.3 Mantoux test records in the OCS database

Although it is recommended that all HIV individuals should be screened for TB at the time of their HIV diagnosis (117), results in our study only found 466 (36%) Mantoux test records among the 1293 individuals diagnosed with HIV. This proportion was surprisingly lower than expected as 54% of the HOOD[10] participants had a TB skin test record (118). Several other studies have also estimated the proportion of patients screening with Mantoux test that range from 54% to 69% (119-121). Only one study reported a lower rate (29%) of patients screened for TB than the rate of our study (14).

Such low numbers of Mantoux test records in the OCS database may be explained by several factors. TB screening is different from other screening, as it requires a second visit, following the initial visit for the Mantoux test to be administered, for the results to be read. Failure to return will result in an incomplete screening and may explain the low proportion of Mantoux test records found in the OCS database. Another reason why Mantoux test record proportion may not be as high as expected could be related to the sensitivity in people with HIV as mentioned earlier in section 9.3. Mantoux test is not very sensitive in people with HIV and therefore physicians may not have always used this test. Consequently, a reliable blood test to detect latent TB may help to improve the completion rates of TB screening. Further, low numbers of Mantoux test records in the OCS database could also be a data capture issue. Records of Mantoux tests administered by Public Health and not HIV clinics may not have been captured by the OCS.

[10] HOOD stands for HIV Ontario Observational Database

9.4 Factors associated with active TB

1293 individuals were diagnosed with HIV during 2001 to 2009, of which 76 (5.8%) had active TB. Multivariate analysis showed that the variables associated with active TB were age and birthplace region.

Age was associated with active TB as individuals in the cohort living with HIV who were older (>50 years) were more likely to have TB. This association was expected since TB is more prevalent among older people in industrialized countries due to the decrease in risk of TB infection over recent decades (86) as well as a general decline of immune system as one gets older.

In terms of birthplace region, individuals from Africa were at a higher risk of having active TB than non-Aboriginals individuals born in Canada. It is well documented that foreign-born individuals are at a much higher risk of TB (8). Foreign-born made account for a large number of TB cases in Europe. In countries such as Norway, Sweden and UK, more than 50% of the TB cases in 2003 were represented by foreign-born (122). The result of this study is consistent with other studies that have identified birthplace region to be a key risk factor that is associated with active TB and HIV (15, 86).

The multivariate analysis did not find Aboriginal Canadians to be at a higher risk of having active TB. There was no significant difference between the proportion of non-Aboriginal

Canadians and Aboriginal Canadians in terms of having active TB (1.7% vs. 1.8%). This was not expected as often Aboriginal Canadians are at a higher risk of having active TB. While Aboriginal Canadians continue to be over-represented in the HIV endemic, only a minority of individuals in the OCS reported themselves as Aboriginals (97). Aboriginal Canadians living on reserve may not visit the HIV clinics linked with OHTN as Health Canada is responsible for providing them with health services. Although living and working conditions are associated with high risk of TB transmission (123), many of the Aboriginal Canadians may be living in cities instead. Aboriginal Canadians living in cities may have a different socio-demographic profile than those living on reserves and thus could be the reason why our analysis did not show this group to be associated with having TB.

Although, the sex variable was not associated with active TB, the proportion of women with active TB was higher than men with active TB. Results showed that 12.8% of women in the group had active TB whereas only 4% of men had active TB. This pattern was also found in another Canadian study where 13% of HIV infected women had TB whereas only 4% of men with HIV had TB (86). Overrepresentation of women in active TB cases could be explained by the fact that most female participants in the OCS come from HIV endemic countries where TB is also prevalent.

9.5 Factors associated with latent TB

Factors associated with having latent TB and HIV were also identified using bivariate and multivariate analysis. In the bivariate analysis, sex, birthplace region, HIV exposure category,

duration of follow up and smoking status were found to be associated with having a latent TB diagnosis. In the multivariate analysis, factors associated with having latent TB were sex and birthplace region as only females and people born in Africa were at an increased risk of having latent TB.

9.6 Factors associated with having a Mantoux test record in the OCS database

Factors associated with having a Mantoux test record in OCS were sex and smoking status. Females were slightly less likely to have a Mantoux test record in OCS than males. It is unclear whether this is related to the gender and screening practices among clinicians, or it is related to the type of data present in OCS. Majority of the females are foreign born in the study and may have had a TB test performed prior to coming to Canada. Since OCS does not collect data from immigration records, such individuals would not have a record of Mantoux test in OCS.

In terms of smoking status, cigarette smoking in individuals with latent TB increase the risk of development of active TB. Therefore, it was expected that individuals who are current or former smokers would have more likely to have a Mantoux test record in OCS. However, multivariate analysis showed that only former smokers were marginally more likely to have a Mantoux test record in OCS than current smokers. As mentioned in section 3.5, smoking is more likely to be associated with having opportunistic infections however, this was not found in the analysis.

9.6 Conclusion

Although the data in OCS was initially composed mainly of gay men, it nevertheless was a diverse cohort of individuals who were fairly representative of the HIV-infected population in Ontario. Although, we cannot be certain that we have found all the TB cases based on diagnosis, screening test records and medication history, we believe the majority of the TB cases were captured. Although HIV clinics are the primary centre for treatment of HIV of the OCS participants, it could be likely that cases were diagnosed and treated elsewhere (e.g. Public Health Ontario or Public Health Toronto) for active or latent TB without the knowledge of HIV clinics.

It is acknowledged that the present study had many limitations relating to data capture. While several studies on HIV/TB have relied on national and surveillance data (84-86) – data that is mandatory to be reported by clinicians, our study has used passive reporting and observational data which is provided by the participants on voluntary basis. Such type of data might induce selection bias as only individuals with similar characteristics would be willing to participate in OCS after their diagnosis of HIV. For example, a person who is severely ill and have a low CD4 count may not be able to enrol in the OCS study.

Our study was also dependent on the specific data elements available in OCS that would help achieve the research objectives of this study. Although we were able to identify the TB cases based on diagnosis and medication history data, other data points such as chest X ray results and TB lab culture results would have provided further confirmatory results. As there was no

availability of chest X ray and lab culture results, the estimates for active TB, particularly MDR-TB would likely to be underestimated. It is also likely that most of the Mantoux test records in OCS were not captured from all the sites. Further, many Mantoux skin test records, related to the TB outcomes appeared to be incomplete, which increased the possibility of underestimating latent TB cases.

Future work should include further TB related studies using OCS data including bacterial culture and chest X rays should be conducted. The data elements gathered across all the HIV sites should also be consistent and future work should contain OHTN site-specific analysis. The collection of medication history could be made more comprehensive by including documented barriers to DOTS or reasons for non-adherence and tolerance of TB treatment. Also, medication history should be linked with Public Health central information system so TB medications administered by Public Health can also be captured in the OCS.

TB remains a major problem in persons infected with HIV with rates disproportionally high among the foreign born population. To identify individuals with higher risk of having TB after HIV diagnosis, better screening tools to identify latent TB are needed. Low rates of Mantoux skin testing present a missed opportunity for active TB prevention among individuals with HIV. The findings of this study support the recommendations made by the Canadian thoracic Society to screen all patients for TB at the time of person's HIV diagnosis (117). In order to optimize the HIV/TB management, a much more comprehensive data collection system is required which would ideally be linked between Public Health and HIV clinics.

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APPENDICES

Appendix A WHO Clinical Staging of HIV/AIDS for Adults and Adolescents

Primary HIV Infection

- Asymptomatic
- Acute retroviral syndrome

Clinical Stage 1

- Asymptomatic
- Persistent generalized lymphadenopathy

Clinical Stage 2

- Moderate unexplained weight loss (<10% of presumed or measured body weight)
- Recurrent respiratory infections (sinusitis, tonsillitis, otitis media, and pharyngitis)
- Herpes zoster
- Angular cheilitis
- Recurrent oral ulceration
- Papular pruritic eruptions
- Seborrheic dermatitis
- Fungal nail infections

Clinical Stage 3

- Unexplained severe weight loss (>10% of presumed or measured body weight)
- Unexplained chronic diarrhea for >1 month
- Unexplained persistent fever for >1 month (>37.6ºC, intermittent or constant)
- Persistent oral candidiasis (thrush)
- Oral hairy leukoplakia
- Pulmonary tuberculosis (current)
- Severe presumed bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia)
- Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis
- Unexplained anemia (hemoglobin <8 g/dL)
- Neutropenia (neutrophils <500 cells/μL)
- Chronic thrombocytopenia (platelets <50,000 cells/μL)

Clinical Stage 4

- HIV wasting syndrome, as defined by the CDC
- *Pneumocystis* pneumonia
- Recurrent severe bacterial pneumonia
- Chronic herpes simplex infection (orolabial, genital, or anorectal site for >1 month or visceral herpes at any site)
- Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs)
- Extrapulmonary tuberculosis
- Kaposi sarcoma
- Cytomegalovirus infection (retinitis or infection of other organs)
- Central nervous system toxoplasmosis
- HIV encephalopathy
- Cryptococcosis, extrapulmonary (including meningitis)
- Disseminated nontuberculosis mycobacteria infection
- Progressive multifocal leukoencephalopathy
- Candida of the trachea, bronchi, or lungs
- Chronic cryptosporidiosis (with diarrhea)
- Chronic isosporiasis
- Disseminated mycosis (e.g., histoplasmosis, coccidioidomycosis, penicilliosis)
- Recurrent nontyphoidal *Salmonella* bacteremia
- Lymphoma (cerebral or B-cell non-Hodgkin)
- Invasive cervical carcinoma
- Atypical disseminated leishmaniasis
- Symptomatic HIV-associated nephropathy
- Symptomatic HIV-associated cardiomyopathy
- Reactivation of American trypanosomiasis (meningoencephalitis or myocarditis)

Appendix B – Frequency Tables

1.1 Sex-Calculated

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Female	274	21.2	21.4	21.4
	Male	1009	78.0	78.6	100.0
	Total	1283	99.2	100.0	
Missing	System	10	.8		
Total		1293	100.0		

1.2 Age Categories (1)

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	30 - 50	805	62.3	62.3	62.3
	> 50	104	8.0	8.0	70.3
	<29	384	29.7	29.7	100.0
	Total	1293	100.0	100.0	

1.2 Age Categories (2)

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	12-19	35	2.7	2.7	2.7
	20 - 24	114	8.8	8.8	11.5
	45 - 64	249	19.3	19.3	30.8
	65 and above	7	.5	.5	31.3
	25 - 44	888	68.7	68.7	100.0
	Total	1293	100.0	100.0	

1.3 Canadian Born vs Foreign Born

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Canadian Born	749	57.9	62.7	62.7
	Foreign Born	445	34.4	37.3	100.0
	Total	1194	92.3	100.0	
Missing	Missing	99	7.7		
Total		1293	100.0		

2.4a Birthplace Region

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Africa	168	13.0	14.1	14.1
	Caribbean and Latin America	114	8.8	9.5	23.6
	Others	163	12.6	13.7	37.3
	Aboriginal Canadians	110	8.5	9.2	46.5
	Canada (non abrg)	639	49.4	53.5	100.0
	Total	1194	92.3	100.0	
Missing	System	99	7.7		
Total		1293	100.0		

1.6b Years in Canada

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Less than 5 Years	102	7.9	25.8	25.8
	More than 5 Years	294	22.7	74.2	100.0
	Total	396	30.6	100.0	
Missing	System	897	69.4		
Total		1293	100.0		

HIV Risk Category (hierarchical)

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	MSM	684	52.9	52.9	52.9
	MSM-IDU	57	4.4	4.4	57.3
	IDU	94	7.3	7.3	64.6
	Clotting factor	7	.5	.5	65.1
	Transfusion	8	.6	.6	65.7
	HIV-endemic	202	15.6	15.6	81.4
	Heterosexual transmission	149	11.5	11.5	92.9
	MTC Mother to child transmission	2	.2	.2	93.0
	NIR Non-identified risk	90	7.0	7.0	100.0
	Total	1293	100.0	100.0	

1.7 Urban / Rural Categorization

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	ON-RURAL	50	3.9	4.4	4.4
	ON-URBAN	1086	84.0	95.6	100.0
	Total	1136	87.9	100.0	
Missing	OUT OF PROVINCE	14	1.1		
	INVALID/MISSING	143	11.1		
	Total	157	12.1		
Total		1293	100.0		

2.16a CD4 at Registration

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	>500	466	36.0	37.7	37.7
	200-500	632	48.9	51.1	88.8
	<200	139	10.8	11.2	100.0
	Total	1237	95.7	100.0	
Missing	System	56	4.3		
Total		1293	100.0		

Appendix C – Multivariate Analysis

Factors associated with active TB

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	sex(1)	.210	.365	.332	1	.565	1.234	.603	2.523
	AgeatHIVdiagnosis_var1			6.096	2	.047			
	AgeatHIVdiagnosis_var1(1)	.570	.346	2.717	1	.099	1.769	.898	3.485
	AgeatHIVdiagnosis_var1(2)	1.320	.549	5.775	1	.016	3.745	1.276	10.995
	Birth_Region			13.462	4	.009			
	Birth_Region(1)	2.029	.703	8.337	1	.004	7.605	1.919	30.140
	Birth_Region(2)	.823	.658	1.563	1	.211	2.277	.627	8.268
	Birth_Region(3)	1.148	.491	5.463	1	.019	3.152	1.204	8.255
	Birth_Region(4)	-.299	.800	.140	1	.708	.741	.154	3.559
	HIVRisk_Var3			6.061	4	.195			
	HIVRisk_Var3(1)	1.174	.700	2.812	1	.094	3.235	.820	12.758
	HIVRisk_Var3(2)	.815	.596	1.870	1	.171	2.259	.702	7.265
	HIVRisk_Var3(3)	1.122	.543	4.275	1	.039	3.071	1.060	8.895
	HIVRisk_Var3(4)	1.327	.857	2.396	1	.122	3.768	.703	20.208
	Followup_Duration_car6(1)	.395	.352	1.260	1	.262	1.485	.745	2.961
	CigaretteHistory_Var2			.209	2	.901			
	CigaretteHistory_Var2(1)	-.071	.391	.033	1	.856	.931	.433	2.004
	CigaretteHistory_Var2(2)	-.223	.491	.207	1	.649	.800	.306	2.094
	Constant	-5.117	.575	79.052	1	.000	.006		

a. Variable(s) entered on step 1: sex, AgeatHIVdiagnosis_var1, Birth_Region, HIVRisk_Var3, Followup_Duration_car6, CigaretteHistory_Var2.

Factors associated with Latent TB

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	sex(1)	.905	.454	3.964	1	.046	2.471	1.014	6.021
	AgeatHIVdiagnosis_var1			.997	2	.608			
	AgeatHIVdiagnosis_var1(1)	.196	.350	.315	1	.575	1.217	.613	2.417
	AgeatHIVdiagnosis_var1(2)	.631	.645	.957	1	.328	1.880	.531	6.657
	Birth_Region			18.478	4	.001			
	Birth_Region(1)	2.469	.813	9.231	1	.002	11.815	2.402	58.109
	Birth_Region(2)	.517	.801	.418	1	.518	1.678	.349	8.057
	Birth_Region(3)	1.602	.495	10.451	1	.001	4.962	1.879	13.102
	Birth_Region(4)	-16.839	3833.309	.000	1	.996	.000	.000	.
	MSM			1.687	4	.793			
	HIV Endemic	-.016	.806	.000	1	.984	.984	.203	4.772
	IDU	-1.057	1.080	.958	1	.328	.347	.042	2.884
	Heterosexual	-.090	.664	.018	1	.893	.914	.249	3.356
	Other	.651	.908	.513	1	.474	1.917	.323	11.376
	Followup_Duration_car6(1)	.527	.398	1.750	1	.186	1.694	.776	3.696
	CigaretteHistory_Var2			.502	2	.778			
	CigaretteHistory_Var2(1)	-.169	.437	.149	1	.700	.845	.359	1.989
	CigaretteHistory_Var2(2)	.151	.519	.085	1	.771	1.163	.421	3.215
	Constant	-4.813	.605	63.350	1	.000	.008		

a. Variable(s) entered on step 1: sex, AgeatHIVdiagnosis_var1, Birth_Region, HIVRisk_Var3, Followup_Duration_car6, CigaretteHistory_Var2.

Factors associated with receiving a Mantoux test

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	sex(1)	-.653	.222	8.675	1	.003	.520	.337	.804
	AgeatHIVdiagnosis_var1			1.206	2	.547			
	AgeatHIVdiagnosis_var1(1)	-.165	.151	1.192	1	.275	.848	.630	1.141
	AgeatHIVdiagnosis_var1(2)	-.084	.271	.097	1	.756	.919	.540	1.564
	Birth_Region			8.261	4	.082			
	Birth_Region(1)	-.925	.395	5.499	1	.019	.396	.183	.859
	Birth_Region(2)	-.086	.276	.097	1	.756	.918	.534	1.577
	Birth_Region(3)	-.132	.201	.429	1	.513	.877	.591	1.300
	Birth_Region(4)	-.312	.231	1.835	1	.176	.732	.466	1.150
	HIVRisk_Var3			11.094	4	.026			
	HIVRisk_Var3(1)	.879	.401	4.799	1	.028	2.409	1.097	5.291
	HIVRisk_Var3(2)	.586	.228	6.584	1	.010	1.797	1.148	2.811
	HIVRisk_Var3(3)	.068	.243	.078	1	.779	1.070	.665	1.724
	HIVRisk_Var3(4)	-.184	.503	.134	1	.714	.832	.310	2.230
	Followup_Duration_car6(1)	.048	.139	.117	1	.733	1.049	.798	1.377
	CigaretteHistory_Var2			7.567	2	.023			
	CigaretteHistory_Var2(1)	.339	.162	4.379	1	.036	1.404	1.022	1.929
	CigaretteHistory_Var2(2)	.477	.192	6.153	1	.013	1.611	1.105	2.349
	Constant	.550	.188	8.581	1	.003	1.733		

a. Variable(s) entered on step 1: sex, AgeatHIVdiagnosis_var1, Birth_Region, HIVRisk_Var3, Followup_Duration_car6, CigaretteHistory_Var2.

Factors associated with active TB (excluding HIV transmission variable)

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Sex (Female)	.607	.343	3.133	1	.077	1.835	.937	3.594
	Age < 30			7.577	2	.023			
	Age 30 - 50	.579	.346	2.803	1	.094	1.784	.906	3.513
	Age > 50	1.480	.543	7.424	1	**.006**	4.391	1.515	12.728
	Canada (non-Abg)			40.745	4	.000			
	Africa	2.639	.435	36.769	1	**.000**	14.005	5.967	32.869
	Caribbean & Latin America	1.184	.538	4.839	1	**.028**	3.266	1.138	9.376
	Others	1.170	.481	5.913	1	.015	3.223	1.255	8.278
	Abg Canadians	-.102	.792	.017	1	.897	.903	.191	4.265
	Follow up > 12 months	.423	.351	1.454	1	.228	1.526	.768	3.035
	Smoking Currently			.566	2	.754			
	Never Smoked	-.235	.378	.388	1	.533	.790	.377	1.657
	Former Smoker	-.323	.483	.447	1	.504	.724	.281	1.865
	Constant	-4.744	.523	82.219	1	.000	.009		

a. Variable(s) entered on step 1: sex, AgeatHIVdiagnosis_var1, Birth_Region, Followup_Duration_car6, CigaretteHistory_Var2.

Factors associated with latent TB (excluding HIV transmission variable)

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Sex (Female)	.910	.380	5.723	1	.017	2.484	1.179	5.235
	Age < 30			.874	2	.646			
	Age 30 - 50	.187	.349	.285	1	.593	1.205	.608	2.390
	Age > 50	.583	.638	.836	1	.360	1.792	.513	6.252
	Canada (non-Abg)			30.943	4	.000			
	Africa	2.513	.489	26.414	1	.000	12.342	4.733	32.181
	Caribbean & Latin America	.571	.706	.655	1	.418	1.771	.444	7.061
	Others	1.691	.491	11.873	1	.001	5.424	2.073	14.192
	Abg Canadians	-17.031	3876.467	.000	1	.996	.000	.000	.
	Follow up > 12 months	.534	.397	1.816	1	.178	1.706	.784	3.712
	Smoking Currently			.347	2	.841			
	Never Smoked	-.064	.428	.023	1	.881	.938	.405	2.169
	Former Smoker	.207	.515	.161	1	.688	1.230	.448	3.374
	Constant	-4.968	.582	72.810	1	.000	.007		

a. Variable(s) entered on step 1: sex, AgeatHIVdiagnosis_var1, Birth_Region, Followup_Duration_car6, CigaretteHistory_Var2.

Factors associated with having a Mantoux test record in OCS (excluding HIV transmission variable)

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Sex (Female)	-.460	.179	6.600	1	.010	.631	.444	.897
	Age < 30			.676	2	.713			
	Age 30 - 50	-.120	.149	.646	1	.421	.887	.662	1.189
	Age > 50	-.040	.268	.023	1	.880	.960	.568	1.623
	Canada (non-Abg)			3.782	4	.436			
	Africa	-.258	.227	1.290	1	.256	.772	.495	1.206
	Caribbean & Latin America	.184	.244	.572	1	.450	1.203	.746	1.940
	Others	-.166	.199	.694	1	.405	.847	.574	1.251
	Abg Canadians	-.220	.225	.958	1	.328	.803	.517	1.247
	Follow up > 12 months	.042	.138	.095	1	.758	1.043	.796	1.368
	Smoking Currently			4.883	2	.087			
	Never Smoked	.239	.157	2.317	1	.128	1.270	.934	1.727
	Former Smoker	.391	.189	4.269	1	.039	1.478	1.020	2.141
	Constant	.637	.180	12.562	1	.000	1.891		

a. Variable(s) entered on step 1: sex, AgeatHIVdiagnosis_var1, Birth_Region, Followup_Duration_car6, CigaretteHistory_Var2.

Appendix D Confidentiality Agreement

Promoting excellence and innovation in HIV research and care

CONFIDENTIALITY AGREEMENT

BETWEEN:

ARSALAN AFZAL (“the Researcher”)

- and -

The Ontario HIV Treatment Network (“the OHTN”)

WHEREAS the Researcher is employed by the OHTN or is engaged in research activities related to the OHTN Cohort Study using the Central Research Database of the OHTN or the HIV Ontario Observational Database for or under the auspices of the OHTN pursuant to a contractual or other relationship with the OHTN and has access to Confidential Information as defined herein;

AND WHEREAS it is essential to the OHTN and its funding agencies that information provided to the OHTN for use in its research endeavours is kept strictly and absolutely confidential and in particular is handled in compliance with the Personal Health Information Protection Act of the Province of Ontario;

AND WHEREAS the Researcher agreed, at the time he or she entered into employment with the OHTN or commenced his or her engagement to perform research or related activities for or under the auspices of the OHTN, to enter into an agreement with respect to confidential information and that he or she has received good and valuable consideration for entering into such agreement;

NOW THEREFORE THE PARTIES HERETO AGREE:

1. For the purposes of this Agreement:

(a) “Confidential Information” means information provided to the OHTN or gathered, known or used by or in the name of the OHTN in connection with its research endeavours or research activities performed under its auspices including but not limited to any data provided or gathered that contains Personal Health Information, De-Identified Participant Information, data, programmes, codes, methods, techniques or processes, formula design, prototype, device, equipment or machine, Financial Information, Intellectual Property and Research and Development, but does not include any which is or becomes a matter of Public Knowledge;

(b) “Financial Information” means information pertaining to the OHTN's funding, costs or operation.

(c) “OHTN Cohort Study Research Policies" means the OHTN policies of the same name as it is from time to time;

(d) “Public Knowledge" means information known generally in the scientific, research and health care communities, or which is easily obtained through lawful, non-confidential sources such as publications.

(e) “Research and Development” means information pertaining to any research, development investigation, study, analysis, experiment, or test carried on or proposed to be carried on by or under the auspices of the OHTN;

(f) “De-identified Participant Information” means information under the custodianship of the OHTN about a living or deceased OHTN Cohort Study participant that has been stripped of all uniquely identifying data elements, such as name, address, health number or social insurance number. De-identified Participant Information can contain both demographic information, that is, information about an individual such as gender, ethnic origin age, level of education, etc., and health information, that is, information about an individual’s health care, such as conditions, treatments or medications.

(g) “Personal Health Information” has the same meaning as that provided in the Personal Health Information Protection Act . Personal Health Information means identifying information about an individual in oral or recorded form, if the information,

i) relates to the physical or mental health of the individual, including information that consists of the health history of the individual’s family,

ii) relates to the providing of health care to the individual, including the identification of a person as a provider of health care to the individual,

iii) is a plan of service within the meaning of the Long-Term Care Act, 1994 for the individual,

iv) relates to payments or eligibility for health care in respect of the individual,

v) relates to the donation by the individual of any body part or bodily substance of the individual or is derived from the testing or examination of any such body part or bodily substance,

vi) is the individual's health number, or

vii) identifies an individual's substitute decision-maker.

2. The researcher shall hold in confidence and keep confident all Confidential Information.

3. The researcher will not use Confidential Information for any purpose other than that for which is was provided to him or her unless the researcher has the OHTN's written authorization to do so.

4. If applicable, the researcher will comply with the conditions and restrictions specified by the research ethics board approval submitted with the researcher's application to use Confidential Information.

5. The researcher will disclose or provide access to Confidential Information in a form in which the individual to whom it relates can be identified only to persons who have entered into Confidentiality Agreements with the OHTN and the researcher and shall be responsible to satisfy himself or herself in that regard. Written confirmation from the Scientific and Executive Director that named individuals have executed such Agreements shall be deemed to compliance with this provision.

6. The researcher will keep all Confidential Information in a physically secure location to which access is given only to the researcher and the persons mentioned above.

7. The researcher will not contact any individual to whom Confidential Information relates, directly or indirectly, without the prior written authority of the OHTN.

8. The researcher shall ensure that no Confidential Information will be used or disclosed in a form in which the individual to whom it relates can be identified without the written authority of the OHTN unless the use or disclosure is otherwise in compliance with this Agreement.

9. The researcher shall notify the OHTN in writing immediately upon becoming aware that any of the conditions set out in this agreement have been breached.

10. The researcher shall handle all Confidential Information in a manner consistent with the "OHTN Cohort Study Research Policies" unless the Policies are in some respect inconsistent with the terms herein, in which case the terms herein shall apply.

ENTERED INTO this ___22nd____ day of __October_____ 2009___

The Researcher per: The Ontario HIV Treatment Network

Appendix E Data Scan Request Form

Promoting excellence and innovation in HIV research and care

Ontario HIV Treatment Network (OHTN)
OHTN Cohort Study (OCS)
Data Scan Request Form
The OCS Data Scan is intended to determine whether there is a sufficient sample size to address Research Question(s) of interest.

Date of Request	July 21, 2010
Date Required	July 26, 2010

◊Investigator Information

Principal Investigator	Clemon George
Email Address	Clemon.George@uoit.ca
Phone Number	905-721-8668x3659

◊Project Title

Tuberculosis prevalence in a diverse cohort of HIV positive individuals in Ontario

◊Project Description & Objective(s)

The study seeks to: 1) Determine the prevalence of latent and active TB in the OHTN cohort study and the incidence of active TB; 2) Determine the prevalence and correlates of drug resistant TB; 3) Determine the occurrence of active TB co-infection as a result of HAART induced immune reconstitution

◊ Inclusion & Exclusion Criteria

PLEASE INDICATE INCLUSION AND EXCLUSION CRITERIA FOR PARTICIPANTS.

Inclusion Criteria:

Diagnosed as HIV+ in 2001 or later

Exclusion Criteria:

Diagnosed as HIV+ earlier than 2001 Incomplete testing data

◊ Data Elements Required for Data Scan

HIV diagnosis date
Dates related to follow up in OCS (earliest seen date to last seen date, consent date) (not reported)
TB testing data from lab tests and adverse events datasets

Site (not reported)
Source (not reported)

◊ Data Summary Requested

PLEASE INDICATE CROSSTABS OR OTHER DESCRIPTIVE SUMMARIES OF KEY DATA ELEMENTS ONLY

- Current number in the OCS who were diagnosed as HIV+ in 2001 or later
- Of these, how many have had a skin test for TB
- Of these, how many have tested positive on their most recent TB skin test

◊ Additional Comments

Data will be reviewed by site and data source. However no summaries will be provided to the PI. We need to understand if TB data is collected differently across sites and how this will affect thesis data analysis plan.