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Analysis of risk factors for Tuberculosis Recurrence using a population-based TB/HIV integrated surveillance database in Chiang Rai, Thailand

by

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Dedication

I would like to dedicate this thesis to my parents, Jiejun Sun and Xiangdong Wu.

Abstract

TB recurrence is defined as a new episode of bacteriologically positive TB in a patient previously declared “successfully completed treatment.” Our study objective was to identify risk factors of recurrence among HIV-infected and HIV-uninfected TB patients.

Based on a population-based TB/HIV surveillance database of Chiang Rai Province, Thailand, a retrospective cohort of TB patients with successful completions of treatment between 1997 and 2008 was constructed. Poisson regression was used to model independent effects of risk factors.

TB recurrence rates were 5.4/1,000 PYs and 9.7/1,000 PYs for HIV-uninfected and infected TB patients, respectively. We identified that among HIV-uninfected patients, older age, being hilltribe, being prisoners, were at higher risk of recurrence. While among HIV-infected patients, younger age, being male, and having been cured from initial episode were associated with higher recurrence rates. Targeted, practical preventive and treatment strategies for those patients need to be implemented to lower the TB recurrence rates.

Key words: Tuberculosis recurrence, HIV, recurrence rate, risk factors.

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List of Abbreviations and Symbols

TB – Tuberculosis

Mycobacterium.tuberculosis – M.tuberculosis

HIV –Human Immunodeficiency Virus

DOTS – Directly Observed Therapy, Short-course

WHO – World Health Organization

PTB –Pulmonary TB

EPTB – Extra-pulmonary TB

DST – Drug Susceptibility Test

MDR-TB – Multi-drug Resistant TB

IP – Intensive Phase

CP – Continuation Phase

R – Rifampin

H – Isoniazid

E – Ethambutal

Z – Pyrazinamide

S – Streptomycin

PY – Person-year

RR – Rate Ratio

p – Significant Level

IQR – Interquartile Range

C.I. – Confidence Interval

HAART – Highly Active Antiretroviral Therapy

DOT – Directly Observed Therapy

RCT – Randomized Control Trial

NTM— Non-tuberculosis Mycobacterium

Chapter 1: Introduction

1.1 Rationale

A recurrence of tuberculosis (TB) refers to a situation where a patient who has been previously declared as "having successfully completed a treatment" develops a new episode of bacteriologically confirmed TB [1]. A recurrent episode can be caused by either endogenous relapse (reactivation) of the same strain of the initial episode, following insufficient bacterial cure, or exogenous new infection of a strain of *Mycobacterium.tuberculosis* (*M.tuberculosis)*. TB recurrence has been reported to occur under an acceptable 5% rate after a wide application of effective anti-TB drugs in combination for at least 6 months in a largely HIV-negative environment [2, 3]. However, recent reports and studies showed that there was a noticeably increasing trend in TB recurrence rates globally [4-7]. In 2004, more than 260,000 recurrent cases were reported worldwide [8]. Evidence from recent studies suggests that the TB recurrence rate has surpassed that of TB incidence [7]. Regarded as an important index to assess the long-term effectiveness of TB control program, the increased recurrence rate has raised significant concerns among researchers and public health practitioners on current TB control strategy, i.e., "Directly Observed Therapy, Short-course (DOTS)". Moreover, heavy burdens imposed by elevated recurrence risk on both individual patients and TB control programs call for intensive investigations and practical interventional strategies to curb this trend.

Human Immunodeficiency Virus (HIV) associated TB is a major and increasing health problem around the world, responsible for the worsened performance of almost all aspects of TB control mainly due to its associated immuno-suppression status [9, 10]. Higher TB recurrence rates among HIV-infected patients than HIV-uninfected patients have been reported by multiple studies under different settings, ranging from 2-fold to 12-fold [6, 11-13]. Underlying reasons for elevated risk of recurrence among HIV-infected patients and its associated risk factors need to be researched so effective interventions can be established to prevent TB recurrence. Under the assumption that different underlying factors might determine the risk of TB recurrence among HIV-infected and

uninfected TB patients, an investigation of associated risk factors separately by TB patients' HIV sero-status would be useful.

Chiang Rai Province, the northernmost province in Thailand, with 14% of its population being hilltribes, has already been heavily burdened by TB and has an extremely high HIV co-infection rate among TB patients. Through the investigation of TB recurrence rates and associated risk factors for TB recurrence by patients' HIV status, the burden from TB recurrence would be quantified and important messages regarding the control of TB recurrence will be conveyed to both local TB control programs and other programs under similar settings.

1.2 Purposes

The main purpose of this study is to identify epidemiological and clinical risk factors associated with TB recurrence among HIV-infected and uninfected TB patients, using a provincial population-based TB/HIV integrated surveillance database in Chiang Rai Province, Thailand, between 1997 and 2008. The ultimate objective of this work is to reduce TB recurrence rates and prevent the development of recurrent episodes among TB patients through establishment of interventional strategies targeted at high-risk groups for local TB control programs, based on identified risk factors.

1.3 Thesis Organization

As the aim of this study is to identify risk factors for TB recurrence and make correspondent, evidence-based recommendations to clinicians and public health practitioners to reduce the risk of TB recurrence, a comprehensive review of current concepts and theories on TB recurrence is needed before starting conducting the investigation. Chapter 2 will provide a full picture of TB recurrence situation, including the general description of worldwide TB burden, current TB control strategies, HIV interacted with TB, prevalence and impact of TB recurrence, as well as

general background information on Thailand and Chiang Rai Province with respect to TB and TB recurrence. Based on a comprehensive literature review, Chapter 3 will describe the fundamental mechanisms of TB recurrence (i.e., relapse and re-infection), and summarize the current state of knowledge on recurrence rates and associated risk factors for HIV-infected and uninfected TB patients, in relation to relapse and re-infection. Description of research methods will be presented in Chapter 4, followed by results from statistical analysis in Chapter 5. Discussion on the results, including comparison with other studies and interpretation based on local situations will be presented in Chapter 6. A concluding statement of this study including recommendations and prospect on future studies will be presented in Chapter 7.

Chapter 2: General description of tuberculosis as a public health problem around the world

2.1. General introduction of TB

2.1.1 TB and TB burden around the world

TB, caused by *M.tuberculosis*, is one of the oldest air-borne infectious diseases with significant global impact on humans. According to World Health Organization (WHO), about 2 billion people around the world are infected with TB, among which 8.4 million new cases occur each year as a result of HIV infection since1990 [14]. The estimated global incidence rate of TB and mortality rate with TB as the cause of death were 139 cases per 100,000 population and 20 deaths per 100,000 population in 2008, respectively [15]. As TB is highly associated with poverty, low socioeconomic conditions and paucity of health services, more than 80% of estimated new cases and deaths (approximately 1 million) occur in developing countries of Asia, Africa, the Middle East and the Latin America [1, 16]. TB affects mostly young adults in their most productive years, therefore forming a vicious cycle between poverty and TB in those epidemic countries [17].

The infection of *M.tuberculosis* is via respiratory transmission by droplet nuclei from a person with infectious pulmonary TB. Most people with a normally-functioning immune system could "wall off" the bacilli to localize the infection and inhibit progression from infection to active disease. Therefore, the development of active TB disease depends largely on the individual's immune function, which is affected by a variety of factors including HIV co-infection, aging, and co-morbidities. Generally, it is estimated that up to 10% of infected individuals with a normally-functioning immune system will eventually develop active TB disease during their lifetime. For HIV-infected individuals, the risk could be increased by 20-40 times [18].

2.1.2 TB diagnosis and treatment

TB diagnosis is usually based on the combination of evidence from patient's medical history, clinical signs and symptoms, laboratory tests, and radiographic test. Signs and symptoms like cough more than 2 weeks, night sweat, and weight loss, are usually the first signals sending patients to diagnosis. High suspicion of TB from healthcare workers is the key to ensure timely diagnosis and treatment. Acid-fast bacillus microscopy of a specimen (usually the sputum smear) is the most common laboratory diagnostic tool for TB. Although mycobacterial culture is the golden standard for its diagnosis, due to the financial and time constrains, three-sputum samples are widely-used for TB microscopic diagnosis in developing countries. Shadowing X-ray image locating at the upper lobe of lung is the typical radiographic manifestation of pulmonary TB (PTB) disease, although atypical X-ray images may present for extra-pulmonary TB (EPTB) and HIV-associated TB. For those TB cases, diagnosis relies more on other invasive diagnostic procedures, patient's medical history (i.e., HIV sero-status) and other supportive clinical manifestations. Drug susceptibility testing (DST) is performed for the identification of drug resistant patterns of *M.tuberculosis* strain to select anti-TB drugs, to prevent treatment failure and the emergence of Multi-drug resistant TB (MDR-TB). However, DST test is not universally applied to new TB patients due to limited resources in the epidemic countries [18].

TB treatment is essential for controlling further transmission and preventing morbidity and mortality [1]. Complete cure of TB disease could be achieved through short-course chemotherapy consisting of two phases (intensive and continuation phases: IP and CP), with 4 first-line anti-TB drugs (Rifampin [R], Isoniazid [H], Pyrazinamide [Z], and Ethambutol [E]) for new smear-positive cases [1]. For effective TB treatment and control, direct observation therapy (DOT) to directly observe patients' intake of anti-TB drugs is highly recommended by WHO and has been widely adopted to prevent non-compliance to treatment and the development of drug resistance. The recommended TB treatment regimens for different diagnostic categories will be presented in Chapter 4. Treatment outcomes of TB are usually categorized into cure, completion of treatment, default, death, treatment failure, and transferred out [1]. Details will also be presented in Chapter 4.

2.1.3 The emerging problems on TB epidemic and control

Drug-resistant TB and MDR-TB

As any other anti-bacterial drugs, anti-TB drugs are responsible for both destroying of pathogenic *M.tuberculosis* as well as the selective pressure favoring the growth of resistant strains against with those drugs [18]. MDR-TB is a special form of TB which fails to respond to both Rifampin and Isoniazid ---two of the most effective first-line anti-TB drugs [18]. Drug resistant TB poses significant threats to global TB control programs due to its world-wide coverage and difficulties in cure. More than 500,000 new MDR-TB cases has been alarmingly reported in 109 countries in 2008, and it has been estimated that 5% of all forms of TB cases were MDR-TB, with peaks of up to 22% in some settings of the former Soviet Union [19]. MDR-TB significantly impairs the performance of TB control due to the use of less effective second-line anti-TB drugs, longer treatment duration (usually 18-24 months), difficulties in the management of severe side effects, the increased unsuccessful treatment outcomes, and increased costs for diagnosis and treatment of MDR-TB patients.

TB and HIV

HIV infection is currently an inseparable component when it comes to the discussion of any aspects of TB control [1]. It was estimated that about 13 million people were co-infected with both causative organisms globally [20]. In 2003, 8% of new TB cases were HIV infected and 14% of TB deaths were probably co-infected with HIV [21]. Countries heavily burdened by HIV are frequently heavily burdened by TB, such as African and Southeast Asian countries, since HIV prevalence and its transmission from HIV-infected patients to much larger HIV-uninfected population significantly alter the TB epidemic as well as effectiveness of TB control [10]. Moreover, from socio-economics point of view, the internal association between HIV and TB linked by similar upstream determinants including poverty, low socio-economic status, disease-associated stigma, and difficulties in accessing healthcare, is significantly contributed to the deadly synergetic effects on each other [10].

The clinical and radiological presentations of TB disease are closely associated with the degree of immuno-suppression among TB patients, due to the role played by the immune function in the development of active TB disease [10]. HIV-infected TB patients with normal-functioning immune system have typical clinical presentation of TB as to HIV-uninfected patients. Advanced HIV stage significantly facilitates the progression of active disease after infection, and also leads to the atypical clinical presentations among those patients [10]. On the other hand, for HIV patients with compromised immune function, TB is one of the most common opportunistic infections: the co-infection rate could reach to 50% under certain settings in some African countries [21]. Aside from higher chance of infection, the lifetime risk of developing active TB for HIV patients is 20-40 times higher than their counterpart [18]. The close linkage between TB and HIV has been calling for the integrated management and control strategies in the epidemic countries to relieve TB and HIV burdens.

2.1.4 Current TB control strategy

After the long history of battling with TB, massive reduction of prevalence and mortality rate since last century have proved that TB is a preventable and treatable disease [1, 2]. DOTS is the current WHO-recommended TB control strategy, which strongly requires 1) political commitment with increased and sustained financing; 2) cases detection through quality-assured bacteriology; 3) standardized treatment with supervision and patient support; 4) an effective drug supply and management system; 5) monitoring and evaluation system [1.] Its wide implementation in the world, especially in the 22 high-burden countries which carry 80% global burden of TB, has proven to be able to effectively control TB [15]. During 1995-2008, a cumulative total of 36 million patients have been successfully treated, and 2-6 million deaths were averted under the DOTS program [15]. There are two indices to evaluate the performance of DOTS ---70% of case detection rate and 85% of treatment success rate. A global 86% of treatment success rate firstly achieved in 2007, with a 67% of case detection rate, indicated the effectiveness of DOTS strategy [15].

DOTS is clearly effective in reducing TB incidence, prevalence, and mortality in the absence of HIV [2, 22-23]. However, it started to show its limitation with the involvement of HIV, since so far, no developing country with serious HIV epidemic has achieved those targets sustainably [24]. More efforts are imperatively required to address this dual epidemic and their synergetic effects on impairing the performance of TB control. Therefore, "Stop TB Strategy", introduced by WHO and the Stop TB Partnership to explicitly address those key challenges, contains 6 major components: 1) DOTS expansion and enhancement; 2) addressing TB/HIV, MDR-TB, and other challenges; 3) health system strengthening; 4) engaging all care providers; 5) empowering patients and communities; 6) enabling and promoting researches [15.] This scaled-up strategy not only aims for tackling the risk factors that make individuals vulnerable to infection and to developing the disease, but also for reducing the adverse effects on its social and economic consequences.

2.2 Introduction of TB recurrence

2.2.1 Overview

The rising of HIV epidemics has been acknowledged to exert its negative influence on TB control performances almost in all aspects around the world, including the significantly increased TB recurrence rates [1, 4]. Recurrent TB has previously been considered to occur rarely (<5%) because of the powerful sterilization effects of first-line anti-TB drugs. Thus, in turn, TB recurrence could be used as an excellent index to evaluate the long-term effectiveness of TB treatment regimen and TB control programs [25]. However, it has not been routinely assessed in most settings and frequently overlooked by clinicians and TB control practitioners due to previously low rate of TB recurrence [25].

2.2.2 Mechanisms for TB recurrence

TB recurrence could be further divided into endogenous relapse (or reactivation) and exogenous re-infection. For relapse, inadequate bacterial cure of the initial episode leads to the persistence of bacilli, albeit the apparent "clinical cure", which could be reactivated later under certain circumstances when patient's immune function is impaired [26]. On the other hand, infection with a

new *M.tuberculosis* strain being transmitted in the community could also be developed into a subsequent active episode [26]. Relapse has long been regarded as the main cause for recurrence, while re-infection has recently been accepted as a possible cause, resulted from the long-term notion that TB patients could gain at least partial immunity rendering from previous TB disease to fight again the new infection, especially for HIV-uninfected TB patients [27]. Molecular technology (DNA fingerprinting) has been applied to distinguish whether the recurrent TB episode is caused by the same strain as the initial episode, or a different strain.

2.2.3 Burden and problems on TB recurrence

TB recurrence has become a more significant threat to TB control after the HIV pandemic around the world. Among adequately treated patients under DOTS, the recurrence rate could reach up to 20% under real-life conditions [6]. According to one recent systematic review investigating the recurrence rate and its risk factors, the median recurrence rate at 12 months post treatment completion was 1,780/100,000 person-years (PYs), significantly surpassed the new TB incidence rate reported by WHO [4]. Compared to low-incidence countries, the recurrence rate was about 4 times higher in high-incidence countries (7,850/100,000 PYs vs 1,780/100,000 PYs), further compounded the burdens of TB control programs in those countries[4]. More importantly, multiple studies have reported that overall TB recurrence rates were much higher among HIV-infected patients than HIV-uninfected ones, with the elevated risk ranging from 2-fold to 12-fold under different settings in both developed and developing countries [4, 5, 12]. Also, earlier occurrence of recurrent cases observed among HIV-infected TB patients after successful treatment indicates their increased vulnerability to recurrent episodes, compared to HIV-uninfected TB patients [5, 29]. All the facts lead to the questions that whether these phenomena should be attributed to the failure of treatment regimen/TB control program, the HIV pandemic and its influence on TB, or increased intrinsic vulnerability of certain populations. Clarification on the fundamental mechanisms for excessive recurrence rates is urgently needed to establish evidence-based intervention strategies.

2.2.4 Impact of TB recurrence

TB recurrence is problematic in a two-fold way. For individual patients, the use of more complex and longer treatment regimen, increased possibilities of unsuccessful treatment outcomes, higher chances to develop drug resistance, and higher risks of morbidity and mortality are main concerns [8]. On the other hand, from the public health points of view, larger amounts of resources (e.g., financial and human resources) needed to be allocated to treat recurrent patients, and transmission of causative bacilli to the general population if recurrent patients left untreated or have been not treated in a timely manner, impose further difficulties and complexities in current TB control [8]. More importantly, since TB/HIV co-infection has been widely spread out around the world, especially in developing countries, management of both HIV and TB simultaneously among recurrent HIV-infected patients raises more concerns about timely diagnosis, choices of treatment regimen (i.e., drug interaction and side effects), and control of high mortality and morbidity rates among co-infected patients[10]. Thus, the impact of TB recurrence on either patients or TB control programs urgently requires research investigations and establishment of intervention strategies to address these issues.

3. General introduction of TB control in Thailand and Chiang Rai province

2.3.1 TB burden and control in Thailand

Thailand is a middle-income country which has been one of the 22 high-burden countries with TB in the world since 1998 (ranked 19th in 2009) [15]. According to WHO in 2005, the estimated incidence rate for sputum smear-positive TB was 64/100,000, with 142/100,000 for all forms of TB, and the estimated mortality rate was 19/100,000 in Thailand [30]. It was also reported that 7.6% of TB cases in people aged 15-49 in Thailand were HIV co-infected in 2005, according to a national survey [30]. In addition, Thailand TB Active Surveillance Network from 4 sentinel provinces showed that HIV co-infection rate varied from 15% in central provinces to 34% in the northern province (Chiang Rai province), and that the treatment success rate was 57% among HIV-infected patients and 76% among HIV-uninfected patients [30]. These low treatment success rates were considered to be associated with large proportion of cases that didn't have documented

treatment outcomes, that defaulted, and that died [31]. The combination of high case detection rates (76% among smear-positive cases in 2005) and low treatment success rates (68% among smear-positive patients) raised significant concern on the emergence and dissemination of drug-resistant TB [30]. According to recent national drug-resistance surveys conducted in 2006, MDR-TB rate was 1.7% among new patients and 34.5% among previously treated patients, almost doubled from 1% and 20% in 2002, respectively [30].

DOTS strategy was adopted by the National TB Program in 1996 as a response to the increased TB cases and deaths due to HIV epidemic in 1990s [30]. Decentralized DOTS is managed through TB clinics at all administration levels (provincial/community/district), featured by the participation of non-professional healthcare workers--health volunteers, lay healthcare workers and patient's family members in the observation of patients' drug intake [30]. After the national implementation, 70% target of case detection rate was achieved, while 85% target for treatment success has not been achieved due to a large proportion of cases who did not have documented treatment outcomes, who defaulted, and who died (possibly associated with HIV) [30-32].

2.3.2 TB burdens and control in Chiang Rai

Chiang Rai, the northernmost province of Thailand, located close to the Myanmar and Laos borders, with a population of 1.4 million, was ranked 2nd of Thailand's 76 provinces for TB rates and has a low treatment success rate: 67% and 73% for new smear-positive TB cases and all TB patients in 2007, respectively, indicating a heavy TB burden and suboptimal performance of local TB control program [33]. TB incidence rate in Chiang Rai has increased from 50/100,000 in 1990 to 153/100,000 in 2000, while the TB prevalence in Thailand was 80/100,000 in 2001 [34]. The proportion of MDR-TB among the previously-treated TB patients was 12.6%, compared to the WHO estimated rate of 5% worldwide [8]. HIV co-infection rate among new TB patients has increased significantly from 3.1% in 1989, to over 15% in late 1990s, and up to 34% in 2008 [31, 35]. It also significantly contributed to the high mortality rate among TB patients: more than 30% of HIV co-infected TB patients died during the treatment (based on the internal database calculation).

In Chiang Rai province, a province-wide, population-based TB/HIV integrated surveillance system was established in 1996 in response to the duel epidemic of TB and HIV, aiming at capturing and identifying every TB patient treated in all 17 public hospitals, and exploring the interrelation between TB and HIV for effective TB control. This collaborative project established by Chiang Rai Provincial Health Office, Chiang Rai Provincial Hospital, and the Research Institute of Tuberculosis, Japan Anti-tuberculosis Association (RIT-JATA), has significantly improved the performance of TB control, by increasing treatment success rate from 47.6% in 1997 to 64.8% in 2007, and decreasing mortality rates from 28.1% to 16.5%, among newly diagnosed smear-positive TB patients (based on the internal database calculation).

Chapter 3: Literature review of studies on TB recurrence

3.1 Aims for literature review

The purposes to conduct this literature review are to 1) make sense of two mechanisms for TB recurrence and their contributions to overall TB recurrence in relation to HIV infection; 2) gain an overall view of TB recurrence rates reported in studies under different settings by HIV status; 3) summarize identified risk factors for TB recurrence and discuss on their hypothesized mechanisms, if available.

3.2 Strategy for literature search

Information complied for this literature review was identified through searches of PubMed and Google Scholar. The search terms “Tuberculosis recurrence (relapse/re-infection)” and “HIV” were used in different combination to search studies published in English. The author also scrutinized the bibliographies of key studies identified in this way to find other relevant publications. The following criteria was used: studies published up to 2010; studies reported recurrence (or “relapse”) rate with explicit HIV sero-status of study population; studies only included patients with successful completion of treatment declared by “cure” and/or “complete of treatment”, with or without bacteriologic confirmation; studies followed Rifampin-containing treatment regimen.

3.3 Results of literature search

The search through electronic databases generated 83 articles for screening. By the abstract review 33 studies were excluded because they didn’t meet the inclusion criteria listed above, or not written in English. Examination of the references of these remaining 45 articles adds another 10 articles, which give us a total of 55 articles for conducting this literature review.

3.4 Endogenous relapse, exogenous re-infection and their association with HIV

3.4.1 Overview

Along with the development of molecular technology, two mechanisms for TB recurrence—relapse and re-infection were well-accepted by now [26]. To find out the underlying reasons for excessive recurrence rates reported around the world, and to address this issue by setting up practical interventions for targeted high risk population, the exploration on the fundamental mechanisms of TB recurrence and associated risk factors has become the focus among researchers and TB control practitioners. There is no doubt that the association between relapse, re-infection and HIV infection has drawn most of the attentions, since HIV has its unique credits on modifying almost all aspects of TB, including increased risk of infection, altered clinical/bacteriological presentations, and worsened treatment outcomes [36].

3.4.2 Endogenous reactivation (relapse) and its risk factors

Endogenous reactivation (relapse) has been regarded as a long-term indicator to TB treatment efficacy since its occurrence is due to the failure of eliminating persistent bacilli, which have brief spurts of metabolic activities during dormant periods [37]. In this sense, relapse cannot be regarded as continuum to treatment failure, which is due to the insufficient ability to kill rapidly dividing bacilli, although both of them can reflect the insufficiency of treatment regimen and thus be used as important indices to evaluate treatment effectiveness. Bacilli persistence is mainly due to absolute/relative inadequacy of treatment efficiency, which could have resulted from the use of inadequate treatment, poor patient adherence to treatment, drug resistance, and initial high bacterial loads [25, 38]. Since the development of relapsed TB also requires further progression from persistent bacilli into active disease, factors which can influence individual's immune function were all reported to be associated with high relapse rates [4, 25, 26]. Regarding the timing of relapse, it

is more likely that relapse occur soon post treatment completion, although some could be manifested after 15 years later [39].

3.4.3 Exogenous re-infection and its risk factors

Re-infection was regarded to occur rarely during the first 2 to 5 years after initial infection, under the assumption that at least partial immunity could be obtained from the initial episode to fight against the new infection, till its early appearance post treatment completion was demonstrated by the molecular technology (DNA fingerprinting) [40] . The risk for re-infection is determined firstly by the risk of exposure to *M.tuberculosis* (determined by the chance of inhalation of viable tubercle bacilli from surrounding environment), and then the progression from new infection to subsequent active disease, which could be accelerated by HIV infection and its associated immuno-suppression, or intrinsically predisposed conditions [26, 29].

Re-infection has drawn a lot of attentions as a "new phenomenon" for TB recurrence, resulting in the increased research investigations recently [4, 6, 26, 27, 39, 40]. However, three common mistakes in those studies must be pointed out before further discussion. First, the definition of re-infection as a new infection from a different strain of *M.tuberculosis* is problematic, since it could be caused by the same strain as the one from initial episode, although this possibility is relatively low [41, 42]. Second, most of studies reported rates of re-infection and relapse in percentage, which together add up 100% of all recurrent cases. However, re-infection and relapse are essentially two independent events determined by different factors, but share the same clinical manifestation and some similar host factors which might predispose this event (e.g., HIV infection) [26]. Thus, it is better to report the rates of those two mechanisms in the person-year format to accurately demonstrate their actual contributions to the overall recurrence rate. Third, it has been argued that re-infection exerts its most effects in settings with high TB incidence, and therefore mostly accounts for the excessive rates [38, 40]. However, this argument was mostly generated from studies conducted in southern African countries where the background incidence was extremely high [5, 6, 50, 66] . In fact, 12-75% range of re-infection proportion demonstrated in studies which differentiated relapse from re-infection didn't support this assumption [6, 43-45]. One of the reasons is that

background incidence could be only used as a proxy indicator for patients' exposure risk to *M.tuberculosis* [29]. Under other special settings with a low background TB incidence, such as prisons and inner-city immigrants' communities in developed countries, re-infection also played the dominant role in excessive recurrence rates [27, 45]. Therefore, it is important to assess the real exposure risk which is actually faced by individual patients, rather than an over-generalized estimate based on background incidence.

The differentiation of re-infection from relapse has important public health implications including vaccine design, chemoprophylaxis, and assessment of treatment regimens and TB control programs [6]. If relapse is the dominant mechanism for excessive recurrence rates, then correspondent strategies including optimizing treatment regimen and enhancing adherence to treatment, should be underscored by control programs. On the other hand, if the main cause is due to re-infection, then different preventive strategies, such as post-treatment Isoniazid preventive therapy, and measures to reduce nocosomial/household transmission should be taken into account [46].

3.4.4 Associations between relapse, re-infection and HIV

Overview

There are two major research focuses on TB recurrence currently. One is the exploration on the roles played by endogenous reactivation and exogenous re-infection, and their respective risk factors, investigated by applying molecular technologies [27, 40, 43, 44, 47]. The other one is the study of the role played by HIV on excessive TB recurrence rates, explored by applying traditional epidemiology method [48, 49, 52]. However, one of the most interesting research questions regarding "the relative contribution of reactivation and re-infection to HIV-infected and uninfected patients", could only be accurately answered by applying the two methods in combination to the same study population [40, 50]. A handful of studies investigating this association have seemingly generated two assumptions: 1) re-infection attributes mainly to the excessive rates among HIV-infected patients, while relapse is the main mechanism among HIV-uninfected patients [6, 38, 50]; 2) early recurrence is

due to relapse and late due to re-infection [46]. However, those "theories" are still in validation and needed to be interpreted with caution.

Regarding the first assumption, there is no doubt that re-infection has become a more significant contributor to TB recurrence with the involvement of HIV [51]. HIV might exert its effect on increasing re-infection rate through increasing risk of re-infection with *M.tuberculosis* after treatment, through increasing the risk of development of disease after re-infection, and possibly through increasing the risk of exposure (e.g., patients' attendance at health facilities) [50]. However, the notion of re-infection being the main cause of excessive recurrence rates among HIV-infected patients is not well-rooted. It was estimated by a meta-analysis including studies reporting on relapse and re-infection rates, that 30% of recurrences were due to re-infection, with 38% among HIV-infected patients, and 23% among HIV-uninfected patients [29], which indicated that relapse was still the dominant reason for TB recurrence among both subgroups of patients. Under the circumstances that the treatment regimen is not optimal or not well-administered, either of which is still quite common under settings in developing countries, the major contributor to the excessive recurrence rates among HIV-infected patients is relapse, rather than re-infection [53, 54.] On the other hand, re-infection could also be an important attributor to the increased recurrence rates among HIV-uninfected patients, especially in some countries with high TB prevalence rate but relatively low HIV prevalence, such as China and India, or special settings such as prisons [55-57]. Thus, when it comes to the discussion of which plays the dominant role in a specific population, no hasty conclusions should be made based on any single factor. Comprehensive assessment of the applied regimen, patients' adherence, exposure risk to a new infection, immunity level of the overall community (i.e., determinant for the possibility of getting infection after exposure), and other setting-specific characteristics, is essential to find out which mechanism plays the dominant role in causing the excessive risk, among HIV-infected and uninfected TB patients.

The main implication of the timing of occurrence for recurrence lies in its guidance on establishing follow-up duration for intensive active case finding and post-treatment prophylaxis [26,

[29]. In addition, researchers also tried to use the time pattern of recurrence as a proxy indicator to differentiate relapse from re-infection in the absence of DNA fingerprinting technology, assuming that relapse generally occur earlier in time and re-infection occurs later and maintain a constant rate over time [5]. In overall, the majority of recurrent cases occurred soon after treatment completion (>50% occurred during the first 6 or 12 months) [4]. Once the treatment completes, the sudden withdrawal of anti-TB drugs could lead to the quick "bounce back" (reactivation) of those persistent bacilli, substantiating the assumption that relapse usually occurs early in time post treatment completion [58]. However, relapse mostly occurs early in time cannot warrant that early recurrent cases are caused by relapse. The main determinant of the timing for TB recurrence is the incubation period of *M.tuberculosis* from either persisted or newly infected bacilli, to active diseases. For HIV-infected patients, early timing of recurrence was observed and assumed to be due to the compressed process from new infection to active TB disease associated with their advanced immune-suppression [10, 29]. In addition, risk of exposure to new strains could be prominent during the first months post treatment. For example, frequent hospital visits during the first several months after treatment, especially among TB/HIV co-infected patients, could put those patients at high risk of exposure since *M.tuberculosis* strains are usually densely-circulated in those places [57].

Highest recurrence rates were usually observed immediately after treatment completion, among both HIV-infected and uninfected patients [29]. For HIV-uninfected patients, the recurrence rate decreased rapidly over time during the first 6 or 12 months after treatment completion and then leveled off at a minimal rate [29, 38]. But different patterns have been observed for HIV-infected patients: some studies showed a constant recurrence rates over time, while other studies showed similar time pattern as it showed among HIV-uninfected patients, but with steeper or smoother "drop" of recurrence rates along with the increase in time [6, 27, 32]. It is assumed that those different patterns in HIV-infected patients could be associated with variations in the relative proportion of relapse and re-infection in the recurrent cases.

It is no doubt that the clarification of the role played by HIV on relapse and re-infection influences both the theoretical development in the research field and strategic planning for TB control programs. However, two limitations on the explorations of their associations should be stated. Firstly, in developing countries with heavy TB burdens, the resources are far from enough to afford timely and broad application of molecular genotyping technology to differentiate relapse from re-infection. In addition, the differentiation of relapse from re-infection has limited significance regarding the selection of different treatment regimen for recurrent patients. Thus, exploration of widely available and easily identifiable indicators as approximate reflections of the risk of TB recurrence should be research priorities. Secondly, the fact that incidence rate of re-infection surpassed the incidence rate of new TB might imply the intrinsic vulnerability among those patients even with successful treatment [43]. However, the genetic predisposition of TB patients influencing either relapse, re-infection, or both, has rarely been set foot in the discussion so far[59].

3.5 Reported TB recurrence rates and associated risk factors

In order to clearly demonstrate recent research findings, comparisons across studies reporting on TB recurrence rates and risk factors are presented in two tables (tables 3.1 and 3.2), by patients' HIV status. Major influences and threats to the validity of those studies are firstly discussed. Comparisons of reported recurrence rates across studies would provide us an overall view of the prevalence of TB recurrence in the world, as well as the disparities observed under different settings. Reported risk factors and their hypothesized mechanisms in relation to relapse and re-infection are also discussed to explore their contributions to TB recurrence for HIV-infected and uninfected TB patients.

Table 3.1 Reported TB recurrence rates by HIV-specific studies

Ref No	Author; publication year	Country	Study design	Recurrence rate among HIV-infected patients Rate (95% CI)	Recurrence rate among HIV-uninfected patients Rate (95% CI)	Follow-up Time
49*	Sterling *et al*; 1999	USA, Baltimore	Consecutive cohort study	6.4% (1.3-18.6)	5.5% (1.2-6.2)	Up to 5 years of follow-up.
6	Sonnerberg *et al*; 2001	South Africa	Prospective cohort study	16.0/100 (11.8-21.7)	6.4/100 (4.3-9.6)	Median: 25 months (IQR: 13.2-33.4)
38*	Jasmer *et al*; 2004	US and Canada	RCT	4.09/100 (2.31-6.65)	3.71 /100 (2.84-4.76)	2 years
60	Khan *et al*;2006	USA	RCT	N/A	7.1%	2 years.
11	Millet *et al;* 2009	Spain, Barcelona	Population-based retrospective cohort study	1.06/100	0.39/100	Median:8.9 years (IQR:7.8-9.6)
12	Picon *et al*; 2007	Brazil	Retrospective cohort study	5.95/100	0.48/100	7.7 +_2.0 years
13	Mallory *et al,* 2000	South Africa	Retrospective cohort study	8.2/100	2.2/100	Average 1.5 years for HIV+, and 2.1 years for HIV-.
61	Lopez-Cortes *et al*; 2005	Spain	Observational prospective study	1.9/100 (1.8-2.0)	N/A	Median: 24 months (IQR: 8.5-41)
62	Johnson *et al*; 1997	Uganda	Nested case-control study within a randomized prospective clinical trial	3.1/100	N/A	Median: 22.3 months
63	Golub *et al*; 2008	Brazil	Retrospective cohort study	2.5/100 (2.0-3.1)	N/A	Average 3.1 years
5	Glynn *et al*; 2010	South Africa	Retrospective cohort	19.7/100 (16.4-23.7)	7.7/100 (6.1-9.8)	>7 years
50	Crampin *et al*; 2010	Malawi	Long-term cohort study	7.8/100 (6.0-10.1)	3.4/100 (2.4-4.9)	Average 2.9 years
64	Fitzgerald *et al;* 2000	Haiti	RCT	4.8/100	0.4/100	2 years
65	Crofts *et al;* 2010	England and Wales	Surveillance based retrospective cohort study	0.76/100 (5.4-10.7)	0.4/100 (3.7-4.3)	Median: 3.3 years (IQR: 1.6-5.1)
66	Swaminathan *et al*; 2010	India	RCT	8.0/100	N/A	27-30 months
29	Korenromp *et al;* 2003		Analytic review	4.5/100 (3.2-5.8)	1.9/100 (1.2-2.7)	Average 34 months.
67*	El-Sadr *et al;* 2001		Review	0-10%	0-3.4%	N/A
68	Perriens *et al;* 1995	Zaire	RCT	9% (0-15)	5.3 % (2.8-7.0)	24 months
69	Nettles *et al;* 2004	USA, Baltimore	Observational cohort study	8.3%	1.7%	7 years

53	Drivers *et al;* 2001	US, New York city	Retrospective cohort study	2.0/100	0.4/100	Up to 3.5 years of follow-up
48	Nahid *et al;* 2007	US, San Francisco	Retrospective cohort study	9.3/100	1.0/100	7.6 months (Range: 0-16.6) for HIV+; 8.6 months (Range: 0-34.5) for HIV-
7*	Connolly *et al;* 1999	South Africa	Prospective cohort study	3.9/100 (1.5-6.3)	3.6/100 (1.1-6.1)	1.2 +_0.4 years
4	Panjabi *et al*; 2007	USA	Review	6.7% (5.9-7.6)	3.3% (2.8-3.9)	
70	Benator *et al*; 2002	USA and Canada	RCT	N/A	4.0%	2 years.
52*	Johnson *et al*; 2000	Uganda	Prospective cohort study	5.9/100 (3.2-8.6)	2.1/100 (0-7.8)	Median 17.7 months (IQR:12.0-24.3) for HIV+; 17.8 months (IQR:16.0-27.2) for HIV-.
71	Okwera *et al*; 2006	Kampala	Prospective cohort study	9.7/100 (5.5-15.8)	N/A	Median: 1.4 years

*: studies didn't assess the statistical significance of the difference for recurrence rate among HIV-infected and uninfected groups.

3.5.1 Overview of reviewed studies

For discussion on the reported recurrence rates and associated risk factors among HIV-infected and uninfected patients, we include 27 studies for review. Among those studies, three were review articles, six investigated recurrence rates among either HIV-infected or HIV-uninfected population (5 of them on HIV-infected population), nineteen gave estimates of recurrence rates in person-years format, twelve among which were conducted in countries with high background incidence of TB. Seventeen articles also investigated the associated risk factors (table 3.2). Five studies collected DNA fingerprinting information to determine the molecular subtypes of TB recurrence. Only three studies investigated TB recurrence rate (in the person-year format) as well as respective risk factors for HIV subgroups among the same population.

Because the number of studies investigating on risk factors among HIV-infected and uninfected patients is relatively small, we conducted a larger-scale review for exploring the mechanisms of risk factors. This round of review includes another 15 studies. Previous inclusion and exclusion criteria also apply here, only without the requirement on specifying patient's HIV status.

3.5.2 Factors that influence the interpretation of study results

Unlike other outcomes of TB treatment, recurrence rates have not been routinely assessed and reported by TB control programs [25]. Thus, among the studies reporting on TB recurrence rates and its associated risk factors, some of them were primarily investigated on other aspects of TB control. For example, clinical trials aimed at comparing different treatment regimens usually reported recurrence rates as an indicator of long-term efficacy. However, a selected population was usually comprised for these investigations, which could lead to the impaired external validity of the study results. For those studies primarily focused on TB recurrence, different study designs (i.e., cross-sectional/case-control/cohort studies), different inclusion/exclusion criteria for study population, especially restrictions on variables that might also be influential factors for TB recurrence (e.g., exclusion of MDR-TB cases and non-compliant patients), variation in methods to measure key indicators and different categorization criteria for interested variables (e.g., non-compliance, smoking and drinking habits), ignorance of data on (selective) loss to follow-up and death, lack of information on population-specific indicators (e.g., the stage of HIV epidemic, quality of local TB control programs), and even different case definitions of TB recurrence (e.g., bacteriologic or culture-confirmed, timing for recurrence), not only influence the interpretations of research findings for individual studies, but also make it extremely hard to generate a consensus across those studies.

Small study sample size and short length of follow-up are the main threats to the validity of study results, due to lack of sufficient statistical power to detect significance. These are common problems among previous studies and partially determined by the nature of the recurrent event, which usually takes a fairly long time to develop and affects a relatively small number of patients. Another prominent source of bias is the suboptimal study design. Case-control and repeated cross-sectional studies have been used to generate estimates of recurrence rates and explore associated risk factors by comparing different distributions of risk factors between patients who recurred and those who didn't. However, TB recurrence is a highly time-dependent event. Follow-up duration should be reported with the estimates of recurrence rates, which is usually missed in a case-control or cross-sectional study design. On the other hand, although RCT is considered to be the optimal

study design to draw causal inferences, they are well-known to have a low level of generalizability because of the highly selected population. In addition, in clinical trials investigating TB recurrence, specialized treatment facilities are usually involved, providing better services and maximizing patient's adherence, leading to better treatment efficiency and more favorable outcomes [4, 6], and thus yielding a low recurrence rate.

3.5.3 Reported TB recurrence rates by HIV status

Due to multiple variations in study methods, it is difficult to conduct a meta-analysis to generate interpretable and meaningful estimates of TB recurrence rates from studies comprised of study populations with different socio-demographic/epidemiologic characteristics, and under different settings with different TB/HIV background incidence. Thus, reported TB recurrence rates from different studies are presented without any statistical analyses. However, based on the 11 studies which reported recurrence incidence rates among both HIV-infected and uninfected groups with statistically significant differences, several facts and assumptions could be obtained as follows: 1) the differences of recurrence rates could vary from 2-fold to 12-fold between HIV-infected group and uninfected group, in both high- and low- background incidence countries; 2) for HIV-uninfected group, TB recurrence rates were usually less than 1.0/100 PYs in both low- and middle-incidence countries, approximately reflecting the recurrence risk among the general population; 3) the lowest reported recurrence rates among HIV-uninfected patients was 0.4/100 PYs in England and Spain, but was still at least 10 times higher than their background incidence rate (<30/100,000); 4) from the study which differentiated re-infection from relapse, re-infection incidence rate was found to be 4-fold higher than the new TB incidence rate [43]; 5) apart from the study conducted under a special setting with extremely high risk of exposure to *M.tuberculosis* and conditions that favoring the development of TB disease (e.g., silicosis) among South African mine workers[5], the highest observed recurrence rate among HIV-infected patients was approximately 10/100 PYs. Only one study with similar high recurrence rate (9.3/100 PYs) was conducted in low-incidence country [48], with very short duration of follow-up (median: 8 months); 6) those reported recurrence rates for HIV-infected patient might be underestimated due to high

competing risk from death, since it is also independently associated with the degree of immuno-suppression [49].

3.5.4 Reported risk factors for TB recurrence

The exploration of the fundamental mechanism for each risk factor in relation to relapse and re-infection plays an important role in identifying high risk group and implementing intervention strategies to reduce the recurrence risk for TB control programs. Among recent studies, the investigations mainly focused on the clinical/treatment-related risk factors [5, 25, 57, 62, 72]. Some socio-demographic factors have also been reported, but with less consistence, mainly due to the variations in applied methods to measure those indicators, as well as applied criteria to categorize study population [4, 73]. The following section presents detailed discussions on reported risk factors, their hypothesized mechanisms in relation to relapse and/or re-infection, and the different spectrums of risk factors for TB recurrence between HIV-uninfected patients and HIV-infected patients.

There are several points needed to be stated before further detailed discussions. First, it is important to acknowledge that among a certain group of population, risk factors for overall recurrence are a combination of those for relapse and re-infection, two very different mechanisms with different determinants [51]. The risk factors identified for overall recurrence depend on the relative proportion of recurrent cases attributable to each of these two mechanisms [29]. Thus, it is important to correctly interpret the risk factors based on the two mechanisms, to generate scientifically-sound prediction of recurrence risk according to identified risk factors in the absence of DNA fingerprinting technology. For examples, residual cavitation at the end of IP is a strong indicator for relapse because it can reflect the inadequate microbiological response to TB treatment, resulting in bacilli persistence [4]. However, it is not an indicator for re-infection, which is determined by the exposure risk of *M.tuberculosis*, and patients' immunity function. Thus, if recurrent cases are mostly comprised of re-infection, the predictive value of residual cavitation is negligible.

In addition, researches have shown that the spectrums of risk factors for TB recurrence have been altered, from pre-HIV era to HIV-era, and between HIV-uninfected and HIV-infected TB patients [55, 62]. For example, the presence of cavitation and positive sputum/culture at the end of IP were highly predictive of recurrence risk for HIV-uninfected patients, but not for HIV-infected patients [69.] In fact, these two indices were less common in HIV-infected TB patients with advanced immuno-suppression due to their inadequate immune response to present those clinical manifestations. In this sense, the absence of residual cavitation or positive sputum/culture at the end of IP is no longer an indicator for treatment efficiency, but merely a reflection of advanced stage of HIV. For HIV-infected TB patients, more HIV-related indicators reflecting advanced immuno-suppression have been demonstrated to be significantly associated with higher recurrence risk, such as the low CD4 cell counts [48, 63, 69]. The different spectrums of risk factors between HIV-uninfected patients and HIV-infected patients are needed to be acknowledged to guide clinical practices and public health strategic planning for interventions.

Table 3.2 Reported risk factors for HIV-infected and uninfected patients from reviewed studies

Ref No	Author, publication year	Country	Study design	Risk factors for HIV-infected patients	Risk factors for HIV-uninfected patients
49	Sterling *et al*; 1999	USA, Baltimore	Consecutive cohort study	Low CD4 level	
4	Panjabi *et al*; 2007	USA	Review	Low initial CD4 level; <37 weeks of treatment.	
70	Benator *et al*; 2002	USA/Canada	RCT		Delayed sputum conversion; Cavitation; Bilateral pulmonary involvement; Underweight; Non-Hispanic white.
60	Khan *et al*; 200	USA	RCT		Weight gain<=5% during IP; Cavity and delayed sputum conversion.
13	Mallory *et al*, 2000	South Africa	Retrospective cohort study	Three-drug regimen; Initial drug resistance.	Three-drug regimen
61	Lopez-Cortes *et al;* 2005	Spain	Observational prospective study	6-month regimen; Lack of efficacy of HAART; No increase of CD4 counts during treatment.	
62	Johnson *et al*; 1997	Uganda	Nested case-control study within a randomized prospective clinical trial	Age>30 years; Poor treatment compliance.	
63	Golub *et al*; 2008	Brazil	Retrospective cohort study	Not receiving HAART; Age <40 years; Low CD4 counts and no increase of CD4 counts during treatment.	
5	Glynn *et al;* 2010	South Africa	Retrospective cohort	>2 years after index episode	>1 previous episode; Isoniazid resistant in the index episode;
64	Fitzgerald *et al;* 2000	Haiti	RCT	Presence of HIV symptoms before TB diagnosis.	
66	Swaminathan *et al*; 2010	India	RCT	6-month thrice-weekly regimen	
29	Korenromp *et al*; 2003	Geneva	Analytic review	Shorter duration of Rifampin treatment	
68	Perriens *et al*; 1995	Zaire	RCT	6-month treatment duration	
69	Nettles *et al*; 2004	USA, Baltimore	Observational cohort study	Low initial CD4 counts	Non-Hispanic white; Cavitation; Delayed sputum culture conversion.
53	Drivers *et al*; 2001	US, New York city	Retrospective cohort study	Mixed TB; Drug abuse; Non-adherence; Treatment<37 weeks.	Treatment<37 weeks
48	Nahid *et al;* 2007	US, San Francisco	Retrospective cohort study	6 months regimen; Intermittent treatment regimen.	

Table 3.2 lists the studies reported on risk factors for TB recurrence, with explicit HIV sero-status.

For the convenience of discussion, those identified risk factors are further categorized into two

groups: clinical/treatment-related risk factors and socio-demographic risk factors, among HIV-infected and uninfected patients. In this summary, we also included risk factors for TB recurrence reported from studies conducted in pre-HIV era without explicit description of HIV sero-status for the study population, assuming that most patients were HIV-uninfected. The reported risk factors are as follow:

Among HIV-uninfected TB patients

a. Clinical and treatment-related risk factors

Initial/residual cavitation; high initial bacilli loads and advanced radiological manifestations (e.g., high initial sputum counts/grade, atypical radiology, bilateral lung involvement); delayed sputum/culture conversion; mono-resistance TB/MDR-TB/poly-resistant TB; suboptimal treatment regimen (e.g., three-drug regimen, intermittent regimen, <37 weeks of treatment duration); poor patients' compliance; underweight and weight gain<5% during treatment;

b. Socio-demographic risk factors

Younger or older age; non-Hispanic white race; smoking; drinking; injection drug use;

Among HIV-infected TB patients

a. Clinical and epidemiological risk factors

Low initial CD4 counts or no increase of CD4 counts during treatment; symptomatic HIV; poor adherence to treatment; no HAART treatment; suboptimal treatment regimen (e.g., <9 months of treatment, three-drug regimen, intermittent regimen); and mixed TB (i.e., involve both PTB and EPTB);

b. Socio-demographic risk factors

Younger or older age; drug abuse.

Based on the summary, we can see both similarities and differences of risk factors between HIV-infected and uninfected patients. Poor patients' compliance and suboptimal treatment regimen are common risk factors for both HIV-infected and uninfected patients. However, the surrogates of

bacillary burden, e.g., initial/residual cavitation, delayed sputum/culture conversion, high sputum count/grade, are no longer predictors of recurrence for HIV-infected patients, as for HIV-uninfected patients. Instead, HIV-related risk factors, such as low CD4 count level, no HAART treatment, are commonly reported to be associated with high TB recurrence rates for HIV-infected patients.

3.5.5 Hypothesized mechanisms for risk factors

A. Clinical and treatment-related risk factors

Severity of TB disease

The severity of TB disease has been reported to be highly associated with TB recurrence, including those indicating radiological/bacteriological extensiveness, such as high initial bacterial loads, extensive areas of lung tissue involvement, mixed TB, and initial cavitation at diagnosis [4, 6, 13, 26, 70]. The common mechanism for those factors is relatively inadequate treatment efficiency due to the use of standard regimen in treating those severer cases. Those indicators were extremely helpful for clinicians to monitor TB patients during treatment. But cautious should be exercised when apply those indicators for HIV-infected patients, since these bacteriological/radiological manifestations could be altered by HIV infection and its associated immuno-suppression to a great extent [62, 69].

Poor microbiologic response to treatment

Residual cavitation and delayed sputum/culture conversion at the end of IP are mainly regarded as reflections of poor bacteriological response to treatment. Cavitation has been one of the most frequently reported risk factors for TB recurrence among studies comprised mostly HIV-uninfected patients [4, 26, 62]. Poor penetration of anti-TB drugs into the cavity walls surrounding fibrotic tissue, which may harbor semi-dormant bacilli, attributed to the elevated risk of relapse by persistent bacilli [4]. An alternative hypothesis suggested that *M.tuberculosis* might have a tendency to infect previously damaged lung tissues, attributing to the higher risk of re-infection [4].

The purpose of intensive phase in TB treatment is to kill the majority (>80%) of the fast-replicated bacilli by powerful first-line sterilization drugs (e.g., R, H, Z) [18]. Thus, at the end of IP, a

noticeable decrease in bacteria loads, reflected by the conversion of smear from positive to negative, is usually expected. Failure of this conversion might indicate high bacteria viability, inadequate response to the chemotherapy, or drug resistance, either of which could directly lead to bacilli persistency. Cautions should also be exercised when predict recurrence risk for HIV-infected patients using those risk factors.

Drug resistance and MDR-TB

Since DST has not been widely available in resource-poor settings in developing countries, only a few studies collected drug resistance data to study their associations with TB recurrence [57, 74]. Extremely higher recurrence rates were observed among mono-resistance TB, MDR-TB, or ploy-resistance TB cases, especially in HIV-infected patients [5, 13, 57, 75]. However, this observed high recurrence rate might not be a direct result of drug resistance, but a result of relative inefficiency of treatment regimen [57]. In developing countries, most of TB patients did not receive DST test, but assumed to be pan drug-susceptible and treated with standard regimen for drug-susceptible cases. Thus, inappropriate use of treatment regimen could lead to treatment inefficiency for patients who have drug resistance, and ultimately lead to bacilli persistency [74, 76].

Inadequate treatment regimen

A group of risk factors for TB recurrence can be ultimately attributable to the use of inadequate treatment regimen, including suboptimal treatment duration (<9-month duration, especially for HIV-infected patients), intermittent treatment regimen (twice/thrice-weekly), fewer numbers of anti-TB drug used (3 drugs) [13, 58, 66]. After the wide application of WHO-recommended Rifampicin-containing regimen, 6-month duration was proved to have adequate efficacy to maintain an acceptable recurrence rate in a largely HIV-negative environment [25]. More discussions on the treatment duration have been focused on HIV-infected patients (see “HIV-related factors” below). A significant “dose-response” relationship between different dosing schedules and recurrence rates has been reported by a systematic review of clinical trials, showing an increased

trend of recurrence rates with less frequently-used treatment regimen [58]. Also, the longer duration of R-containing regimen (6-month vs 2-month) has also been reported to lower recurrence rates [25].

Poor adherence to treatment

Patients' compliance to TB treatment is one of the most important factors in determining of individuals' treatment outcomes and overall performance of TB control programs [12, 24, 25, 53]. Although standard treatment regimen has been proved to be fully capable of curing TB, under program conditions, it might not guarantee successful treatment outcomes if patients don't fully adhere to the regimen, which significantly reduces treatment efficiency and increases the risk of endogenous relapse [26, 75]. It should be noted that the effect of poor patients' adherence on excessive recurrence rates is often confounded by multiple socio-demographic/behavioral factors, such as drinking, smoking, drug abuse, and being male [73, 77].

HIV-related factors

For HIV-infected individuals, immune-suppression status and inadequate treatment efficiency are the main concerns regarding TB recurrence risk. Standard treatment regimen for HIV-infected patients might not be as effective as for HIV-uninfected patients, since recurrence rates for HIV-infected patients were significantly higher, given the same regimen applied [29, 46, 48]. For HIV-infected patients, plenty of evidence suggested that R taken throughout the whole treatment could significantly lower recurrence rates, compared to R taken only in IP [46]. Also, the extension of 4-month CP with R and H to 6-month also resulted in the decrease of recurrence rates [46, 66]. In addition, post-treatment Isoniazid prophylaxis after standard 6-months R-containing treatment for another 12 months can significantly reduce recurrence rates, possibly through prevention of both relapse and re-infection [64]. Applying of those regimens not only resulted in lower rates of TB recurrence, but also led to the decrease of mortality rates [46, 48, 64, 66].

Researches also demonstrated that low initial CD4 counts, lack of increase in CD4 counts during treatment, and the presence of HIV symptoms, were highly associated with higher recurrence rates, reflecting the advanced stage of immuno-suppression [29, 48, 61, 63, 69]. The use of HAART was

found to be able to significantly reduce the recurrence rates among HIV-infected patients, especially for those patients whose CD4 counts were less than 200 cells/*ul* [48, 61, 63, 66]. This beneficial effect is assumed to act through immune reconstruction, lowering the risks of both relapse and re-infection [46].

Other clinical and treatment-related factors

Other reported risk factors include low weight and lack of weight gain during treatment, and the presence of co-morbidities (e.g., diabetes, Chronic Obstructive Pulmonary Disease) [60, 72]. A recent clinical trial demonstrated that weight gain < 5% during IP was associated with an increased recurrence rates among underweighted HIV-uninfected patients, even after controlling for other risk factors such as cavitation and delayed sputum conversion [60]. This indicator could be used as an approximate indicator of poor microbiological response to TB treatment in resource-poor settings to help assess and predict recurrence risk for HIV-uninfected patients.

Diabetes Mellitus was one of commonly reported co-morbidities associated with high TB recurrence rates due to patients' compromised immune function [72]. Silicosis and Chronic Obstructive Pulmonary Disease were also occasionally reported to be associated with TB recurrence [6].

B. Socio-demographic risk factors

Socio-demographic risk factors for TB recurrence have also been explored and reported, including younger or older age, male, smoking, drinking, drug use, non-Hispanic white race, and immigrants[11, 49, 62, 63, 65, 73, 75]. It is difficult to clearly demonstrate the effect of each individual factor on recurrence rates due to their complex associations with each other, as well as with HIV-infection and non-compliance, through all which together synergetic effects are formed to increase recurrence rates. For example, smoking, drinking, drug use, and being immigrants might be related to, or reflective of patients' non-compliance, high risk of HIV infection, and patients' weakened immune function [4, 9, 19, 23, 74]. Other than synergetic effects, some of the risk factors also have their independent contributions to increase recurrence rates. In developed countries with low

background TB incidence, immigrants from developing countries might face higher risk of re-infection than their counterpart, since they usually lived in over-crowded residences within their ethnic communities, where the density of circulated *M.tuberculosis* is high [27]. Stress and malnutrition experienced by those immigrants were also assumed to lead to inadequate immune function, facilitating the development of active TB disease. In addition, smoking and drinking were also reported to contribute to the higher recurrence rates by interfering with the absorption and metabolism of the drugs, resulting in imparied treatment efficiency [11, 65].

3.5.6 Limitations

First, this review on reported risk factors might face publication bias. Researchers intended to report research findings with statistical significance, which might lead to the underestimation of other important risk factors which didn't show significance due to insufficient statistical power. Second, cautions should be exercised when to draw causal inferences between identified risk factors and TB recurrence, in light of confounding effects and temporal relationship between them Third, only studies published in English were reviewed. There is high chance that some important research findings published in other language were missed, especially for those studies conducted in developing countries heavily burdened by TB and/or HIV. Last but not least, among recent studies, there were a few discussions focusing on the influence of setting-specific characteristics in determining of recurrence rates, such as the performance of local TB control programs and population characteristics that related to TB/HIV transmission and treatment. However, those characteristics could be of great value for the interpretation of underlying reasons for recurrence from a large point of view and for the prediction of recurrence risk of the general population.

Chapter 4: Methods

4.1 Description of study setting

TB control in Chiang Rai is undertaken based on the existing healthcare system (shown in Figure 4.1). Under the provincial health office, public and privates hospitals, as well as health centers are responsible for providing TB services, including education and counseling, case finding, diagnosis and treatment. TB services are provided by 17 public hospitals to Thai citizens free of charge. District health offices are mainly responsible for logistic work, such as maintaining TB registry and vital registry. Specialized TB clinics which reside in every public hospital and function as the basic TB management units are responsible for definite TB diagnosis, supervision of patient's drug intake, and patient's home visit and follow-up. Health centers also participate in the referral of suspicious patients to hospitals for diagnosis, supervision of drug intake and follow-up. A province-wide population-based TB/HIV integrated surveillance database functions as a TB registration database, containing detailed personal information (clinical, laboratory, epidemiological) for every patient identified from every public hospital, through patient interview at diagnosis and medical chart review (including laboratory test results and treatment-related information).

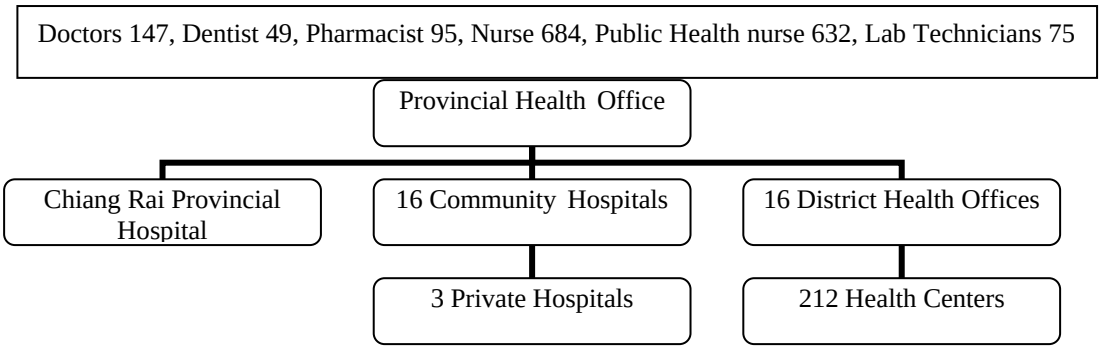

Figure 4.1 Structure of healthcare system in Chiang Rai Province

4.1.1 Standard TB diagnosis and treatment procedure

Patients who experience symptoms and/or physical discomfort present themselves or are referred by health centers to hospitals where registration nurses preliminarily assess their symptoms (e.g.,

cough for more than 2 weeks, weight loss) and medical history. TB cases identified through this passive case finding method constitute the majority of reported TB cases in Chiang Rai. Active case finding among HIV-infected patients is another important channel to identify TB cases. In the hospital, if TB is suspected, patients are further referred to the outpatient department clinics, where they undergo detailed inquiry into medical history, clinical signs/symptoms and a full physical examination, including sputum smear tests (using Ziehl-Neelson method), culture test (using Lowenstein-Jensen method), X-ray, other necessary tests, and an anti-TB trial treatment. Suspected extra-pulmonary TB case is investigated with appropriate specimens. After a definite diagnosis, patients are then referred to specialized TB clinic where their information is entered into the TB registry. Health education regarding TB treatment-related issues and disease transmission prevention is also offered to patients also at the clinic. At the same time, information is gathered from consenting patients through a completion of TB registry form and an interview by a nurse (after 1998) on detailed patient personal profiles. An on-site pharmacist is available to prescribe appropriate TB drugs based on treatment categories in line with WHO TB Treatment Guidelines (2003) and to educate patients on TB drugs. Patients with smear positive TB or with severe clinical manifestation of TB are required to be hospitalized. Those with smear negative TB or less severe TB are sent home for treatment: local health centers or community hospitals are notified in order to ensure DOT supervision. DOT is recommended under the supervision of health staff at healthcare facilities, or lay healthcare workers (such as village health volunteers or other community leaders), or family members, but not universally administered. This special feature of DOT administration is a result of a severe shortage of professional healthcare personnel in Chiang Rai and Thailand as a whole. At least two additional visits to TB clinics during the treatment period are required to patients: one at the end of the intensive phase, and the other at the end of treatment. At each visit, patients are given physical examinations, tested for blood and sputum, and questioned regarding medications taken and possible adverse effects. Home health visitors contact patients who fail to report for scheduled follow-up visits. Other channels to follow up TB patients include hospital inpatient departments and HIV clinics.

4.1.2 TB Treatment regimen

In Chiang Rai Province, treatment regimen follows the WHO recommendation based on different diagnostic categories, namely CAT 1-4 [1]. CAT 1 is applied to all smear-positive new TB patients, comprised of 2 months of HRZE, followed by 4 months of HR (2HRZE/4HR) daily for smear-positive new cases. CAT 2 is applied to patients with a history of previous treatment, either with treatment default, treatment failure, or a recurrence. Their regimen includes 3 months of HRZE and 5 months of HRE. CAT 3 is used for smear-negative TB cases, including 2 months of HRZ, plus 4 months of HR. CAT 4 is applied to chronic TB and MDR-TB cases, using second-line drugs (depending on the results of DST test) over a period of 12-24 months. The same set of regimens is also applied to HIV co-infected TB patients.

4.1.3 Sputum, Culture and DST test

Three sputum samples are recommended for microbiologic diagnosis of TB. One is directly obtained on site, and the other two are recommended to be obtained in the following two mornings at patient's home, but rarely done. In every lab, a sputum sample is firstly divided into three isolates. One is for diagnostic purpose, another is going to be sent to the provincial lab for culture, and the third one is preserved for quality control within the lab, or for auditing from outside of the lab. Only the Chiang Rai Provincial Hospital could perform the culture test. Community hospitals are required to submit at least one sputum specimen to provincial hospital for culture for every newly diagnosed TB patient, ideally during the first month of TB treatment. Two methods are applied for culture: one liquid-base and the other solid-base. Although regarded as the gold standard to diagnose TB, culture is not routinely performed for the purpose of diagnosis, but for preparation of DST test and the differentiation of mycobacterium TB from non-tuberculosis mycobacterium (NTM) TB cases. Laboratory in Chiang Rai Provincial Hospital is responsible to culture the sputum and send the isolates to national TB laboratories in Bangkok or Chiang Mai for DST to the first-line anti-TB drugs (H, R, Z, E, S). Patients usually have to wait for 2 months for DST results. If results come back as MDR-TB, patients will be sent to Chiang Rai Provincial

Hospital to receive MDR-TB treatment. However, this process is not universally followed by every public hospital in Chiang Rai Province.

4.1.4 HIV diagnosis and treatment

Along with HIV epidemic, free HIV counseling and testing were recommended to every TB patients since 1996. Informed consent is obtained for HIV testing, in accordance with routine government policies regarding HIV testing services. HIV antibody testing in Chiang Rai is conducted using commercial enzyme immunoassays. Specimens reactive to two different enzyme immunoassay tests are considered HIV-positive. If the HIV test result is negative at the beginning of TB treatment, patients will be tested again 3 months later. If it changes to positive, then the patient is notified and his/her initial HIV-negative status in registry is changed. For TB patients with a positive HIV test result, physicians assess the need to measure CD4 cell counts, as an index for providing prophylaxis for opportunistic infection and initiation of HAART treatment. CD4 cell counts are assessed by flow cytometry. Free HAART treatment for patients living with HIV with CD4 counts<250 was available after 2005. TB/HIV co-infected patients in Chiang Rai are treated under HAART regimen following WHO recommendation for resource-limited settings and Thai National Guidelines for TB/HIV treatment. According to Thailand's 2008 report to UNAIDS, only 32% of HIV-infected TB patients received HAART in 2006.

4.1.5 TB treatment outcome

TB treatment outcomes (cure, treatment completed, treatment failure, default, transfer out, death, and change of diagnosis) are assessed at the end of treatment according to the national TB program and WHO guidelines [1, 31]. Death is routinely checked using hospital records and mortality registry from the national vital statistics database. Treatment outcomes for defaulted patients who are confirmed to have died within two months of loss-to-follow-up is changed to death. The definition of each outcome is as follows.

Cure: a person initially with pulmonary, sputum-smear-positive TB who has a) completed treatment, b) had two negative sputum smears, and c) whose last two negative sputum smears include one taken during the last month of treatment.

Treatment Completed: a person initially with pulmonary, sputum-smear-positive TB who does not fulfill the criteria for cured, but has one negative sputum result during the treatment period. Or a person with pulmonary, smear-negative TB or extra-pulmonary TB who has completed and remains smear-negative during treatment

Treatment failure: a person initially with pulmonary, sputum-smear-positive TB who is smear-positive after 5 or more months of treatment; or a person with pulmonary, smear-negative TB or extra-pulmonary TB who is smear-positive after at least 2 months of treatment.

Default: a person whose treatment was interrupted for two consecutive months or more.

Transfer out: a person who has been transferred to a TB control program in another district and for whom the treatment outcome is not known.

Died: a person who dies for any reason during the course of treatment.

Change of diagnosis: a person who began TB treatment but was stopped because the possibility of TB disease diagnosis has been eliminated (e.g. patient is found to have lung cancer, or NTM, but not TB).

4.2 Case Definition

TB recurrence is defined as "a person previously treated for TB who has been declared successful completion of treatment, but re-diagnosed with bacteriologically-confirmed TB" [1]. Both "cure" and "treatment completion" are regarded as "successful completion of treatment" [1]. Smear-negative TB cases occurred after successful treatment will not be considered as recurrent cases, due to its rareness and less contagious nature [1]. In our study, we neither require a minimal observation period after treatment completion to define recurrence, nor further differentiated re-infection and relapse by DNA fingerprints.

4.3 Study population

Under our case definition of TB recurrence, every patient who had presented themselves to the hospital, had received a diagnosis, and completed treatment successfully was at risk of experiencing a subsequent episode of TB and thus was eligible for this study. Specific criteria

listed below took into account both the eligibility of study population and availability of information to conduct statistical analysis.

Inclusion criteria: 1) all patients registered in the surveillance system between Jan 1st, 1997 and Dec 31st, 2008 and completed treatment successfully afterward were included, where their original registration type could be "new", "treatment after default" or "treatment after failure"; 2) only recurrent patients with confirmed positive smear test results were included; 3) all Thai patients and hilltribe patients who hold Thai Citizen Identification Card (in order to track down their vital status through national registry) were included; and 4) EPTB patients were included.

Exclusion criteria: 1) paediatric TB patients (age under 15 years old) were excluded considering the difficulties in diagnosis and lower severities of paediatric TB cases; 2) patients whose previous registration type was either "chronic", "transferred in", "others" were excluded due to either their potential intrinsic vulnerability to TB ("chronic"), or inaccessibility of their previous treatment records ("transfer in"), or smear-negative recurrent TB they experienced ("others"); 3) known NTM cases were excluded; 4) patients without valid dates for treatment completion due to missing or error were excluded; and 5) patients with multiple recurrences were excluded due to high possibility of intrinsic vulnerability.

Patients need to present their Citizen Identification Card to receive TB diagnosis and treatment free of charge. This card is assigned to every Thai citizen with unique numbers. Thus, it is guaranteed that the database could capture the same TB patients when they re-register as recurrent cases.

4.4 Database and variables

The province-wide population-based TB/HIV integrated surveillance system in Chiang Rai Province was established in 1996, aiming at capturing and identifying every TB patient treated in all 17 public health hospitals in the province, including hilltribes and ethnic Thai patients, with support/collaboration of Research Institute of Tuberculosis, Johns Hopkins School of Public Health and Chiang Rai Provincial Health office. This surveillance database was designed to enhance research on TB and HIV/AIDS, aiming to measure TB incidence, treatment outcomes

(e.g., default, death), TB/HIV co-infection incidence, and other indices on TB burden and control in Chiang Rai Province. There are three sources of information that is entered into the surveillance database. Patient interview at diagnosis/registration is conducted based on a standard TB registration form designed by the Thailand national TB surveillance program, including additional questions constructed for the purpose of ongoing specific research studies in Chiang Rai Province. The interview is undertaken by trained nurses on patients' demographic characteristics, such as age, sex, ethnicity, whether a prison inmate or not, and their TB-related characteristics, such as registration type (see below), clinical type (PTB/EPTB/mixed TB), assigned treatment regimen (CAT 1-4), which hospital they registered at, whether DOT is assigned to patients and supervised by who. Information gathered from laboratory records includes X-ray results (cavity/non cavity/infiltration/normal limit), smear sputum grade at the diagnosis and follow-up (during treatment), culture test result, DST test results, whether a NTM case or not, HIV status, and CD4 count. Information on patient's treatment outcomes is obtained through their treatment records, linked with the national registry of vital status. Patient's case ID assigned at diagnosis was used to link all the information for the same patient, which were computerized into the surveillance database in a standardized format with proper quality control (double entry by two independent clerks, and re-check through patient's medical chart).

Although a large amount of information was collected, we are unable to include every potential factor into our analysis due to data incompleteness. Some information such as drug resistance pattern was not systematically collected for every patient until 2005. A large amount of missing data (>20%) limit the analyses on cavitaion and delayed sputum conversion. Patient's compliance to the treatment was not assessed, either. Thus, variables for this analysis include: age group (15-25/25-35/35-45/45-55/55-65/>65); gender (female/male); assigned regimen type at initial episode (CAT1/others); whether received DOT or not; registered hospital (Chiang Rai Provincial hospital/other community hospitals); being prisoner or not; ethnicity (Hilltribe/Thai); TB clinical type (PTB/EPB/mixed TB); TB registration type (new/default or fail); treatment outcome from initial episode (cure/complete). Variables were categorized according to biological/clinical meaning with practical and statistical considerations.

Although this database only captures TB patients who have been treated in public hospitals, the number of patients who seek treatment in private hospitals is small: there have been only 68 culture-positive TB cases per year on average treated in the private hospitals, based on the reports from provincial central laboratory where culture tests were performed for all patients treated in every hospital (including private hospitals).

4.5 Study design

Due to the variation in study methods and biases/errors caused by suboptimal study design among previous studies on TB recurrence, there are major concerns that true differences in recurrence risk cannot be reflected in reported rates. Thus, minimization of potential biases/errors in the design stage is the key for generating sound results. In this sense, a cohort study with a sufficient study sample size and length of follow-up can yield accurate estimates of recurrence risk and identification of risk factors. A retrospective cohort was constructed from the surveillance system containing all registered patients with the successful treatment outcomes identified between Jan 1st, 1997 and Dec 31st, 2008, and passively "followed-up" until the earliest of the followings: they re-appeared in the registry as a recurrent case; died; or the latest updated date of the surveillance database (Feb 6th, 2010. Patients' personal IDs were used to link the initial and recurrent episodes for the same patients. All patients from a non-recurrent TB episode entered in this cohort at various points in time as soon as they successfully completed the treatment. Comparisons of different distributions of clinical/epidemiological characteristics which were collected for the initial episode, between those who recurred and those who didn't, will be conducted to identify risk factors for TB recurrence among HIV-infected and uninfected patients, separately.

4.6 Statistical analysis

Exploratory data analysis was performed to determine cut-offs for categorical variables. Descriptive analyses on patient demographic, clinical, and treatment-related characteristics were summarized for HIV-infected, HIV-uninfected and HIV-unknown patients. Those characteristics evaluated included: age group, gender, ethnicity, assigned treatment regimen, registered hospital,

being prisoner or not, DOT administration, TB clinical type, and treatment outcome. Chi-square test and Wilcoxon-Mann-Whitney test were used to assess differences of these characteristics across the three groups.

Person-years at risk for recurrence starting on the day when the treatment of initial episode successfully completed and ending on the earliest day of recurrence, death, or latest updated date of the surveillance database were calculated for each patient. Recurrence incidence rates and their exact 95% confidence intervals were calculated based on Poisson probability models. Bivariate analysis was performed to assess the association between recurrence and gender, age group, ethnicity, registered hospital, assigned regimen, DOT or self-administration, being prisoner or not, TB clinical type, treatment outcome from initial episode, and registration type at patient's initial episode, among HIV-infected and negative TB patients, separately.

Two separate multivariable Poisson regression models for HIV-infected and uninfected patients incorporating variables associated with recurrence with a p-value <=0.15 identified from bivariate analyses, and time-dependent variable "years since treatment completion", were built to assess the independent risk factors for recurrence, using log person-years as an offset. No specific interaction effect was studied in the model. The multivariable Poisson regression model is constructed as follows:

Systematic part:

$$\log \text{Recurrence Rate} = \log(\text{E[Recurrence cases]/Person years})$$
$$= \beta_0 + \beta_1 \times \text{Age-group1} + \ldots + \beta_6 \times \text{Age-group6} + \beta_7 \times \text{Gender} + \cdots + \beta_i \times (1^{\text{st}} \text{ year after treatment}) + \ldots$$
$$+ \beta_{(i+12)} \times (13^{th} \text{ year after treatment})$$

Random part:

$$\text{Recurrence cases} \sim \text{Poisson (E[Recurrence cases])}$$

All statistical analyses were conducted using SAS statistical software version 9.2 (SAS Institute, Cary, NC, USA) and R version 2.9 (R Foundation for Statistical Computing, Vienna, Austria).

4.7 Ethical considerations

Ethical approval was obtained from the Human Ethics Research Board of University of Alberta to perform secondary data analysis of anonymized data provided by the TB/HIV Research Foundation in Chiang Rai Province, Thailand.

Chapter 5: Results

5.1 Description of study population

Before the description of our study cohort, a simple descriptive analysis for all patients registered in the surveillance database by their treatment outcomes was conducted, providing the general background information on TB prevalence and the performance of the local TB control program, between 1997 and 2008. Overall, there were 23,640 patients identified during this period, with 77% patients registered as "new", 1.8% patients registered as "recurrence", 3.5% as "retreatment after default", and 1.3% as "retreatment after failure". Approximately 56% of identified patients completed treatment successfully, but only 40% of them got "cured" with negative sputum test as confirmation. Table 5.1 displays the major treatment outcomes for registered TB patients, with respect to their registration type, HIV status, and their ethnicity and prison inmate statuses. Treatment success rate was highest among HIV-uninfected patients (65.1%), and lowest among HIV-infected patients (43.6%) and among patients with previous treatment history (46.7% among patients from default/failure). High default rate was observed among patients from a previously defaulted treatment (23.2%) or being hilltribe minority (15.8%). Mortality rates exceeded 20% among all types of patients, except for hilltribe patients (14.1%), which could be due to their absence from the registry system of vital status. Figure 5.1 shows the time trend of 5 major treatment outcomes for all TB patients. Generally, the treatment success rate showed an increasing trend, while the mortality rate showed a decreasing trend.

Table 5.1 Major treatment outcome of TB patients in Chiang Rai Province, 1997-2008

Patient type	No registered	Treatment outcomes, (N, % of registered)				
		Cured	Completed	Died	Failed	Defaulted
New smear+ PTB	11793 (45.8)	5678 (48.2)	1072 (9.1)	2585 (21.9)	47 (0.7)	1398 (11.9)
New smear- PTB	7184 (27.9)	0	3875 (53.9)	1694 (23.6)	423 (3.6)	914 (12.7)
Retreat after failure	341 (1.3)	137 (40.2)	22 (6.5)	72 (21.1)	41 (12.0)	47 (13.8)
Retreat after default	913 (3.5)	145 (15.9)	282 (30.9)	191 (20.9)	25 (2.7)	212 (23.2)
Recurrence	453 (1.8)	186 (41.1)	39 (8.6)	141 (31.1)	24 (4.2)	40 (8.8)
HIV-uninfected	11583 (44.9)	3960 (34.2)	3581 (30.9)	1421 (12.3)	333 (2.9)	1440 (12.4)
HIV-infected	9557 (37.1)	1176 (12.3)	2988 (31.3)	3812 (40.0)	131 (1.4)	790 (8.3)

Prisoner	603 (2.3)	255 (42.3)	100 (16.6)	148 (24.5)	20 (3.3)	17 (2.8)
Hilltribe	3938 (15.3)	1066 (27.1)	1320 (33.5)	556 (14.1)	129 (3.3)	623 (15.8)

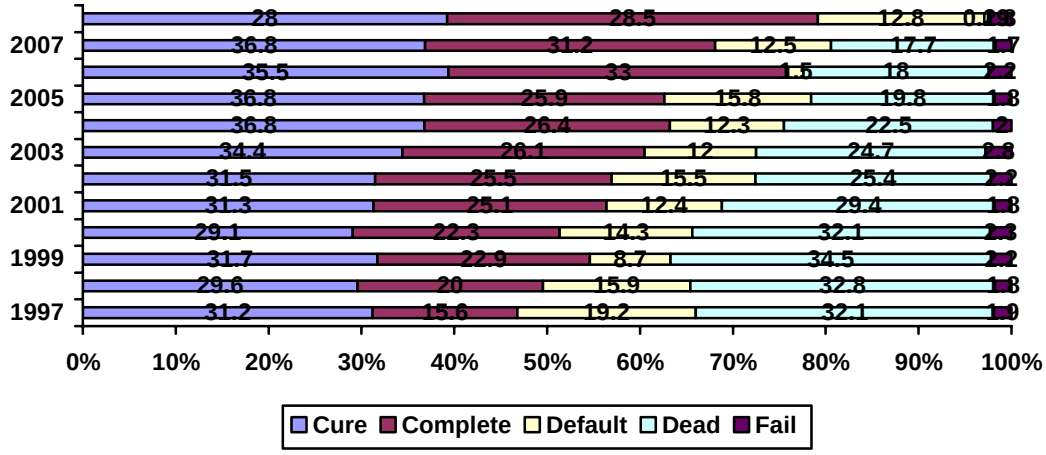

Figure 5.1 Treatment outcomes of TB patients in Chiang Rai Province by calendar year, 1997-2008.

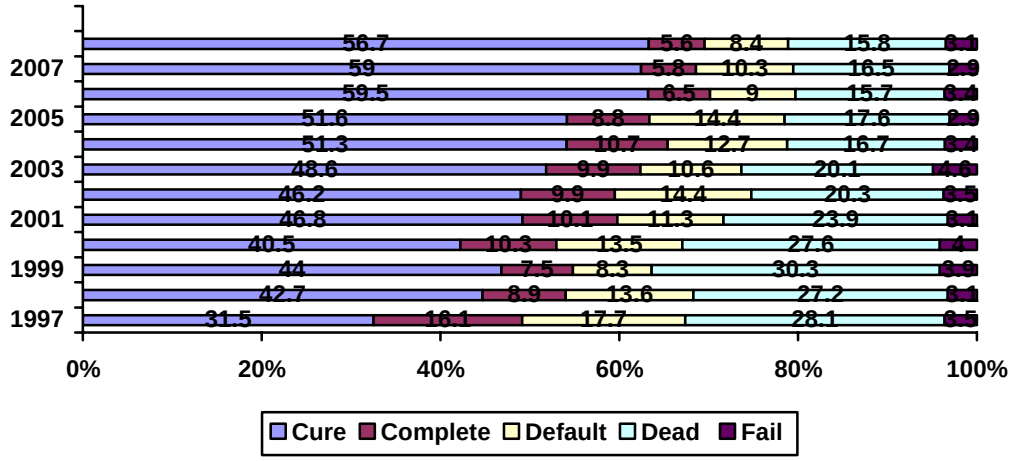

Figure 5.2 Treatment outcomes of new smear-positive patients in Chiang Rai Province by calendar year, 1997-2008.

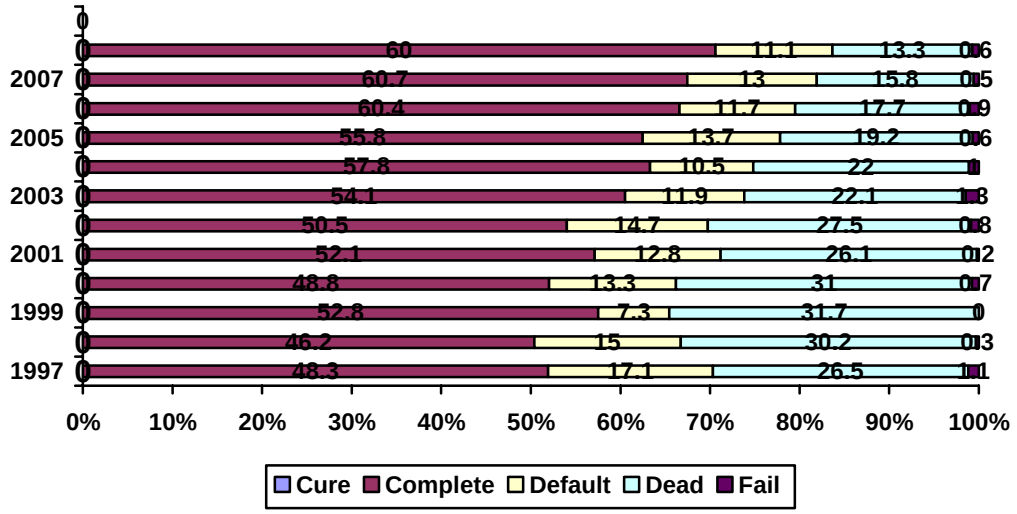

Figure 5.3 Treatment outcomes of smear-negative patients in Chiang Rai Province by calendar year, 1997-2008.

5.2 Description of the study cohort

From the total of 23,640 patients identified during the study period, 10,724 patients were excluded because they didn't have a successful treatment outcome from their initial episodes. Among the remaining 12,916 patients, another 1,397 patients were excluded due to registration type being "other", "chronic", or "transfer in". Childhood TB cases (N=412), NTM cases (N=84), and hilltribe cases without citizen identification (N=1,949) were also excluded. There was a further exclusion of 178 cases without valid dates for calculating follow-up duration. Of the remaining 8,896 patients who constituted our study cohort after "infiltration" based on the other exclusion criteria, 2684 (30.2%) patients were HIV-infected, 4791 (53.9%) patients were HIV-uninfected,

and 1421 (15.9%) had unknown HIV sero-status [figure 5.2].

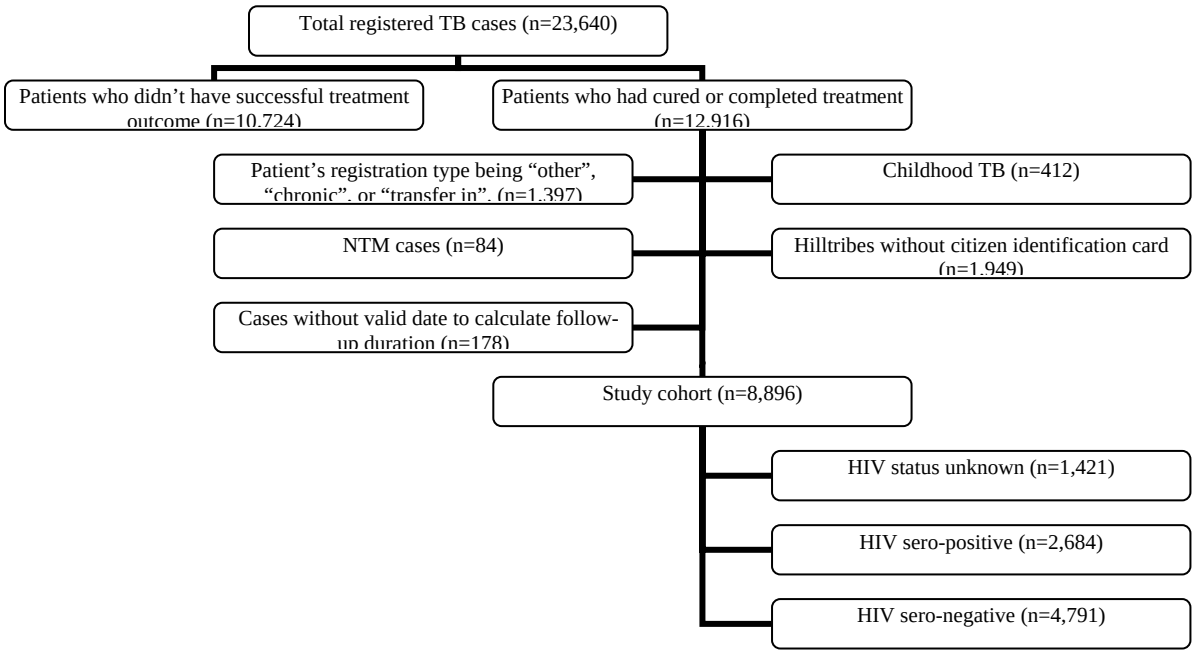

Figure 5.4 Flow chart of recruitment of study cohort

5.3 Baseline characteristics of study cohort

Cumulative incidence curves were used to describe the cumulative probability of recurrence and that of mortality among patients with different HIV sero-status, treating each other as competing risk (Figure 5.5 and Figure 5.6). Cumulative incidence curves were also constructed to describe the recurrence rates among different subgroups of patients with different HIV sero-status (Figure 5.7-Figure 5.12).

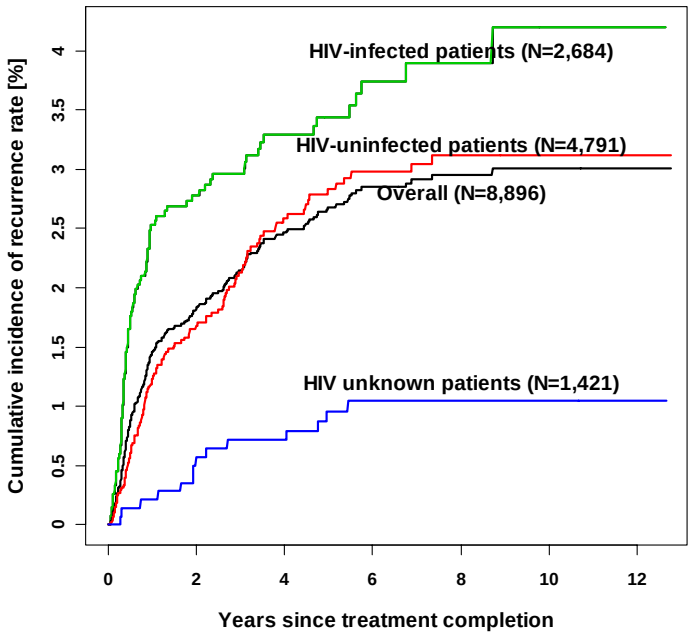

Figure 5.5 Cumulative incidence curves of TB recurrence by HIV status.

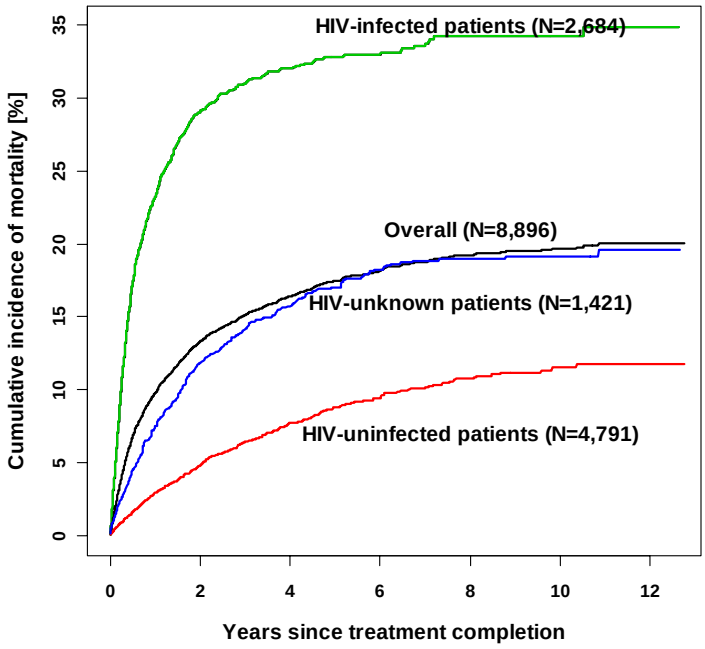

Figure 5.6 Cumulative incidence curves of mortality by HIV status.

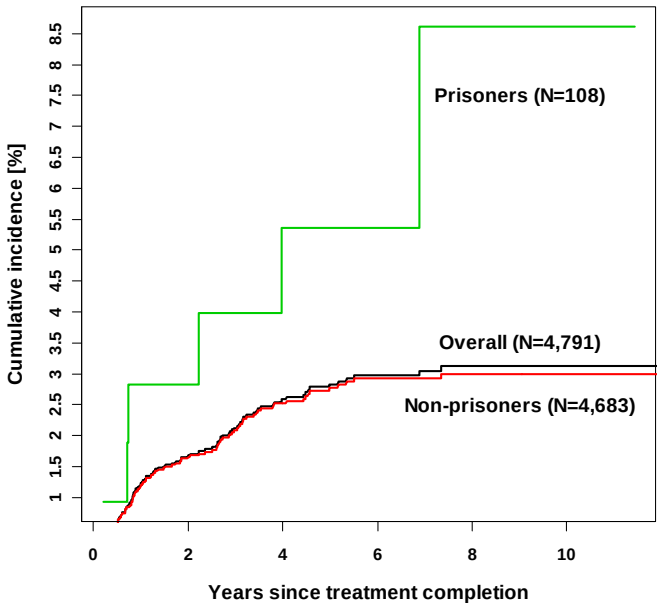

Figure 5.7 Cumulative incidence curves of TB recurrence by prison among HIV-uninfected TB patients.

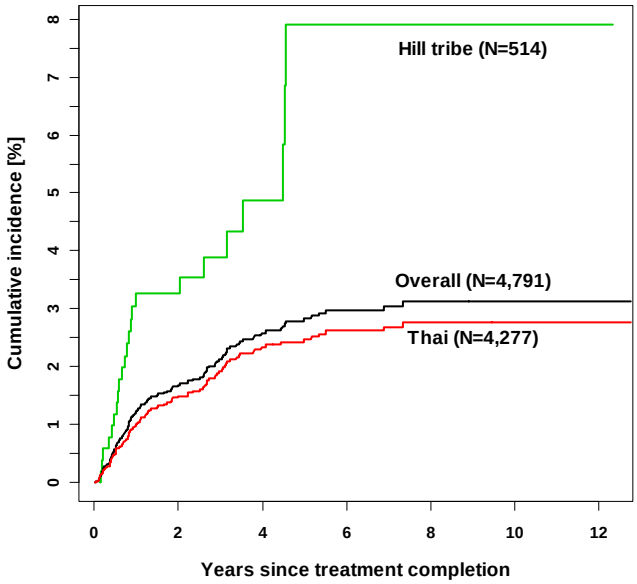

Figure 5.8 Cumulative incidence curves of TB recurrence by ethnicity among HIV-uninfected TB patients.

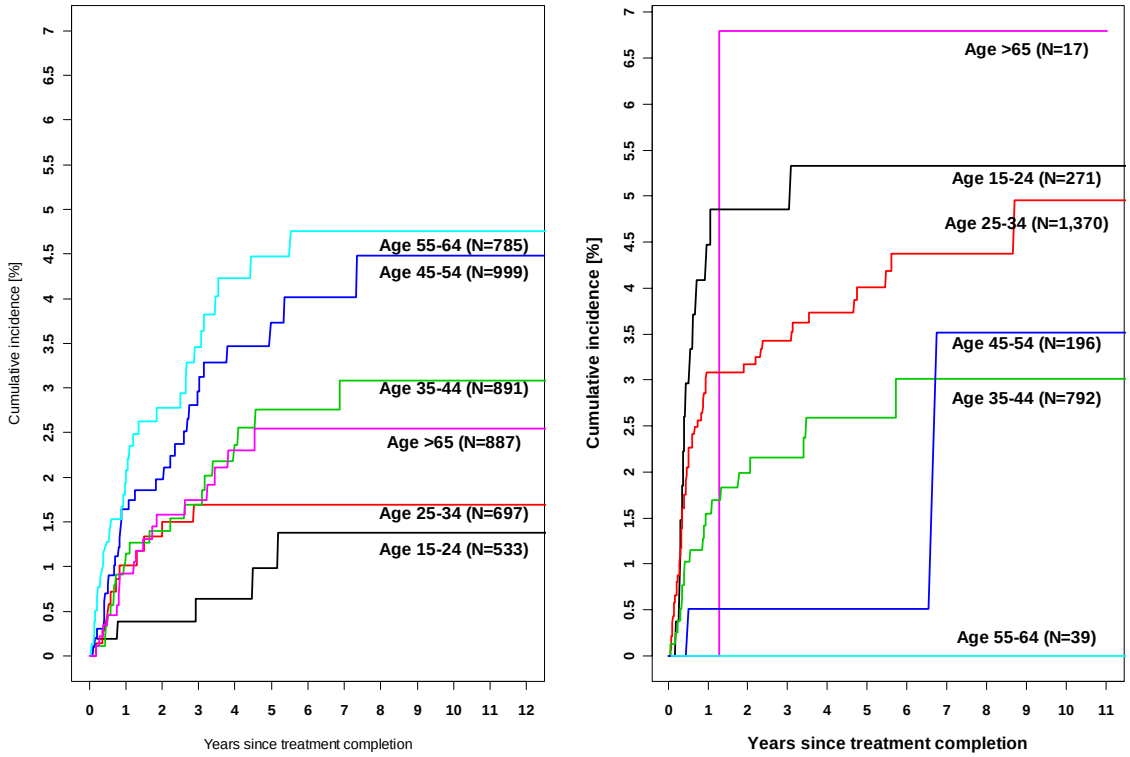

Figure 5.9 Cumulative incidence curves of TB recurrence by age group among HIV-uninfected and infected patients.

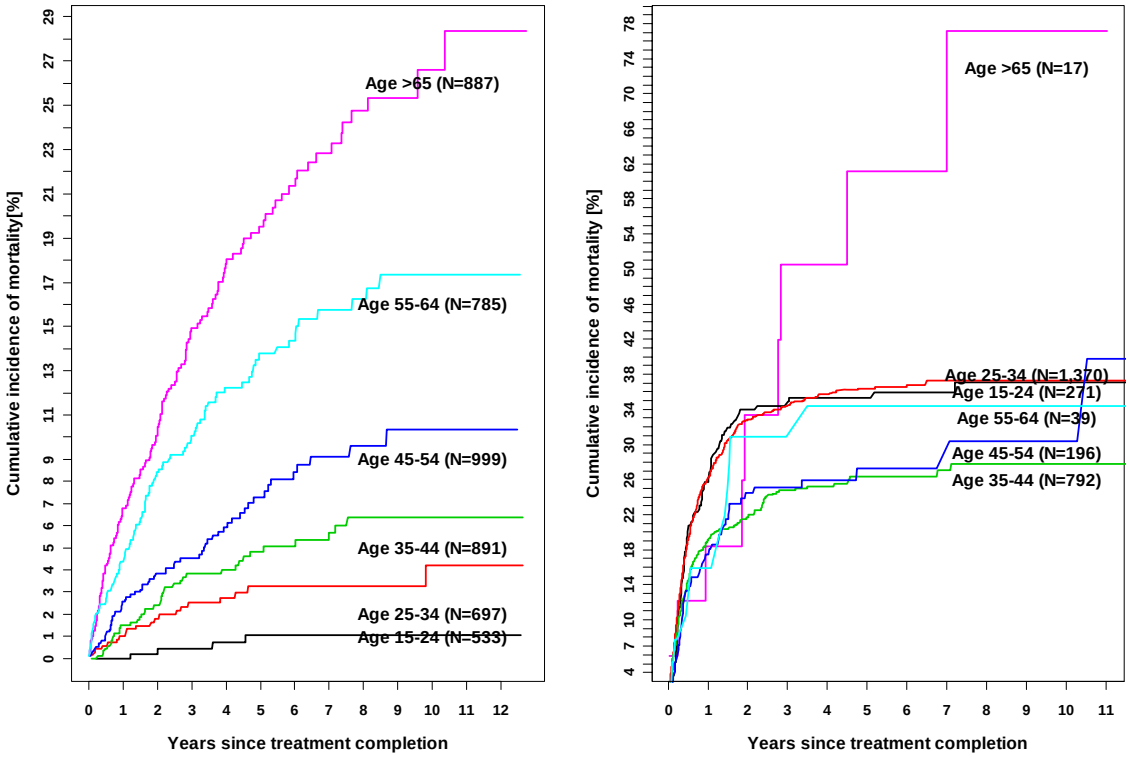

Figure 5.10 Cumulative incidence curves of mortality by age group among HIV-uninfected and infected patients.

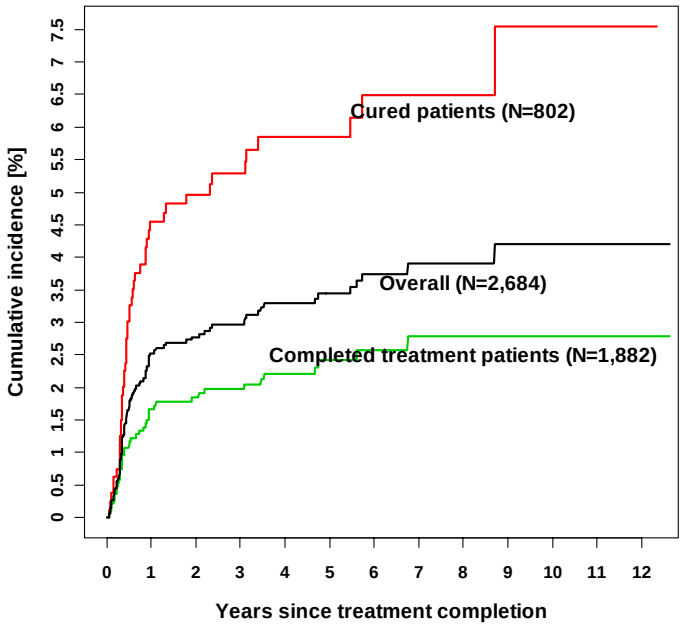

Figure 5.2 Cumulative incidence curves of TB recurrence by treatment outcome of initial episode among HIV-infected patients.

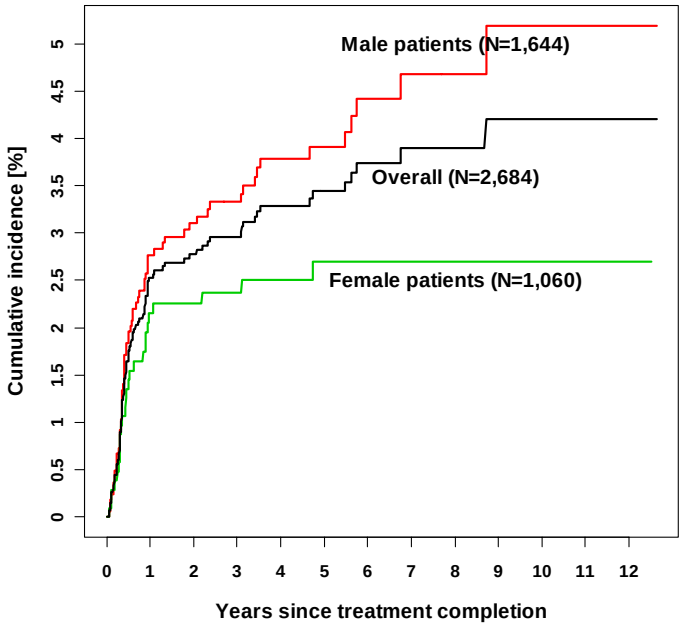

Figure 5.3 Cumulative incidence curves of TB recurrence by gender among HIV-infected TB patients.

Baseline characteristics, at the time of successful completion of TB treatment, of these patients in our study cohort are described in Table 5.2, stratified by their HIV status. The HIV co-infection rate was higher among Thai (95% vs 89%), younger age (61% vs 26% between age 15 and 35), and female TB patients (39% vs 31%), than their counterparts. Compared to HIV-uninfected patients, HIV-infected TB patients were more likely to be registered in provincial hospital (44% vs 36%), to have extra-pulmonary TB or mixed TB (44% vs 16%), not receiving DOT supervision (45% vs 35%), and died during follow-up period (33% vs 9%). Overall, the passive follow-up duration was 2.1 years [IQR: 0.6-4.6] and 3.5 years [IQR: 1.9-6.0] for HIV-infected and uninfected TB patients, respectively. The time to recur among HIV-infected patients was half the time it took among HIV-uninfected TB patients (6.1 months vs 12.6 months, p=0.03). After 2005, the number of HIV unknown cases became markedly smaller, and the number of HIV-infected cases increased moderately. Although some previous studies assumed that HIV-unknown patients mostly comprised of HIV-uninfected patients, after comparisons of the distributions of patients' baseline characteristics among the three HIV groups, we could not make such an assumption about

HIV unknown group. This was because the distributions of some characteristics in the HIV-unknown group were similar to those of the HIV-uninfected group (e.g., registered hospital, TB clinical type), while others were more similar to those of the HIV-infected group (e.g., ethnicity, gender, DOT), implying a complex composition of the unknown group. Therefore, based on the information we have in this database, we are unable explain the markedly low TB recurrence rate observed among HIV-unknown patients.

Table 5.2 Baseline characteristics of study cohort by HIV status

Characteristics	HIV-uninfected (N=4791)	HIV-infected (N=2684)	HIV unknown (N=1421)
Assigned regimen*			
CAT1	4513 (94)	2485 (93)	1262 (89)
Others	278 (6)	199 (7)	159 (11)
Registered Hospital*			
Provincial Hospital	1745 (36)	1168 (44)	461 (32)
Community hospitals	3046 (64)	1516 (56)	960 (68)
Prisoners			
Yes	108 (2)	58 (2)	44 (3)
No	4683 (98)	2626 (98)	1377 (97)
Ethnicity*			
Thai	4277 (89)	2555 (95)	1362 (96)
Hilltribe	514 (11)	129 (5)	59 (4)
Age group*			
15-34	1229 (26)	1640 (61)	282 (20)
35-64	2675 (56)	1027 (38)	742 (52)
>=65	887 (18)	17 (1)	397 (28)
Gender*			
Male	3289 (69)	1644 (61)	889 (63)
Female	1502 (31)	1040 (39)	532 (37)
DOT administration*			
Yes	3044 (64)	1414 (53)	618 (43)
No	1692 (35)	1217 (45)	774 (54)
Unknown	55 (1)	53 (2)	29 (2)
TB clinical type*			
PTB only	4033 (84)	1514 (56)	1087(77)
EPTB only	660 (14)	999 (37)	313 (22)
Mixed TB	98 (2)	171 (6)	21(1)
Died during follow-up*			
Yes	416 (9)	893 (33)	266 (19)
No	3569 (74)	1453 (54)	793 (56)
Unknown	806 (17)	338 (13)	362 (25)
Treatment outcome*			
Complete	2141 (45)	1882 (70)	1031 (73)
Cure	2650 (55)	802 (30)	390 (27)
Calendar year*			
1997	195 (4)	170 (6)	135 (10)
1998	225 (5)	188 (7)	181 (13)
1999	291 (6)	208 (8)	182 (13)
2000	314 (7)	188 (7)	144 (10)
2001	328 (7)	210 (8)	143 (10)
2002	287 (6)	207 (8)	171 (12)
2003	374 (8)	268(10)	157 (11)
2004	466 (10)	309 (11)	169 (12)
2005	580 (12)	265 (10)	64 (5)
2006	583 (12)	241 (9)	33 (2)

2007	570 (12)	223 (8)	26 (2)
2008	578 (12)	207 (8)	13 (1)
Cumulative recurrence rates at the end of follow-up	3.1%	4.2%	1.0%
Median duration of follow-up (years)	3.5 (IQR: 1.9-6.0)	2.1 (IQR: 0.6-4.6)	5.7 (IQR: 3.0-8.7)
Median duration of treatment (days)	186 (IQR: 180-214)	188 (IQR: 179-229)	183 (IQR: 176-207)
Median time to recur (mo)	12.6 (IQR: 6.3-33.3)	6.1 (IQR: 3.7-13.0)	24.0 (IQR: 14.0-49.3)

The numbers in () are %
*: $p<0.05$.
**: $p<0.01$.

5.4 Recurrence rates

Our follow-up of the study cohort totaled to 41,641 person-years (PYs), a median follow-up of 4.2 years (IQR: 1.8-7.1 years) after successful treatment completions. The overall recurrence rate was 5.3/1,000 PYs. Stratified by HIV status, we obtained a total of 9,281 PYs for HIV-infected patient group and 22,979 PYs among HIV-uninfected patient group, which lead to the recurrence rates of 9.7/1,000 PYs (95% CI: 7.8-11.9/1,000 PYs) and 5.1/1,000 PYs (95% CI: 4.3-6.2/1,000 PYs), respectively, for a crude rate ratio of 1.89 (95% CI: 1.44-2.48 $p<0.000$) between HIV-infected and uninfected groups. The mortality rates among HIV-infected patients were significantly higher than HIV-uninfected patients (90.6/1,000 PYs vs 16.5/1,000 PYs, $p<0.0001$), while the differences in the loss-to-follow-up rate was similar (36.4/1,000 PYs vs 35.1/1,000 PYs, $p=0.56$) (see Table 6.3).

Table 5.3 lists the recurrence rate for subgroups of patients. Statistical significance of the bivariate association between recurrence rate and each of the assessed variables was also displayed.
Among HIV-negative patients, recurrence rates didn't differ by assigned regimen, gender, registration type of initial episode, or DOT administration (p-value all > 0.15). Significantly higher recurrence rates were observed among patients who were prisoners (11.6/1,000 PYs) than non-prisoners (5.0/1,000 PYs, $p=0.043$), hilltribes (14.8/1,000 PYs) than Thais (4.4/1,000 PYs, $p=0.0001$), aged over 45 (7.3/1,000 PYs) than aged between 15-24 (1.7/1,000 PYs, $p<0.05$), those who were treated in community hospitals (6.3/1,000 PYs) than those who were treated in the provincial hospital (3.2/1,000 PYs, $p=0.0015$), those with pulmonary TB (PTB) only (6.0/1,000 PYs) than those with extra-pulmonary TB (EPTB) only (0.6/1,000 PYs, $p<0.0001$), and patients

who were "cured" from their initial episode (6.7/1,000 PYs, p=0.0002) than patients who "completed treatment" from their initial episode (3.2/1,000 PYs).

Among HIV-positive patients, recurrence rates didn't differ by registered hospital, ethnicity, registration type of initial episode, or DOT administration (p-value all > 0.15). Higher recurrence rates were observed among patients who were prisoners (27.4/1,000 PYs) than non-prisoners (9.3/1,000 PYs, p=0.044), aged between 15-25 (13.5/1,000 PYs) than aged between 45-55 (3.0/1,000 PYs, p=0.046), males (11.6/1,000 PYs) than females (6.9/1,000 PYs, p=0.017), those who received CAT1 (10.3/1,000 PYs) than other regimen (3.7/1,000 PYs, p=0.041), had PTB only (13.4/1,000 PYs) than had EPTB only (4.6/1,000 PYs, p<0.0001), and patients who were "cured" from their initial episode (18.1/1,000 PYs, p<0.0001) than patients who "completed treatment" from their initial episode (6.4/1,000 PYs).

Highest recurrence rates were observed within 1 year after successful treatment completions among both HIV-infected and uninfected patients, but with different patterns of decline (Figure 5.3): among HIV-uninfected patients, rates dropped steadily after a sharp drop within 1 year (12.6/1,000 PYs); while among HIV-infected patients, rates dropped much more sharply within 1 year (30.3/1,000 PYs)), but kept at a constant rate afterward with some fluctuations.

Table 5.3 Recurrence rates among sub-groups of patient by HIV status

Characteristics	HIV-uninfected patients					HIV-infected patients				
	No of Event	**PYs**	**Rates**	**95% CI**	**P-value**	**No of Event**	**PYs**	**Rates**	**95% CI**	**P-value**
Overall recurrence rate	118	22979	5.1	4.3-6.2		90	9281	9.7	7.8-11.9	
Overall mortality rate (death prior to recurrence)	380	22979	16.5	14.9-18.3		841	9281	90.6	84.6-97.0	
Assigned Regimen					0.62					*0.083*
CAT1	110	21662	5.1	4.2-6.1	Ref	87	8472	10.3	8.2-12.7	Ref
Others	8	1317	6.1	2.6-12.0	0.62	3	808	3.7	0.8-10.8	0.083
Registered Hospital					*0.015*					0.81
Provincial Hospital	27	8575	3.2	2.1-4.6	Ref	36	3826	9.4	6.6-13.0	Ref
Community hospitals	91	14404	6.3	5.1-7.8	*0.015*	54	5455	9.9	7.4-12.9	0.81
Prisoners					*0.043*					*0.020*
No	112	22463	5.0	4.1-6.0	Ref	85	9098	9.3	7.5-9.3	Ref
Yes	6	515	11.6	5.3-26.3	*0.043*	5	182	27.4	8.8-64.0	*0.019*
Ethnicity					*0.0001*					0.78
Thai	95	21427	4.4	3.6-5.4	Ref	87	8917	9.8	7.8-12.0	Ref
Hilltribe	23	1552	14.8	9.4-22.2	*0.0001*	3	364	8.3	1.7-24.1	0.78
Age group					*0.0002*					*0.021*
15-24	5	2881	1.7	0.6-4.1	Ref	14	1041	13.5	7.4-22.6	Ref
25-34	11	3822	2.9	1.4-5.2	0.35	54	4659	11.6	8.7-15.1	0.62
35-44	21	4594	4.6	2.8-7.0	0.052	19	2684	7.1	4.3-11.1	0.069
45-54	32	4375	7.3	5.0-10.3	*0.028*	2	674	3.0	0.3-10.7	*0.046*

55-64	31	3642	8.5	5.8-12.1	*0.0010*	0	175	0.0	0.0-21.01	>0.99
>=65	18	3663	4.9	2.9-7.8	*0.040*	1	48	20.8	0.3-115.9	0.67
Gender					0.19					*0.019*
Female	32	7407	4.3	4.4-6.8	Ref	26	3760	6.9	4.5-10.1	Ref
Male	86	15571	5.5	3.0-6.1	0.19	64	5520	11.6	8.9-14.8	*0.020*
DOT administration					0.95					0.49
Yes	68	13038	5.2	4.1-6.6	Ref	46	4460	10.3	7.6-13.8	Ref
No	49	9687	5.1	3.7-6.7	0.80	42	4724	8.9	6.4-12.0	0.49
Unknown	1	254	3.9	0.1-21.9	0.87	2	96	20.8	2.3-75.2	0.33
TB clinical type					*<0.0001*					*<0.0001*
PTB only	116	19257	6.0	5.0-7.2	Ref	70	5237	13.4	10.4-16.9	Ref
EPTB only	2	3158	0.6	0.1-2.3	*0.0016*	16	3481	4.6	2.6-7.5	*<0.0001*
Mixed TB	0	564	0.0	0.0-6.6	>0.99	4	563	7.1	1.9-18.2	0.22
Registration type					0.80					0.60
New	112	21927	5.1	4.2-6.2	Ref	87	9019	9.7	7.7-11.9	Ref
Default/Fail	6	1052	5.7	2.1-12.4	0.80	3	262	11.5	2.3-33.5	0.60
Treatment outcome					*0.0002*					*<0.0001*
Complete	33	10202	3.2	2.2-4.5	Ref	43	6679	6.4	4.7-8.7	Ref
Cure	85	12777	6.7	5.3-8.2	*0.0002*	47	2602	18.1	13.3-24.0	*<0.0001*
Years since treatment completion					*<0.0001*					*<0.0001*
0	58	4612	12.6	9.6-16.3	Ref	67	2211	30.3	23.5-38.5	Ref
1	19	3984	4.8	2.9-7.5	*0.0003*	6	1695	3.5	1.3-7.7	*<0.0001*
2	16	3357	4.8	2.7-7.8	*0.0010*	4	1400	2.9	0.8-7.3	*<0.0001*
3	14	2742	5.1	2.8-8.6	*0.0056*	6	1138	5.3	1.9-11.5	*<0.0001*
4	6	2187	2.7	1.0-6.0	*0.0011*	2	901	2.2	0.3-8.0	*0.0003*
5	3	1732	1.7	0.4-5.1	*0.0021*	3	649	4.6	0.9-13.5	*0.0014*
6	1	1388	0.7	0.0-4.0	*0.0078*	1	449	2.2	0.0-12.4	*0.0096*
7	1	1099	0.9	0.0-5.1	*0.016*	0	316	0.0	0.0-11.7	>0.99
8	0	820	0.0	0.0-4.5	>0.99	1	222	4.5	0.1-25.0	>0.99
9	0	552	0.0	0.0-6.7	>0.99	0	151	0.0	0.0-24.4	>0.99
10	0	331	0.0	0.0-11.2	>0.99	0	92	0.0	0.0-39.9	>0.99
11	0	152	0.0	0.0-24.3	>0.99	0	50	0.0	0.0-74.2	>0.99
12	0	22	0.0	0.0-168.7	>0.99	0	7	0.0	0.0-567.9	>0.99

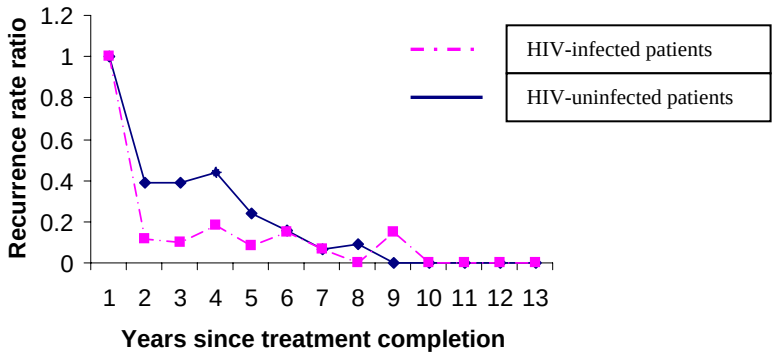

Figure 5.4 Adjusted recurrence rate ratio by years since treatment completion among HIV-infected and uninfected patients.

5.5 Risk factor analysis

To assess independent associations of multiple risk factors with recurrence rates, multivariable Poisson regression was used, including as covariates all potential risk factors showing a p-value<=0.15 from previous bivariate analyses, with “years since treatment completion” as a time-

dependent variable. This regression analysis was performed among HIV-infected and uninfected groups, separately (Table 5.4).

For HIV-uninfected patients, age, ethnicity, being prisoner, registered hospital, TB clinical type, treatment outcomes, and years since treatment completion were included to assess the independent associations. Identified risk factors were older age (age>=45 years), being hilltribe minority, being prisoner, and had PTB only. The greatest risk factor for recurrence was being prisoners (adjusted RR=3.06, 95% CI: 1.25-7.50, p=0.014), compared to non prisoners. Increased age was significantly associated with higher rates of recurrence: compared to patients who were between 15 and 25 years old at initial diagnosis, patients who were between 45 and 55 years old had a 3.80-fold (95% CI: 1.47-9.80, p=0.0059) elevated rates, patients aged between 55 and 65 years old had a 4.91-fold (95% CI: 1.89-12.78, p=0.011), and patients aged over 65 had a 2.80-fold (95% CI: 1.02-7.63, p=0.045) rate of recurrence. The adjusted rate ratio of recurrence for patients who were hilltribes was 2.75 (95%CI: 1.72-4.41, P<0.0001), compared to ethnic Thais. Patients with only EPTB had a much lower risk of recurrence (adjusted RR=0.20, 95% CI: 0.05-0.84, P=0.0028) than patients with PTB only. Those who were treated in the provincial hospital had a marginally elevated rate of recurrence (adjusted RR=1.51, 95% CI: 0.95-2.41, p=0.08), compared to those who were treated in community hospitals.

For HIV-infected patients, gender, assigned regimen, age group, TB clinical type, treatment outcome, and years since treatment completion were included in the multivariate model. CAT1 and being prisoner were no longer significantly associated with recurrence rate for HIV-infected patients after adjusting for the other factors. Identified risk factors are being male, younger age (age<35 years), cured from initial episode, and had PTB only. Rates of recurrence were much lower among patients who had EPTB only (adjusted RR=0.47, 95% CI: 0.25-0.89, p<0.0001), compared to patients who had PTB only. Also, recurrence rates were lower among patients who were between 35 and 45 years old (adjusted RR=0.43, 95% CI: 0.22-0.88, p=0.019), and between 45 and 55 years old (adjusted RR=0.17, 95% CI: 0.04-0.76, p=0.020), compared to patients aged between 15 and 25 years old. Male patients had a 1.73 times (95% CI: 1.09-2.74, p=0.020) rates of recurrence, compared to female patients. Patients who were cured from the initial episode had a

1.89-fold elevated risk for recurrence (95% CI: 1.16-3.05, p=0.01), compared to patients who completed treatment.

Table 5.4 Stratified analysis of risk factors for TB recurrence by HIV status

Variables	HIV-uninfected patients			HIV-infected patients		
	Adjusted RR	95%CI	P-value	Adjusted RR	95% CI	P-value
Gender						*0.020*
Female	-	-	-	1.00	Ref	Ref
Male	-	-	-	1.73	1.09-2.74	*0.020*
Assigned Regimen						0.15
CAT1	-	-	-	1.00	Ref	Ref
Others	-	-	-	0.42	0.13-1.35	0.15
Age group			*0.0002*			*0.009*
15-24	1.00	Ref	Ref	1.00	Ref	Ref
25-34	1.81	0.63-5.22	0.27	0.78	0.43-1.40	0.40
35-44	2.49	0.94-6.61	0.068	0.43	0.22-0.88	*0.019*
45-54	3.80	1.47-9.80	*0.0059*	0.17	0.04-0.76	*0.020*
55-64	4.91	1.89-12.78	*0.0011*	0.00	0.00-0.00	>0.99
>=65	2.80	1.02-7.63	*0.045*	0.78	0.10-5.98	0.81
Ethnicity			*<0.0001*			
Thai	1.00	Ref	Ref	-	-	-
Hilltribe	2.75	1.72-4.41	*<0.0001*	-	-	-
Prisoner			*0.012*			0.33
No	1.00	Ref	Ref	1.00	Ref	Ref
Yes	3.06	1.25-7.50	*0.012*	1.61	0.62-4.21	0.33
Registered Hospital			0.08			
Provincial hospital	1.00	Ref	Ref	-	-	-
Community hospitals	1.51	0.95-2.41	0.08	-	-	-
Treatment outcome from the initial episode			0.09			*0.01*
Complete	1.00	Ref	Ref	1.00	Ref	Ref
Cure	1.44	0.94-2.18	0.09	1.89	1.16-3.05	*0.01*
TB clinical type			*0.0001*			*0.0001*
PTB	1.00	Ref	Ref	1.00	Ref	Ref
EPTB	0.20	0.046-0.84	*0.028*	0.47	0.25-0.89	*0.020*
Mixed TB	0.00	0.00-0.00	>0.99	0.60	0.22-1.67	0.33
Years since TX completion			*<0.0001*			*<0.0001*
0	1.00	Ref	Ref	1.00	Ref	Ref
1	0.39	0.23-0.65	*0.0003*	0.12	0.05-0.28	*<0.0001*
2	0.39	0.22-0.68	*0.0010*	0.10	0.04-0.27	*<0.0001*
3	0.44	0.24-0.77	*0.0056*	0.18	0.08-0.41	*<0.0001*
4	0.24	0.10-0.55	*0.0011*	0.08	0.02-0.30	*0.0003*
5	0.16	0.05-0.50	*0.0021*	0.15	0.05-0.47	*0.0014*
6	0.07	0.01-0.48	*0.0078*	0.07	0.01-0.52	*0.0093*
7	0.09	0.01-0.62	*0.016*	0.00	0.00-0.00	>0.99
8	0.00	0.00-0.00	>0.99	0.15	0.02-1.07	0.060
9	0.00	0.00-0.00	>0.99	0.00	0.00-0.00	>0.99
10	0.00	0.00-0.00	>0.99	0.00	0.00-0.00	>0.99
11	0.00	0.00-0.00	>0.99	0.00	0.00-0.00	>0.99
12	0.00	0.00-0.00	>0.99	0.00	0.00-0.00	>0.99

Chapter 6: Discussion

6.1 Overview

Based on this population-based TB/HIV integrated surveillance database, we found that in Chiang Rai Province which has a TB incidence rate (126/100,000 PYs) and a high HIV co-infection rate (>30%) among TB patients, TB recurred at rates of 5.3/1,000 PYs for overall population, and 9.7/1,000 PYs among HIV-infected TB patients and 5.1/1,000 PYs among HIV-uninfected TB patients. Moreover, we indentified that among HIV-uninfected TB patients, age over 45 years, being hilltribe minority, being prison inmates, and had PTB only at their initial episode, were at higher risk of recurrence. While among HIV-infected TB patients, age between 15 and 35, being male, had PTB only, and having been cured from initial episode were associated with higher recurrence rates. Both groups of patients were at the highest risk of recurrence within 1 year after successful treatment completions.

6.2 TB recurrence rates

Our estimates on recurrence rates for HIV-infected and uninfected TB patients were consistent with other studies: previously reported rates ranged from 7.6/1,000 to 197/1,000 PYs among HIV-infected patients, and from 4/1,000 to 77/1,000 PYs among HIV-uninfected patients [6, 12, 38, 50, 52, 64, 65]. Our recurrence rates were both at the lower ends of the ranges. Given the background TB incidence rate and high HIV co-infection rate in Chiang Rai, this is surprising. A previous meta-analysis estimated that recurrence rates were 45/1,000 PYs for HIV infected patients and 19/1,000 PYs for HIV uninfected TB patients during an average follow-up of 34 months, with R-containing treatment for 6 months and a background TB incidence of 250/100,000 PYs [29]. According to their model of a 14/1,000 PY increase of recurrence rate by a 100/100,000 increase in background TB incidence, recurrence rates of 31/1,000 PY and 5/1,000 PY for HIV-infected and uninfected patients, respectively, under our setting can be expected. Their estimated recurrence rate among HIV-uninfected patients was similar to our estimates, while among HIV-infected patients, our

estimate was much smaller. In addition, based on a review conducted by Panajabi *et al*, the median of overall recurrence rates in high incidence countries were 103.1/1,000 PY and 78.5/1,000 PY at 6 and 12 months of follow up post treatment completion [4]. Although they didn't give an estimate of HIV-specific recurrence rate, we could still observe that our recurrence rates were lower.

6.2.1 Main influences on observed TB recurrence rates

There may be several reasons for the low recurrence rates we observed: First, optimal TB treatment regimen was offered for all HIV-infected and uninfected TB patients in Chiang Rai. WHO recommended R-containing regimen was universally offered daily both at the intensive and continuation phases to all new smear-positive patients since 1996 in Chiang Rai Province, which is considered to be most effective in reducing recurrence risk, compared to intermittent regimen [1, 58].

Poor patient compliance has long been recognized as a strong predictor of recurrence for both HIV infected and uninfected TB patients, even among patients with successful treatment outcomes [7, 11]. In Chiang Rai, patients adherence was not assessed using pill counts or urine test routinely under TB control programs. Thus, we didn't have any information in the surveillance database to explore the effect of non-compliance on recurrence risk. However, several efforts have been made toward enhancing treatment compliance among TB patients, in response to observed large proportion of unsuccessful treatment outcomes (default/death/recurrence) among TB patients in Chiang Rai. Firstly, it has been acknowledged that optimizing patient self-management is fundamental on patient adherence [25, 78]. In Chiang Rai, within the specialized TB clinics located at all levels of healthcare facilities (provincial/community/district), detailed TB education and counseling to both patients and close relatives at the beginning of treatment are routinely offered. Adequate knowledge on TB transmission, side effects of anti-TB drugs and how the treatment works could help patients prepare themselves better during the treatment. Secondly, studies have shown that supports from family members/relatives and patient's interaction with healthcare workers are one of the key factors to increase patient commitment to treatment [79]. As an important and effective establishment of TB control in Thailand, decentralized TB clinics offer close monitoring and

healthcare support during treatment process by professional and lay healthcare workers were expected to have a significant positive influence on patient's adherence to treatment. In addition, patients' social support from wide participation of community leaders, village health volunteers, and lay healthcare workers, into the observation of their drug intake could enhance their commitment to the treatment. Several other strategies have also been implemented to relieve financial burden on patients, such as free treatment to all citizens and moderate financial support mainly for nutrition and transportation needs. However, significant improvement of the treatment outcome has not been observed yet after the implementation of those strategies, possibly due to several reasons including inadequate resources, especially severely understaffed situation, to widely apply those strategies to all patients, increased complexities in treating large proportion of HIV-infected patients, and large amount of self-administered patients who were supposed to be supervised under DOT (see discussion below). Further investigations should focus on explore the underlying reasons for this phenomenon, in order to improve the overall performance of TB control in Chiang Rai, including reduce TB recurrence rate.

6.2.2 Influence of DOT administration on TB recurrence rates

As DOT administration has widely been recognized as the supreme method to enhance patient's compliance, however, in our study, DOT administration didn't show the beneficial effect on reducing recurrence rate, compared to self-administration, among both HIV-infected and uninfected patients. In Thailand, the involvement of lay healthcare workers, health volunteers, and family members in DOT administration is a special feature in response to the national-wide severe shortage of professional healthcare workers, especially outside Bangkok. However, this special way in DOT administration didn't show a superior result in enhancing patient compliance, compared to DOT by family members/relative, or to self-administration, in randomized controlled trials [78, 80]. Firstly, although there has been an increase in the DOT administration (comparing to self-administration) observed among TB patients since 1998 in Chiang Rai, this increase was mostly contributable to the increase of the family members in the direct observation, which usually ended up as patients' self-administration, according to anecdotal experiences from home visitors. Secondly, when obstacles such as transportation difficulties exist, it is also common that

patients switch themselves from supervision of healthcare workers in TB clinic to self-administration [81]. Thus, the beneficial effect of DOT administration in reducing TB recurrence might be diluted due to those practical issues. On the other hand, it is also likely that DOT administration might have limited benefits on enhancing patient's compliance to treatment to reduce the risk of recurrence. DOT has been argued to have limitations in real-life settings, by requiring weak patients to expend time, energy, and money to attend healthcare facilities regularly over at least 6 months [25] In our study, whether received DOT or not could be only regarded as an assignment at patients' registration, rather than a measure of patients' compliance, which limited its predictive capacity on recurrence risk. Future researches should try to explore the ways to maintain patients to their assigned group of DOT administration (or self-administration) in order to reveal the effect of DOT on reducing TB recurrence.

6.2.3 Influence of high mortality rate on TB recurrence rates among HIV-infected patients

As stated in the literature review part, optimal treatment regimen and high compliance of patients are said to be the most important factors affecting recurrence risk, particularly for HIV-uninfected patients. Regarding the relatively low recurrence rate observed in our HIV-infected patients, a very high mortality rate during follow-up after treatment completion could lower the risk of recurrence since death is a competing-risk event for recurrence, both of which are independently associated with advanced immuno-suppression for HIV-infected patients [6, 9]. Among HIV-infected TB patients, we observed 90.6/1,000 PYs mortality rate within 1 year after treatment completion which substantiated this explanation. In Thailand, it is common that HIV co-infected TB patients are admitted into hospitals with severe immune-suppression, because of delayed diagnosis of HIV, difficulties in accessing healthcare, and/or unavailability of timely HAART treatment, all of which can be responsible for fast progression to death or a subsequent active TB episode [30]. For HIV co-infected TB patients who successfully completed their TB treatment, the major threat remains to be the high risk of death, rather than that of TB recurrence. Thus, timely diagnosis of HIV and the initiation of HAART treatment are extremely important in reducing both mortality and recurrence rate, improving the overall TB control performance for HIV-infected patients.

6.2.4 Other potential influences on TB recurrence rates

It is also possible that these low recurrence rates observed here were partially due to an underestimation of the true recurrence rate. Our follow-up to identify recurrent cases was not an active follow up of cohort members relying on patients themselves to voluntarily present themselves to hospitals and get registered in the surveillance system. This follow-up scheme could fail to trace hard-to-reach patients who might have more difficulties in accessing healthcare facilities, such as hilltribe patients without citizenship card and highly mobilized patients such as young patients who seek temporary/seasonal work outside of Chiang Rai. This follow-up scheme should be recognized as a limitation in this study. In addition, according to the case definition of TB recurrence in our study, we might lose a certain amount of recurrent cases with negative smear result but can be confirmed as positive by culture, which might lead to the underestimation of the actual recurrence risk among TB patients, especially among HIV-infected patients. For HIV-uninfected patients, the underestimated of recurrence risk was not a major threat to individual patients and the community, since smear-TB cases among HIV-uninfected patients are usually with less severity and ability for further transmission. However, for HIV-infected patients, sputum negativity can be a reflection of advanced immuno-suppression, probably with higher risk of death, recurrence and other opportunistic infection. In this sense, detecting TB cases based on culture test among HIV-infected patients might be important for identification of recurrent patients in a timely manner to avert negative downstream consequences.

6.3 Identified risk factors for TB recurrence among HIV-infected and uninfected patients

6.3.1 Influence of age effects on TB recurrence

Age effects on recurrence risk has not been widely discussed and inconclusive in past studies: some found elderly patients having higher recurrence risk, while the others found the contrary [62,

[64, 65]. In our study, we did a thorough investigation of the associations between age and recurrence rate among HIV-infected and uninfected patients: age was significantly associated with recurrence in both HIV-infected and uninfected patients, but with opposite directions. Among HIV-uninfected TB patients, elder patients (>45 years old) were at higher risk of recurrence, while among HIV-infected TB patients, younger patients (15-35 years old) were at higher risk. Both of these associations demonstrated a monotone association of age and recurrence rates. In addition, cumulative incidence curves of mortality also showed the similar trends as TB recurrence, among both HIV-infected and uninfected patients, suggesting the contribution of impaired immune function in determination of both recurrence and death. For HIV-uninfected patients, higher recurrence among elderly people was reported to be associated with poor patient adherence, as well as their lower immune function due to aging and co-morbidities [5]. On the contrary, the higher recurrence rate among 15-35 years old could be associated with the increase the exposure risk to *M.tuberculosis* due to frequent social contacts, and HIV-related risk behaviors such as smoking, drinking, and drug abuse [82, 83], all of which could contribute to TB recurrence through increasing non-compliance and impairing their immune function.

6.3.2 Influence of ethnicity on TB recurrence

Among HIV-uninfected patients, other than older age, being hilltribe and being prisoners were also associated with higher rates of recurrence. In Chiang Rai Province, 14% of the population is hilltribe minority and the TB incidence rate among them was approximately 300/100,000 based on our database calculation in 2007 (data not shown), which was almost 3 times higher than their Thai-citizen counterpart. Hilltribes were widely recognized as the poor and isolated (mostly living in the mountain areas) minority whose citizenship has not been fully accepted by the Thai government. Significant inequalities regarding health/conditions and access to healthcare have been reported, implying an even-higher risk of developing TB than the estimates [84-88]. The majority of hilltribes in Chiang Rai live in remote mountainous area, which directly resulted in extreme difficulties in accessing healthcare and obtaining healthcare supports during the treatment [88]. Without adequate supervision and supports from healthcare worker, there is a great chance that

their treatment is not optimal, even with standard regimen and apparent clinical successful treatment outcome. Anecdotal experiences of healthcare workers also showed that illiteracy, cultural misbelieves, and inferior feelings to deal with healthcare workers created an environment that leads to non-compliance. On the other hand, re-infection should also be taken into account as an important mechanism for high recurrence risk among them due to high background incidence within their isolated communities. Besides, being socially and economically disadvantaged population, overcrowded household, poor ventilation, and poor nutrition are common living conditions for hilltribes, which also greatly increased the risk for re-infection. In conclusion, both relapse and re-infection are highly possible for the elevated recurrence rates observed among HIV-uninfected hilltribe patients. Moreover, we cannot rule out the possibility of genetic susceptibility of developing TB disease among hilltribe patients, compared to ethnic Thais, considering that they were comprised of immigrants from neighborhood countries such as China, Cambodia, Vietnam, and Laos.

However, for HIV-infected patients, being hilltribe was not significantly associated with high recurrence risk. Insufficient statistical power to detect the difference underlies this non-significant association. Further study including sufficient numbers of hilltribes, possibly with genetic analysis, would be helpful to establish a more solid explanation for the association between TB recurrence and ethnicity among HIV-infected and uninfected TB patients.

6.3.3 Influence of imprisonment on TB recurrence

Treatment adherence of HIV-uninfected TB prisoners was assumed to be significant higher than the general population, since optimal treatment was given directly in either hospital or prison, supported by the lowest “default” rate in prisoners among the overall study population (2.8%). It is, therefore, unlikely that the high recurrence among HIV-uninfected prisoners were due to relapse. On the other hand, according to a study conducted in southern Thailand, TB prevalence was reported to be 8 times higher in prison and a substantial number of TB cases were acquired in prisons, suggesting a high possibility of re-infection due to high chance of exposure to *M.Tuberculosis* in over-crowded cells [30, 89]. Malnutrition prevalent among prisoners could also

accelerate the disease progression after new infection [90]. In addition, prison inmates frequently have alcoholism and drug use [11, 89], which might weaken their immune function. However, for HIV-infected TB patients, insufficient statistical power might be responsible for the insignificant association between imprisonment and recurrence. But a recurrence rate of 27.3/1,000 PYs observed among HIV-infected prisoners warned us the great possibility of extremely high risk of recurrence among those patients under the synergetic effect of various associated risk factors. Thus, prisoner should be on the watch list of high risk group for control of TB recurrence. Active case finding, prophylaxis chemotherapy after treatment completion, and timely initiation of HAART should be implemented, regardless of their HIV status.

6.3.4 Influence of gender on TB recurrence

We identified that HIV-infected male patients were at higher risk of recurrence, compared to female patients. Being male has been reported to be associated with higher risk of developing TB, as well as recurrent TB, irrespective of age groups [77]. Sex differences in TB rates are not well understood, although a few hypotheses have been discussed. Differences in transmission dynamics between female and male TB patients, high prevalence of smoking and alcoholism, as well as poor compliance to treatment among male TB patients, all favor the development of active TB disease [77]. Generally, men are assumed to have high chance of exposure to *M.tuberculosis* due to more frequent social contacts than women. In addition, as in other Asia countries, alcohol and tobacco are commonly consumed by males [83], both of which lower immune function and interfere with adherence to treatment [73, 77]. Also, compared to men, women usually present themselves to TB diagnosis and treatment earlier in the time course of the disease due to higher levels of self-awareness and knowledge on TB, and therefore tend to have less severe form of TB disease [77]. They also seem to have a stronger commitment to TB treatment, resulting in better adherence [91]. Another hypothesis ascribes the lower risk of developing TB among females to their better immune function modulated by sex hormones [77]. In summary, it seems both relapse and re-infection could contribute to the higher risk of recurrence among HIV-infected men. However, this gender difference in recurrence rates was not seen among HIV-uninfected patients, implying an

essential role HIV played in differential recurrence risk between sexes through interaction with above risk factors.

6.3.5 Influence of TB clinical type on TB recurrence

Compared to patients who had PTB only in their initial episode, EPTB patients showed significantly lower rates of recurrence in both HIV infected and uninfected groups. However, we can not draw a firm conclusion that patients with EPTB have lower risk of recurrence, compared to patients with PTB due to the following reasons. Firstly, unlike mixed TB usually indicating a severe form of TB disease, EPTB is a general term to describe all clinical forms of TB located outside the lungs with various degrees of clinical/bacteriological severity, the risk of relapse would vary accordingly, especially after taking into account of different levels of effectiveness of anti-TB drugs to exert its function on different extra-pulmonary sites [1, 18]. It is hypothesized that a reactivation of dormant bacilli usually is more likely to occur at the original extra-pulmonary site, due to the vulnerability of already damaged tissues. On the other hand, re-infection is also a possible reason of recurrence for EPTB cases, independent of the disease severity and treatment efficiency. Re-infection of a new strain could lead to a development of an independent new PTB, regardless of the original site of EPTB. Since EPTB cases are usually more likely to be presented as smear-negative as to PTB cases, different bacteriological manifestations of recurrent cases are thus depended on whether the new episode is a relapse at the original extra-pulmonary site or a new re-infection at the lung. Thus, the use of our case definition to identify TB recurrent cases might only include most of the re-infected cases and a small amount of relapsed cases with positive smear, and lose a certain amount of relapsed cases with negative smear recurred at the original extra-pulmonary sites. We should be highly aware of these of smear-negative recurrent cases, especially for HIV co-infected TB patients. Further studies investigating recurrence risk for EPTB only patients need to consider detecting recurrent cases by culture test. Also, DNA fingerprinting test might also be needed to discover the proportion of re-infection and relapse among recurrent cases for EPTB patients to figure out whether there is a dominant role played by relapse or re-infection, in relation to the clinical site of recurrent cases.

6.3.6 Influence of time patterns on TB recurrence

Timing of recurrence needs to be carefully considered because it could guide the monitoring of patients after treatment completion for case finding and preventive therapy. Consistent with other studies, the highest recurrence rates was observed within 1 year after treatment completion, among both HIV-infected and uninfected patients. HIV-infected patients showed much higher recurrence rates in the 1st year post treatment completion, compared to HIV-uninfected patients, presumably due to their advanced immuno-suppression status facilitating the progression to active disease. Thus, for monitoring TB patients after treatment completion, 1-year follow-up duration is vital. Immediately after treatment completion, both groups showed a significant drop in recurrence rates, possibly due to quick reactivation of persistent bacilli upon the withdrawal of anti-TB drugs, especially when immune functions are compromised which cannot keep the remaining bacilli "under control" (self-healing). Fast progression into disease due to the impaired immune system could explain the earlier timing of recurrence among HIV-infected patients we observed here (a median of 6.1 months vs a median of 12.6 months), consistent with other studies [29, 50].

After up to 6 years since treatment completion, recurrence rate remained less than 1% among HIV-uninfected patients, while among HIV-infected patients, a fluctuation in recurrence rates centered around 3%, indicating a fairly constant and appreciable risk of re-infection. HIV-infected TB patients might have higher exposure risk and be more susceptible to new strains resulting from frequent visiting hospitals and clinics for HIV treatment or follow-up right after TB treatment, where the services for TB and HIV usually overlap and the density of circulated *M.Tuberculosis* is high. If the possibility of nocosomial transmission is as high as expected, then home visits by healthcare worker should replace patient's visits to hospitals. For protection of both patients and their close contacts, it might be necessary to screen patients' family members and close contacts for TB infection.

Some studies only include TB recurrence that occurred after 6 months or 1 year after treatment completion by considering the early recurrence (relapse) as a continuation of treatment failure, especially among patients who only completed treatment instead of having been cured [11, 63, 65].

According to these studies, a certain length of time is required for persistent bacilli or new infected *M.tuberculosis* to develop into active disease, and therefore "failure" rather than "relapse" is a more plausible explanation for early "recurrence". However, we cannot preclude the possibility of fast progression of persistent bacilli into active disease under weakened immune functions, due to HIV-infection or under other conditions among HIV-uninfected patients (e.g., co-morbidities, aging). This extra requirement on timing of recurrence to define recurrent cases should be carefully debated further.

6.3.7 Other influences on TB recurrence

None of registered hospital type, or assigned regimen type, or treatment outcome from initial episode was significantly associated with recurrence risk for HIV-uninfected patients in the multivariable analysis. Variables as types of registered hospital and assigned regimen could approximately stand for treated hospital and regimen applied in treatment, partially reflecting the performance of TB management and services of different hospitals/regimens. Based on anecdotal experiences from field healthcare workers in Chiang Rai, community hospitals should have better TB management and services than the provincial hospital. The relatively small-scale of community hospitals with less heavy TB caseloads should allow a better focus on each TB case, and a closer relationship between patients and healthcare worker. As an important aspect of the decentralized TB services, frequent home visits and follow-ups by healthcare staff from community hospitals and health centers are possible for every TB patient, even for those who live in remote areas [80]. All of these beneficial factors should contribute to better treatment adherence, resulting in higher treatment efficiency among patients treated in community hospitals. On the other hand, as a tertiary-care hospital, Chiang Rai Provincial Hospital faces a much heavier TB caseload and more complex TB cases such as MDR-TB and HIV-infected TB, which demand special and intensive attentions, thus potentially resulting in an inadequate care for common TB cases. However, our analysis showed a 2-fold increased recurrence rate (though not statistically significant) among HIV-uninfected patients who were treated in community hospitals than those treated in Chiang Rai Provincial Hospital. Before conducting any further investigation on the

association between treated hospital and recurrence risk, we should acknowledge the fact that hospitals where patients initially registered in could be different from hospitals where patients actually treated due to the emergence of practical issues.

Among both HIV-uninfected and infected patients, we observed a higher recurrence rate in those who got cured from their initial episode, than those who completed treatment, although this association was only marginally significant among HIV-uninfected patients. While we are unable to fully explain the underlying reasons for this observation, one of the possible explanations involves the definition of "treatment completion". TB patients who completed treatment could be mostly consisted of patients who were smear-negative or have EPTB at the beginning and can only be confirmed as "treatment completion" at the end of treatment, among whom a lower recurrence rate is expected as a result of the case definition (see discussion above). However, among HIV-infected patients, after further stratifying them into smear-positive and smear-negative at the beginning of initial episode, a higher TB recurrence rate was also observed in patients who got "cured" than "completed", although the difference was not statistically significant (18.2/1,000 PYs vs 12.4/1,000 PYs, P=0.11). We are unable to fully explain the reasons for this difference. Since we observed appreciable recurrence rates among the cured, a fairly high re-infection risk should be considered in Chiang Rai Province, especially for HIV-infected patients among whom we observed a significantly increased rate of recurrence after having been "cured". Thus, from a practical point of view, public health practitioners should keep in mind the possibility of high re-infection risk in Chiang Rai Province, regardless of HIV sero-status, to set up proper preventive strategies.

6.4 Strengths and limitations

The provincial TB/HIV surveillance database was the foundation for assessing TB recurrence in Chiang Rai Province in this study. It provided a unique opportunity for several reasons. First, this database is a population-based, provincial-wide system that collects information directly from patients who are treated in public hospitals. Professional healthcare workers fill in the standard

questionnaire form by asking patients questions on demographic background and by searching patients' medical record for detailed laboratory/medical/clinical conditions and treatment process. This ensures the data quality in the database. Second, this system has been collecting data since 1996, sufficiently long enough for building a cohort with "cured" and "completed treatment" and following up for analysis of recurrence. The large number of TB patients registered in the database, coupled with the sufficient length of follow-up, provided a well-characterized cohort for the study of recurrence rates. Third, this database could guarantee to capture the same TB patient who has been treated previously and presented themselves to the hospital afterward for recurrent episodes, through patients' provision of their unique citizen identification card number to receive TB diagnosis and treatment free of charge.

However, several limitations in our study need to be taken into account in interpreting our results. First, passive detection of recurrent cases through the surveillance registry are more likely to underreport. Such underreporting occurs more frequently among subgroups with difficulties in healthcare access such as hilltribe patients, and those who are highly mobile such as young people seeking job opportunities outside of the province. In addition, information we used in this study were collected at the beginning of treatment. Thus, except for demographic characteristics, all assessed risk factors including assigned regimen, registered hospitals, and DOT assignment, might have changed and influenced TB recurrence. Moreover, we didn't assess other previously reported clinical/socio-demographic predictors due to lack of/incomplete information, such as atypical radiographs, residual cavitation, delayed sputum conversion, MDR-TB, patients' adherence and HIV-related information (i.e., CD4 counts, HAART treatment), smoking, drinking and drug abuse. Of those, HAART treatment would be of particular importance for HIV-positive TB patients. Finally, we didn't differentiate recurrence by endogenous reactivation and that by exogenous re-infection. However, in Thailand and other developing countries where TB and HIV are highly prevalent, our study results could provide a practical perspective to evaluate patient's risk for recurrence through looking into their demographic and clinical/treatment profiles.

Chapter 7: Conclusions

7.1 Knowledge Translation

The disparity in recurrence rates observed between HIV-infected and uninfected TB patients reconfirmed the impact of HIV on TB recurrence. Although higher recurrence rates observed among HIV-infected patients is problematic and should be highly aware of, from a broader perspective, for TB patients who were also co-infected with HIV in Chiang Rai province, the extremely high mortality rates imposed much heavier burdens on individual patients as well as TB/HIV control programs. Thus, timely diagnosis of TB and/or HIV, enhanced accessibility to HAART treatment, as well as timely initiation of HAART treatment, would be the effective measures to prevent premature death as well as TB recurrence. Under other real-life settings where HAART is not widely available to high risk HIV-infected TB patients with advanced immuno-supppression, active case finding and secondary post-treatment prophylaxis would be helpful to reduce the risk of TB recurrence and death (from TB).

Based on our exploratory interpretation of identified risk factors in relation to the two mechanisms for TB recurrence, an important message we would like to convey is that in Chiang Rai province, both relapse and re-infection could play important roles in TB recurrence among either HIV-infected or uninfected patients. Any preventive or therapeutic strategies aiming for application during and/or after treatment should be built upon this notion. Without the wide availability of DNA fingerprinting technology, three key determinants for TB recurrence would be helpful for preliminary assessments of the recurrence risk for general population: patient adherence to treatment regimen, background incidence/ specific high-risk settings, and immunity level of individuals/communities. Tailored strategies such as treating co-morbidities among elderly patients, close monitoring during treatment to enhance compliance, screening household contacts for hilltribe and elderly patients, active case finding and post-treatment preventive chemotherapy, would be considered for application. Also, for HIV-infected patients, young patients and male patients would require more targeted efforts to reduce their high risk of TB recurrence, through

enhancing treatment adherence by education and healthcare supports, post-treatment preventive chemotherapy, as well as promotion of abstention of harmful behaviours (e.g., smoking cessation).

7.2 Future research

As a major limitation in our study, the interpretation with respect to relapse and/or re-infection was based on proxy indicators and assumptions. Thus, more scientifically-sound explanation of our research findings on whether and how relapse and/or re-infection contributed to each risk factor should be supported by laboratory results of molecular technology. To balance the methodological requirement on ample sample size to yield sufficient statistical power to detect significant differences, and the restrains of limited application of DNA fingerprinting technologies in resource-poor settings, a nested case-control study would be the optimal study design to conduct this combined investigation. In addition, genetic analysis for high risk group, which has rarely been investigated so far, would give us some clues about whether and to which level the intrinsically genetic vulnerability plays a role in determining of the recurrence risk.

In future research, researchers could confirm our explanation of the observed “opposite” age effects on recurrence rate for HIV-infected and uninfected patients, in order to setup targeted intervention strategies for those two groups of patients. Researchers could also look into the actual effect of DOT administration on TB recurrence, compared to self-administration. In addition, more exploratory investigations to discover the underlying reasons for higher TB recurrence rates observed among “cured” patients, compared to treatment completed patients, could render better understanding of this “reversed” phenomenon. After confirmation of our hypothesized explanations raised from this study, cost-effectiveness investigations of potential intervention strategies would be helpful for the guidance of wide implementation.

7.3 Summary

In conclusion, due to the raising trend of TB recurrence observed around the world, tailored preventive and therapeutic strategies are in great need. Acknowledge of HIV’s impact on TB recurrence and its association with relapse and re-infection are fundamental for researchers to fully

understand the underlying reasons for high recurrence risk among TB patients with successful treatment, from where evidence-based, practical interventions to reduce this risk can be established. Our study included eligible TB patients with successful treatment who were identified through a population-based TB/HIV surveillance system, and were followed up to 12 years after treatment completion, rendered important research findings to explore the underlying mechanisms of TB recurrence, as well as insights for local control of TB recurrence. To ultimately achieve the goal of maintaining TB recurrence rates under an acceptable range in a global context, more research-oriented and application-oriented investigations are needed in future to provide the most cost-effective intervention strategies.

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