CHAPTER 2

Literature Review

This chapter reviews the literature related to medication adherence among newly diagnosed pulmonary tuberculosis patients. The content in this chapter includes pulmonary tuberculosis, treatment of pulmonary tuberculosis patients, medication adherence, improving medication adherence, social cognitive theory, and the theoretical framework of this study.

2.1 Pulmonary tuberculosis

Tuberculosis is a disease caused by *M. tuberculosis*. These bacterial bacilli are known as tubercle bacilli or acid-fast bacilli (AFB). The bacteria usually infect lungs, but can involve any other organs. About 5% to 10% of adults infected with *M. tuberculosis* will develop TB in their lifetime, most within five years after infection (Maher, 2009). Various stresses may trigger progression of infection to disease; the most important trigger is weakening of immune resistance, especially by HIV infection. Three-quarters of new TB cases are PTB, which is defined as a tuberculous disease that involves the lung parenchyma and trachea (Hoffmann & Churchyard, 2009; WHO, 2007). Without treatment, 50% of PTB patients will be dead, 25% will be healthy and 25% will remain ill with chronic infectious TB by the end of five years after diagnosis (WHO, 2004).

2.1.1 Case definitions of pulmonary tuberculosis

Case definitions of PTB by site and the result of sputum smear recommended by WHO (2004; 2007) are as follow:

1) Sputum smear-positive PTB. Sputum smear-positive PTB is defined as a PTB patient who has two or more initial sputum smear examinations positive for AFB; or who has one sputum smear positive for AFB and chest x-ray (CXR) abnormalities

consistent with active PTB, as determined by a physician; or who has one sputum smear positive for AFB, which is also culture positive for *M. tuberculosis*.

2) Sputum smear-negative PTB. Sputum smear-negative PTB is defined as a PTB patient who does not meet the definition for sputum smear-positive PTB. In keeping with good clinical and public health practices, diagnostic criteria should include: at least three sputum smears negative for AFB, CXR abnormalities consistent with active PTB, and decision by a physician to treat with a full course of anti-TB treatment.

3) Extra-pulmonary TB. Extra-pulmonary TB is defined as a patient who has TB in organs other than the lung (e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints, bones, or meninges). Diagnosis is based on one culture-positive specimen, or histological or strong clinical evidence consistent with active extra-pulmonary TB, followed by a physician's decision to treat with a full course of anti-TB treatment. A patient diagnosed with both pulmonary and extra-pulmonary TB should be classified as a PTB case.

2.1.2 Pulmonary tuberculosis transmission

The transmission of *M. tuberculosis* is almost exclusively airborne; the most important source of infection is a coughing sputum smear-positive PTB patient. Cough-generated aerosol cultures were positive in 25% of patients with smear positive PTB (Fennelly et al., 2004). Coughing produces droplets (as does talking, sneezing, spitting or singing) that may contain tubercle bacilli (Loudon & Roberts, 1967; Maher, 2009). As the droplets are expelled into the air, some droplet nuclei, which are infectious particles of respiratory secretions usually less than five µm in diameter and containing 1-10 tubercle bacilli (Hoffmann & Churchyard, 2009; Maher, 2009) are spread. A single cough can produce 3,000 droplet nuclei that can remain suspended in the air for several hours, presenting an infection risk long after a person with PTB has left an indoor space (Hoffmann & Churchyard, 2009; Maher, 2009). Whereas larger particles either fall to the ground or, if inhaled, are trapped either in the nose or in the mucociliary system of the tracheobronchial tree, droplet nuclei are so small that they avoid the defenses of the bronchi and penetrate the terminal alveoli of the lungs where infection begins. Because the particles containing tubercle bacilli on the clothing, bedcovers, or belongings of a

PTB patient cannot be dispersed in aerosols, they do not play a significant part in infection. These bacilli degrade rapidly in outdoor environments because ultraviolet light from sunlight destroys the bacilli (Maher, 2009).

2.1.3 Pathophysiology of pulmonary tuberculosis

The well-aerated regions close to the pleura in the lower lung fields are the most common place for the bacilli-containing droplets to settle (Hoffmann & Churchyard, 2009). After being loaded into the alveoli, non-activated alveolar macrophages ingest the bacilli in an attempt to destroy them. It is believed that at least 5-200 bacilli are necessary to overcome the macrophage response and cause infection (Hoffmann & Churchyard, 2009). As the quantity of bacilli increases, inflammation develops, forming a collection of bacilli, macrophages, lymphocytes and debris known as the Ghon focus. During early mycobacterial replication, the burden of bacilli in the Ghon focus is insufficient to trigger a systemic immune response. As the burden of bacilli grows, additional activated alveolar macrophages and T-lymphocytes are recruited to this site, and a systemic response is activated. Bacilli are also trafficked from the Ghon focus to the mediastinal and perihilar lymph nodes (either within macrophages or along lymphatic channels) and may become hematogenously distributed, developing foci of replication in regions with high oxygen tension: the meninges, epiphyses of long bones, kidneys, vertebral bones, lymph nodes and apicoposterior areas of the lungs (Dannenberg, 1993; Maher, 2009; Hoffmann & Churchyard, 2009).

The development of the immune response (delayed hypersensitivity and cellular immunity) about 4-6 weeks after the primary infection is indicated by a positive tuberculin skin test and occasionally by a clinical hypersensitivity reaction such as erythema nodosum, phlyctenular conjunctivitis, or dactylitis (Dannenberg, 1993; Maher, 2009). For most individuals, the systemic immune response is sufficient to control future growth of bacilli. The original Ghon focus and associated perihilar lymph node infections, known as the Ranke complex, are often eradicated within months of infection, whereas disseminated foci become walled off by granulomatus inflammation (Hoffmann & Churchyard, 2009; Piessens & Nardell, 1993). When the disseminated focus is in the lung apex, the site is known as Simon’s focus (Hoffmann & Churchyard, 2009).

2.1.4 Symptoms and signs of pulmonary tuberculosis patients

The symptoms and signs of PTB are divided into two phases: primary PTB and post-primary PTB**.**

1) Primary PTB. Primary PTB infection may be asymptomatic while causing fevers and pleuritic pain and rarely progresses to a life-threatening disease. During primary pulmonary infection, symptoms may occur as the burden of bacilli increases, and the host mounts a systemic immune response; fever is the most common symptom. Fever onset is usually gradual and is not usually accompanied by other symptoms, although some patients develop pleuritic or retrosternal pain. Cough, arthralgias and fatigue rarely occur. While hematogenous seeding of distant sites is common, rarely does it cause symptomatic disease among individuals with an intact immune system. The most common extra-pulmonary manifestations are lymphadenitis and meningitis (Hoffmann & Churchyard, 2009). Among individuals with a weakened immune response including those with advanced age, HIV, kidney failure, or poorly controlled diabetes mellitus, progression to disseminated or local disease occurs more frequently.

2) Post-primary PTB. Post-primary refers to all PTB resulting from reactivation of controlled (latent) infection, late progression of primary infection or exogenous re-infection. The classic presentation of post-primary PTB is characterized by weeks to months of chronic cough (usually more than two or three weeks), weight loss, fatigue, fevers, night sweats, and hemoptysis (Garay, 2004). However, no single symptom or constellation of symptoms clearly distinguishes patients who have PTB from those who do not. A mild, non-productive cough commonly occurs in the morning. This morning cough results from the accumulation of secretions during sleeping hours. During disease progression, this cough often becomes more continuous throughout the day and may become productive of yellow or yellow-green, occasionally blood-streaked, sputum. Nocturnal coughing is associated with advanced pulmonary disease, often with cavitations. Pleuritic pain may occur with coughing (Hoffmann & Churchyard, 2009; Reichman & Hershfield, 1993). Fever in post-primary PTB is classically diurnal with an afebrile period early in the morning, a gradually rising temperature throughout the day, and a fever peaking in the late afternoon or evening.

Night time defervescence is often accompanied by diaphoresis leading to drenching night sweats. Both fever and night sweats are more common among patients with advanced PTB, often with significant parenchymal disease and cavitary lesions (Hoffmann & Churchyard, 2009).

2.1.5 Diagnosis of pulmonary tuberculosis

The methods for diagnosing pulmonary tuberculosis patients are as follow:

1) Medical history. Medical history is important for diagnosis and treatment of the patient's medical condition. The history of the patient should include exposure to a person with infectious PTB, symptoms of PTB disease, past TB infection or TB disease, and risk factors for developing the disease.

2) Physical examination. Physical examination of an individual with PTB is usually non-specific. Classic findings are pallor, cachexia, tachycardia, and post-tussive crackles over affected lungs (Hoffmann & Churchyard, 2009; WHO, 2004).

3) Laboratory investigations. Laboratory investigations are useful, as some PTB patients are anemic and have leucocytosis. Normochromic, normocytic anemia occurs most commonly. Normal or low leucocyte counts are also consistent with diagnosis of PTB. Mild monocytosis or eosinophilia may also be observed. The erythrocyte sedimentation rate may be normal or increased. The platelet count, alkaline phosphatase, lactate dehydrogenase, and ferritin may also be increased; however, these findings are not sensitive to or specific for the diagnosis of PTB (Morris, Bird, & Nell, 1989).

4) Chest radiography or CXR. Chest radiography in primary PTB is often normal. In post-primary PTB, most patients exhibit abnormalities on chest radiography, even in the absence of respiratory symptoms (Barnes, Verdegem, Vachon, Leedom, & Overturf, 1988). Conversely, chest radiographs may be normal in a small fraction of symptomatic individuals, especially in the setting of HIV co-infection (Day et al., 2006). Classic findings in post-primary PTB are alveolar infiltrates, interstitial infiltrates or cavitary lesions in the lung apex or upper zones of the lower lobes. Effusion, lymphadenopathy, lower lung zone infiltrates, and a miliary pattern are atypical (Hoffmann & Churchyard, 2009). In most cases of sputum smear-positive PTB, a CXR is not necessary. However, in case only one sputum out of three smear positive

for AFB, an abnormal CXR is a necessary additional criterion for the diagnosis of sputum smear-positive PTB (WHO, 2004).

5) Sputum smear and culture. The diagnosis of PTB is usually based on sputum examination and, optimally, culture. Thus, quality assurance of collection, handling, and processing of sputum is essential. The chances of finding TB bacilli are greater with three samples than with only one or two samples. Because secretions build up in the airways overnight, an early morning sputum sample is more likely to contain TB bacilli than one taken later in the day. The practical methods for collecting outpatient sputum samples suggested by WHO (2004) are as follows. On day one, the patient provides an “on-the-spot” sample for Sample one under supervision when presenting to the health facility. The patient is then given a sputum container to take home for an early morning sample the following morning. On day two, the patient brings an early morning sample for Sample two and provides another “on-the-spot” sample under supervision to be used for Sample three. Culture results may not be helpful in making a rapid individual diagnosis because *M. tuberculosis* is a slow-growing organism; it often takes between six and eight weeks before cultures become positive. However, they can be helpful for drug sensitivity analysis (WHO, 2004).

The results of sputum smear are reported in five categories; 0 means no AFB bacilli per 100 oil immersion fields; scanty means 1-9 number of AFB bacilli per 100 oil immersion fields; 1+ means 10-99 number of AFB bacilli per 100 oil immersion fields; 2+ means 1-10 number of AFB bacilli per oil immersion field; and 3+ means more than 10 number of AFB bacilli per oil immersion field (WHO, 2004).

2.1.6 Tuberculosis control

The goals of TB control are to reduce mortality, morbidity, disease transmission and preventing drug resistance until TB no longer poses a threat to public health. The aim is also to reduce human suffering and the social and economic burdens on families and communities as a consequence of TB. In order to achieve this, it is necessary to ensure access to diagnosis, treatment, and a cure for each patient. By 2005, the targets of global TB control, originally launched by WHO in 1991, were to achieve a case detection rate of at least 70% for new sputum smear-positive PTB cases and to successfully treat at least 85% of these cases under the DOTS strategy (WHO, 2009).

Particular attention was given to detecting and curing people with sputum smear-positive PTB because they are the most infectious, and thus the most likely to cause further transmission of TB in the population without proper treatment. Additionally, the "Stop TB" partnership targets launched by WHO in 2006 are: 1) to reduce the global prevalence and death rates per capita by 50%, compared with their levels in 1990, by 2015 and 2) to reduce the global incidence of active TB to less than one case per million populations per year by 2050 (WHO, 2010a).

1) Directly observed treatment, short-course. The five essential elements of DOTS strategy (WHO, 2004; WHO, 2013) are as follow:

1.1) Secure political commitment, with adequate and sustained financing. Make TB control a nationwide activity integral to the national health system.

1.2) Ensure early case detection, and diagnosis through quality-assured bacteriology. Special attention to case detection is necessary among HIV-infected people and other high-risk groups.

1.3) Provided standardized treatment with supervision, and patient support. Proper case management conditions imply technically sound and socially supportive treatment services. DOT is an element of DOTS; one certain way to ensure patient adherence to treatment by having someone to support the patient during the course of treatment and to watch the patient swallow the tablets (WHO, 2004).

1.4) Ensure effective drug supply and management. Uninterrupted supply of quality-assured drugs with reliable drug procurement and distribution systems.

1.5) Monitor and evaluate performance and impact. Ensure a recording and reporting system enabling outcome assessment of every patient and assessment of overall program performance.

2) The stop TB strategy. The stop TB strategy is the approach recommended by WHO to reduce the burden of TB, in line with global targets set for 2015. The six components of the Stop TB strategy include pursuing high-quality DOTS expansion and enhancement; addressing TB/HIV, MDR-TB, and addressing the needs of poor and vulnerable populations; contributing to health system strengthening based on primary health care; engaging all care providers; empowering both people with TB

and communities through partnerships; and enabling and promoting research (WHO, 2010a).

2.2 Treatment of pulmonary tuberculosis patients

Tuberculosis is one of the very few diseases for which the standards of treatment have been so rigorously defined and recommendations so universally accepted. The aims of anti-TB drug treatment include: curing the patient of TB, preventing death from active TB or its late effects, preventing TB relapse or recurrent disease, preventing the development of drug resistance, and decreasing TB transmission (WHO, 2004). SCC is recognized as one of the most cost-effective of standard treatments and recommendations for TB patients, properly applied SCC fulfils the aims of anti-TB drugs. The principles of TB treatment are 1) the use of multiple drugs to which the tubercle bacilli are susceptible, 2) continuation of treatment for a sufficient period of time to control and usually eradicate the disease, and 3) regular ingestion of medication by the patient (Grzemska, 2009).

2.2.1 Treatment regimen for newly diagnosed pulmonary tuberculosis patients

Treatment regimen for newly diagnosed PTB patients is divided into two phases: an initial or intensive phase lasting two months with four drugs and a continuation phase lasting four months with two drugs. Drugs are usually taken daily. The treatment regimen is 2HRZE/4HR (WHO, 2010b). The abbreviation means anti-TB drugs which include isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E). The number preceding a phase represents the duration of that phase in months (WHO, 2004). The initial phase is designed for the rapid killing of actively growing bacilli, as well as the killing of semi-dormant bacilli, resulting in a shorter duration of infectiousness. The majority of patients with sputum smear-positive PTB who have received effective treatment become sputum smear-negative within two months. At the time the continuation phase is started, there is a low number of bacilli, and hence less chance of selecting drug-resistant mutants. Thus, although fewer drugs are necessary, they are needed for a longer period time in order to eliminate the remaining TB bacilli. Killing the persisters prevents relapse after completion of treatment.

2.2.2 Pulmonary tuberculosis medications

The medications used for managing newly diagnosed PTB patients are isoniazid, rifampicin, pyrazinamide, and ethambutol.

1) Isoniasid is highly active against *M. tuberculosis*, especially against actively dividing bacilli, through inhibition of mycolic acid synthesis and, consequently, bacilli on which isoniazid acts lose their acid-fastness (Fujiwara, Simone, & Munsiff, 2001). It is a small water-soluble molecule easily absorbed through the gastrointestinal tract and usually given orally. The usual daily dose is 5 mg/kg for adult, maximum 300 mg daily (Fujiwara et al., 2001; Ministry of Public Health, 2008; WHO, 2004).

2) Rifampin is a potent agent against actively dividing intracellular organisms, but also has activity against semi-dormant bacilli. It works primarily by inhibiting DNA-dependent RNA polymerase and blocking RNA transcription. It is usually given orally in a daily dosage of 10 mg/kg (maximum 600 mg daily) (Fujiwara et al., 2001; Ministry of Public Health, 2008; WHO, 2004).

3) Pyrazinamide is a potent sterilizing agent that plays a key role in effective short-course chemotherapy regimens (Steele & Des Prez, 1988). It is most active in acidic environments, especially in the intracellular environment of macrophages. The precise mechanism action of pyrazinamide on tubercle bacilli is not known. The daily dose of pyrazinamide is 15-30 mg/kg, given orally (Fujiwara et al., 2001; Ministry of Public Health, 2008; WHO, 2004).

4) Ethambutol inhibits the transfer of mycolic acids into the cell wall. It is active against both intracellular and extra-cellular organisms. Because it can deter the selection of resistant mutants by other anti-tuberculosis drugs, ethambutol plays an important role as part of the initial regimen for cases in which isoniazid resistance is possible (Fujiwara et al., 2001). Ethambutol is administered orally at a daily dosage of 15-25 mg/kg (Fujiwara et al., 2001; Ministry of Public Health, 2008; WHO, 2004).

2.2.3 Fixed-dose combinations (FDCs) of anti-tuberculosis drugs

FDCs of anti-TB drugs refers to drugs composed of two (isoniazid and rifampicin), three (isoniazid, rifampicin, and pyrazinamide), or four (isoniazid, rifampicin, pyrazinamide, and ethambutol) drugs in a single tablet. Compounding multiple medications into a single preparation has been proposed as a means to reduce non-adherence with prescribed therapy (American Thoracic Society, 1994; Moulding, Redeker, & Kanel, 1989). By incorporating more than one major drug into a single pill, it has been argued that patients are more likely to take their medications regularly, since the process will entail fewer pills and a simpler routine: both factors proven to favorably impact drug-taking behavior (Sbarbaro, 1979). More importantly, FDCs drugs prevent "selective discontinuation" of one or more of the drugs, which, in addition to causing treatment failure, promotes the selection of drug-resistant mutants. Other advantages of using FDCs drugs include ensuring that patients always take more than one type of medication; decreasing possibility of making medication errors; and the simplification of procurement, storage, and distribution of drugs. The disadvantage of FDCs drugs include higher cost, the patient has to continue taking a high number of pills, and the possibility of under-dosing if the patient takes fewer tablets than prescribed (Fujiwara et al., 2001). An additional limitation of using FDCs drugs is side-effects developing of some drugs included in the tablet (WHO, 2010b). WHO suggests that FDCs drugs should be recommended wherever they are available, especially when direct observation is not fully guaranteed (WHO, 2004).

2.2.4 Modes of action of anti-tuberculosis drugs

A population of TB bacilli in a TB patient consisting of the following groups; metabolically active, continuously growing bacilli inside cavities; bacilli inside cell, e.g. macrophages; semi-dormant bacilli (persisters), which undergo occasional spurts of metabolic activity; and dormant bacilli, which fade away and die on their own. Different anti-TB drugs act against different groups of bacilli. Anti-TB drug treatment takes a long time because it is difficult to kill the semi-dormant TB bacilli (Donald & Mclleron, 2009; WHO, 2004). A dynamic combination of host, microbe, and drug factors determines the three main properties desirable of anti-TB agents, the details are as follow (Donald & Mclleron, 2009):

1) Rapidly eliminating the actively metabolizing bacilli. Rapidly eliminating the actively metabolizing bacilli refer to isoniazid killing 90% of the total population of bacilli in the congenial surroundings of pulmonary cavities, where there is adequate oxygen and an alkaline pH, during the first few days of treatment. It is most

effective against the metabolically active, continuously growing bacilli. Rifampicin can kill the semi-dormant bacilli or intermittently metabolizing organisms in caseation tissue that isoniazid cannot. Pyrazinamide kills bacilli in acidic surroundings, such as those in areas of active inflammation or within macrophage phagolysosomes.

2) Sterilizing action. Sterilization action means killing all of the bacilli. Persisters are hardest to kill and are probably not killed by any of the currently available anti-TB agents. The aim of killing all the bacilli is to prevent relapse. Rifampicin is the most effective sterilizing drug; its effectiveness makes short-course chemotherapy possible. Pyrazinamide is also a good sterilizing drug, since it kills bacilli protected inside cells.

3) Preventing drug resistance. A population of TB bacilli never previously exposed to anti-TB drugs will include a few naturally occurring drug-resistant mutant bacilli. Faced with anti-TB drugs, these drug-resistant mutant bacilli will grow and replace the drug-sensitive bacilli under either inadequate anti-TB drug combinations or inadequate application of anti-TB drug treatment. Isoniazid and rifampicin are most effective in preventing resistance to other drugs; ethambutol is slightly less effective (Donald & Mclleron, 2009; WHO, 2004).

2.2.5 Drug side-effects and management

Most TB patients complete their treatment without any significant drug side-effects; however, a few patients do develop side-effects. Consequently, clinical monitoring of all TB patients for side-effects is important during TB treatment, although routine laboratory monitoring is not necessary. Health care workers should monitor patients for drugs side-effects by teaching both patients and their medication taking assistants how to recognize symptoms of common side-effects. Furthermore, health care workers should ask patients specifically about these symptoms when they see all patients at least monthly during treatment. When patients have minor drug side-effects, the situation should be explained to them, offered symptomatic treatment, and encouraged to continue treatment. When a patient has a major reaction, health care workers should stop the suspected responsible drugs. The symptom-based approach used to manage drug side-effects is shown in Table 2.1.

Table 2.1 Symptom-based Approach to Management of Drug Side-effects

Side-effects	**Drug(s) Probably Responsible**	**Management**
Minor		**Continue anti-TB drugs**
Anorexia, nausea, abdominal pain	Isoniazid Rifampicin Pyrazinamide	Give drugs with small meals or just before bedtime, and advice patient to swallow pills slowly with small sips of water. If symptoms persist or worsen, or there are protracted with vomiting or any sign of bleeding, consider the side-effect to be major and refer to clinician urgently.
Joint pain	Pyrazinamide	Give aspirin or paracetamol or a non-steroidal anti-inflammatory drug
Peripheral neuropathy/ burning, numbness or tingling sensation in hands or feet	Isoniazid	Give pyridoxine 50-100 mg/day (prophylactic dose are 6-50 mg/day)
Drowsiness	Isoniazid	Reassurance. Give drugs before bedtime
Influenza-like syndrome (fever, chills, malaise, headache, bone pain)	Rifampicin	Give paracetamol or decreasing rifampicin dosage
Orange/red urine	Rifampicin	Reassurance. Patients should be told when starting treatment that this may happen and is normal

Table 2.1 (Continued)

Side-effects	**Drug(s) Probably Responsible**	**Management**
Major		**Stop drug(s) responsible**
Skin itching/rash	Isoniazid Rifampicin Pyrazinamide	Stop anti-TB drug (see details below)
Hepatitis/jaundice (other causes excluded)	Isoniazid Rifampicin Pyrazinamide	Stop anti-TB drugs until jaundice resolves (see details below)
Vomiting and confusion (suspected drug-induced acute liver failure if there is jaundice)	Most anti-TB drugs	Stop all anti-TB drugs, urgent liver function tests
Visual impairment (other causes excluded)	Ethambutol	Stop ethambutol
Generalized, including shock, purpura, acute renal failure	Rifampicin	Stop rifampicin

Note. Adapted from TB/HIV: A clinical manual (p.132), by WHO, 2004, Geneva: WHO, & Treatment of tuberculosis guideline (p.61), by WHO, 2010b, Geneva: WHO.

1) Management of skin itching and rash. If patient starts to itch, this symptom must be excluded from other obvious causes. The treatment with antihistamines should be considered, continue anti-TB treatment, and observe closely. In some cases, the itching will be resolved; in other cases, a rash will develop. In this case, stop the anti-TB drugs and wait for the rash to resolve. If the reaction is severe, the patient may need supportive treatment through steroid treatment (Ministry of Public Health, 2008; WHO, 2004).

2) Management of hepatitis. Most anti-TB drugs can damage the liver. Isoniazid and parazinamide are most commonly responsible; ethambutol is rarely responsible. Hepatitis presents anorexia, jaundice, and, often, liver enlargement. If a drug-induced hepatitis is diagnosed, the anti-TB drugs should be stopped until the jaundice or hepatitis symptoms have resolved and the liver enzymes have returned to

baseline. If liver enzymes cannot be measured, then it is advisable to wait two weeks after the jaundice has disappeared before recommencing anti-TB treatment. Most patients can restart the same anti-TB drugs without hepatitis returning; this can be done if the hepatitis was mild. If the hepatitis has been life-threatening, it is probably safer to use the standard regimen of streptomycin, isoniazid and ethambutol. A severely ill TB patient may die without anti-TB drugs. In this case, treat the patient with two of the least hepatotoxic drugs, streptomycin and ethambutol. When the hepatitis resolves, restart treating the patient with the usual anti-TB treatment (Ministry of Public Health, 2008; WHO, 2004)

2.2.6 Monitoring patients with pulmonary tuberculosis during treatment

It is important to monitor TB patients during treatment in order to assess the progress of individual TB patients and to evaluate NTP performance. Bacteriological monitoring is readily available only for patients with sputum smear-positive PTB. Routine monitoring of treatment response by CXR is unnecessary and wasteful of resources (WHO, 2004). Bacteriological monitoring of patients with sputum smear positive PTB starts at baseline at the time of diagnosis, at the end of the initial phase, in the continuation phase (month five), and during last month of treatment (month six), respectively. The majority of patients have a negative sputum smear at the end of the initial phase. If the sputum smear is still positive at the end of the initial phase, continue initial phase treatment with the same four drugs for four more weeks. Check the sputum smear again at this point it is unlikely still to be positive. Go on the continuation phase even if the sputum smear is still positive after the four extra weeks of initial phase treatment. A positive sputum smear at five months or at any time after five months means treatment failure. A common cause of treatment failure is the failure of the program to ensure patient adherence to treatment (Ministry of Public Health, 2008; WHO, 2004).

2.2.7 Pulmonary tuberculosis treatment outcome

At the end of the treatment course in each individual PTB patient, the treatment outcomes should be recorded as follow (WHO, 2010b):

Cure. Cure is defined as a patient whose sputum smear or culture was positive at the beginning of the treatment but become negative in the last month of treatment and on at least one previous occasion.

Treatment completed. Treatment completed is defined as a patient having completed treatment but does not have a negative sputum smear or culture result in the last month of treatment and on at least one previous occasion. Therefore, the results of normal chest radiography, and signs and symptoms improvement of a patient are used to support the result of treatment completed.

Treatment failure. Treatment failure is defined as a patient whose sputum smear- or culture- is still positive at five months or later during treatment.

Died. Died is defined as a patient dying for any reason during the course of treatment.

Defaulted. Defaulted or treatment interrupted is defined as a patient whose treatment was interrupted for two or more consecutive months.

Transferred out. Transferred out is defined as a patient having been transferred to another recording and reporting unit and whose treatment outcome is unknown.

Treatment success. Treatment success is defined as the sum of patients cured and those who have completed treatment.

2.3 Medication adherence

WHO (2003) attempted to change the term "compliance" by introducing the term "adherence", based on the assumption that adherence implies that the patient has agreed with the prescribed recommendations rather than passively obeying. Adherence focuses more on patient involvement and the patient-provider relationship. The term "adherence" is preferred due to its broader interpretation and understanding of factors that affect a patient's ability to follow treatment recommendations. An important aspect of adherence is recognizing the patient's right to choose whether or not to follow treatment recommendations. Because of these factors, adherence is seen as being more patient-centered than compliance (Vlasnik, Aliotta, & Delor, 2005). However, a concept analysis of adherence concluded that no difference was found between the terms "adherence" and "compliance" as used in healthcare literature (Bissonnette, 2008).

2.3.1 Definition of adherence

Adherence is defined as the extent to which patients follow the instructions they are given for prescribed treatments (Haynes et al., 2008). The prescribed treatments include taking medication, following a diet or exercise, and/or executing lifestyle changes (Rand, 1993; Robinson et al., 2008). In addition, adherence is a collaborative effort between health care providers and health care consumers to achieve mutually derived goals of health (Barofsky, 1978; Becker, 1985; Fine et al., 2009). Consumers are active participants in designing treatment regimens or are considered independent for making healthcare or treatment regimen decisions (Becker, 1985; Carpenter, 2005; Robinson et al., 2008; Schlenk, Bernardo, Organist, Klem, & Engberg, 2008), but health care providers continue to determine what constitutes acceptable outcomes of treatment (Barofsky, 1978; Becker, 1985). Adherence is intended to be non-judgmental a statement of fact rather than of blame of the patient, prescriber, or treatment (Haynes et al., 2008). WHO (2004) also defined patient adherence to TB treatment as the patient taking every dose of the recommended treatment regimen.

Additionally, adherence can be viewed in terms of behavior, including not having a prescription filled, forgetting or intentionally not taking a medication, consuming an incorrect amount of a medication, taking a medication at the wrong time, ceasing therapy too soon, or continuing therapy after being advised to discontinue (Chisholm, 2002; Johnson, 2002). Most forms of improper medication taking behavior jeopardize health outcomes.

In conclusion, adherence is defined as the patient's behavior to follow all recommended courses of treatment, both in terms of medication and other medical treatments, such as diet or exercise. Medication adherence is defined as the behavior of patients to take medication as regimens that are mutual goals set between patients and healthcare workers. These behaviors include taking all medications for the entire length of time necessary and taking the right medicine, including the right amount of medicine, the right dose, and at the correct time. Hence, this study defined medication adherence as the behavior of taking anti-tuberculosis drugs as regimens that are mutually set goals between patient and nurse or physician. These behaviors include continuously taking all medications for six months, along with taking the right medicine, the right amount of medicine, the right dose, and at the correct time.

2.3.2 Measuring medication adherence

Measuring medication adherence is often difficult because of confusing terminology and the use of different methods of measurement with variable degrees of validity and reliability. The complexity of the problem has prevented the development of a gold standard method of measurement (Vermeire, Hearnshaw, Van Royen, & Denekens, 2001). Regardless, the accurate measurement of medication adherence serves two purposes. First, it is important as a means of motivating patients to continue adherence. Second, it is also important in determining the efficacy of the prescribed treatment (Robinson et al., 2008). The ideal method of measuring medication-taking behavior should be simultaneously unobtrusive (to avoid patient sensitization and maximize cooperation), objective (to produce discrete and reproducible data for each subject), and practical (to maximize portability and minimize cost) (Chisholm, 2002; Rudd, 1979). There are a number of measures of patients' adherence in taking medication, including both direct and indirect methods.

1) Direct methods. Direct methods include directly observed therapy, measurement of the level of medicine or its metabolite in blood or urine, and measurement of the biologic marker (added to the drug formulation) in blood or urine.

1.1) Directly observed therapy. In this method, patients are directly observed daily that every dose of the treatment regimen is taken and ingested (WHO, 2004). Direct approaches are most accurate. On the other hand, they are expensive, a burden to the health care providers, and are susceptible to distortion by patients. Patients can hide pills in the mouth and then discard them; impractical for routine use due to limited budget and staff (Osterberg & Blaschke, 2005). Focussing on TB patients, DOT is considered disrespectful by some patients. Some Thai TB patients refused DOT by healthcare worker or community member because of its stigma (Phokaew et al., 2001).

1.2) Measurement of the level of medicine or its metabolite in blood or urine. Blood-drug and urine-drug measurements are objective and quantitative. However, they are often expensive and inconvenient; there are a limited range of drugs that can be measured. Additionally, they may not account for the variability of pharmacokinetic factors of medications and individuals, laboratory error is possible, and patients may increase medication use prior to measurement thereby giving the false impression of proper medication adherence (Chisholm, 2002; Osterberg & Blaschke, 2005; Robinson et al., 2008).

1.3) Measurement of the biologic marker in blood or urine. Non-toxic biological markers can be added to medications and their presence in blood or urine can provide evidence that a patient recently received a dose of the medication under examination. This method is objective; in clinical trials, can also be used to measure placebos. However, it requires expensive quantitative assays, collection of bodily fluids, and the findings are influenced by a variety of individual factors including diet, absorption and rate of excretion (Osterberg & Blaschke, 2005; WHO, 2003).

2) Indirect methods. Indirect methods include patient questionnaires or self-reporting, pill counts, rates of prescription refills, electronic medication monitors, and assessment of the patient's clinical response.

2.1) Patient questionnaires or self-reporting. This method is to ask patients for their subjective ratings of adherence behavior. The method is easy to use; simple; inexpensive; provide immediate feedback; and is generally perceived by patients as the health care provider exhibiting a caring attitude for patients (Chisholm, 2002; Osterberg & Blaschke, 2005; Robinson et al., 2008; Vermeire et al., 2001). The most useful method in the clinical setting is patient questionnaires or self-reporting. However, the analysis of patients' subjective reports has been problematic. Patients who reveal they have not followed treatment advice tend to describe their behavior accurately, whereas patients who deny their failure to follow recommendations report their behavior inaccurately (WHO, 2003). Questioning the patient can be susceptible to misrepresentation and tends to result in the health care provider's over- or underestimating the patient's adherence. Additionally, susceptible to error with increases in time between visits and results are easily distorted by the patients (Osterberg & Blaschke, 2005; WHO, 2003).

2.2) Pill counts. The most common method used to measure adherence, other than patient questioning, has been pill counts (counting the number of pills that remain in the patient's medication bottles or packages). Although the simplicity and empiric nature of this method are attractive to investigators, the method is subject to many problems. Patients can switch medicines between bottles and may discard pills before visits in order to appear to be following the regimen. For these reasons, pill counts should not be a good measure of adherence. In addition, this method provides no important information on other aspects of taking medications, such as timing of dosage and patterns of missed dosages. Both of which may be important in determining clinical outcomes (Osterberg & Blaschke, 2005; WHO, 2003).

2.3) Rates of prescription refills. Pharmacy databases can be used to check when prescriptions are initially filled, refilled over time, and prematurely discontinued. One problem with this approach is that obtaining the medicine does not ensure its use. Also, such information can be incomplete because patients may use more than one pharmacy or data may not be routinely captured. This method requires a closed pharmacy system (Osterberg & Blaschke, 2005; WHO, 2003).

2.4) Electronic medication monitors. A recent innovation is the electronic monitoring device (Medication Event Monitoring System: MEMS) which records the time and date when a medication container was opened, thus better describing the way patients take their medications. Unfortunately, the expense of these devices precludes their widespread use. Additionally, this method requires return visits and downloading data from medication containers and do not indicate whether patient actually ingested the correct drug or correct dose. Patients may open a container and not take the medication, take the wrong amount of medication, or invalidate the data by placing the medication into another container or taking multiple doses out of the container at the same time (Chisholm, 2002; Osterberg & Blaschke, 2005; WHO, 2003). A comparison study of multiple measures of adherence to HIV protease inhibitors showed that adherence underestimated by MEMS and overestimated by pill count and interview (Liu et al., 2001).

2.5) Assessment of the patient’s clinical response. This method is simple and generally easy to perform. However, factors other than medication adherence can affect clinical response (Osterberg & Blaschke, 2005). Medication adherence among PTB patients may be measured using clinical response. The clinical response in the short-term used to measure TB medication adherence is sputum conversion at the end of initial phase (2^{nd} or 3^{rd} month), whereas the clinical response in the long-term is success of treatment measured at the end of treatment, which is a pragmatic, albeit a proxy indicator (Urquhart, 1996; WHO, 2003).

In conclusion, no single method of medication adherence measurement is without limitations, and no one method is superior in all aspects to another. A multi-method approach that combines feasible self-reporting and reasonable objective measures is the current state-of-the-art in measurement of medication adherence (WHO, 2003). Additionally, using at least two different adherence measurement methods, each assessed at multiple times, is recommended to derive reliable and valid measurements of medication adherence, which is predictive of biological outcomes (Llabre et al., 2006). Therefore, the combined methods of self-reporting and assessment of the patient’s clinical response, which measures medication adherence at multiple times were applied for this study.

2.3.3 Situation of medication adherence among pulmonary tuberculosis patients

Approximately half of the TB patients do not complete the treatment course under routine practice conditions (Kruk et al., 2008; Menzies et al., 2008). Focusing on newly diagnosed PTB with sputum smear-positive patients; in Russia, 15.6% of the patients missed more than 20% of the prescribed doses during the treatment period (Gelmanova et al., 2007); in southern Ethiopia, 20% missed drug treatment for more than eight consecutive weeks (Shargie & Lindtjorn, 2007); in Nepal, 25.21% missed drug treatment for more than seven consecutive days (Bam et al., 2006); in the Syrian Arab Republic, 30% missed drug treatment for at least one day (Bashour & Mamaree, 2003); and in South Africa, 40.44% missed drug treatment for more than two consecutive weeks (Peltzer, Onya, Seoka, Tladi, & Malema, 2002). In Thailand, non-medication adherence rates vary widely (11-60%) due to the difference in definition and measurement. Approximately 23% missed drug treatment for less than two consecutive weeks, 11% missed drug treatment greater than two consecutive weeks (Lertmaharit et al., 2005), 28.74-33.82% missed drug treatment more than two consecutive months (Ariyothai, Kladphuang, Thanasomboon, & Kongsamsri, 2005; Kladphuang, Limpasaichon, & Boonpendetch, 1995), and 60% had poor or average levels of drugs compliance (Chatwiriyacharoen, 2003).

Medication adherence among TB patients has been linked to the length and complexity of treatment, as well as to the fact that most patients felt markedly better after the first or second month of treatment (Bam et al., 2006; Jaiswal et al., 2003; Shargie & Lindtjorn, 2007). Thus, there is a perception that a substantial proportion of patients leave treatment in the early phases. A systematic review of 14 studies, to assess the timing of default from TB treatment, indicated that the majority of default occurred after the two-month intensive phase (Kruk et al., 2008). Additionally, 63% of new PTB patients who defaulted, along with 36% of those successfully treated, had interrupted treatment during the intensive phase, while 30% of those who defaulted and 45% of those with a successful outcome had interrupted treatment during the continuation phase. The length of treatment interruptions was 1-125 days during the intensive phase and 1-127 days during the continuation phase among patients with all outcomes (Jakubowiak, Bogorodskaya, Borisov, Danilova, & Kourbatova, 2009). Similarly, a study in Thailand found that TB defaulters were mostly (71.61%) found in the first two months of the incentive phase; the proportion of returning defaulters after being followed up on was only 24.75%, and 80% came back within two to three months after defaulting (Kladphuang et al., 1995).

2.3.4 Effect of medication adherence on treatment success

Medication adherence is a key factor in the treatment success of TB patients. The premature interruption of treatment presents a problem for patients, their families, and those who care for them. Medication adherence is a critical determinant of successful TB control; poor adherence may result in treatment failures, as 13.9% of defaulted new PTB patients became an outcome failure (Jakubowiak et al., 2009). A study by Arkaravichien et al. (2003) found that drug omission for upwards of four days caused a significant reduction in the cure rate. Non-adherence to TB treatment leads to serious results such delayed sputum conversion and higher relapse rates; patients who took treatment irregularly were two times more likely to have a relapse than adherent patients (OR=2.5) (Thomas et al., 2005), or develop MDR that is untreatable and fatal in 50% of cases (Breathnach et al., 1998; Espinal et al., 2000; Grzemska, 2009).

Successful TB treatment is heavily dependent on effective treatment of patients, requiring adherence throughout the full course of treatment (Blanc & Martinez, 2007). Bashour and Mamaree (2003) reported that the significant risk factors for a negative treatment outcome among newly diagnosed sputum smear-positive PTB patients were non-adherence with treatment during the initial and continuation phases (RR=2.6 and 10.8, respectively). Similarly, one study in Thailand found that the prediction factors for successful TB treatment among new sputum smear-positive PTB patients were the regular intake of medication as prescribed and regimented, continuing to take medication while understanding that the disease was cured, and not forgetting to take medication (OR= 7.44, 19.46, and 18.60, respectively) (Tipaht, 2008). In addition, the logistic regression analysis indicated that the new Thai TB patients who did not strictly comply with standard treatment regimens were more likely to remain infectious, compared to those who fully complied (OR=184.5) (Phuangngernmak, 2001). These results were supported by Chatwiriyachareon's (2003) finding that new PTB patients who had poor or average levels of treatment compliance were more often uncured than those who had a good level of treatment compliance (OR=6.30).

2.3.5 Factors influencing medication adherence

There are multifaceted factors linked to medication adherence. The factors influencing medication adherence are not only influenced by patient-level factors but also by factors at the micro-(provider and social support), meso-(healthcare organization), and macro-(health policy) levels (Berben, Dobbels, Engberg, Hill, & De Geest, 2012). Patient-related factors are organized in intentional and unintentional factors. Intentional non-adherence is an underlying assumption that patients undertake an active, reasoned decision-making process in relation to following or disregarding professional advice. Unintentional non-adherence is the result of a passive process which is less strongly associated with individuals' beliefs and cognitions than factors related to intentional non-adherence (Lehane & McCarthy, 2007; Lowry, Dudley, Oddone, & Bosworth, 2005). Factors influencing medication adherence among newly diagnosed PTB patients can be organized following two domains, patient-related factors and outside factors. Details of each factor are described as follow:

1) Patient-related factors. The important patient-related factors which influence medication adherence among newly diagnosed PTB patients include cognitive function, psychological and emotional characteristics, underlying illness condition, and substance abuse.

1.1) Cognitive function. Accurate medication adherence has a number of cognitive components including comprehension of medication instructions, organization of the individual medication instruction into a medication plan and temporal sequence that integrates multiple medications and doses, retention of the medication plan and remembering to take the medication at the planned time (Reynolds, 2003). Forgetfulness has been repeatedly reported as a factor interfering with anti-TB drugs adherence (Kowatanakul et al., 2001; Nithakorn, 1999; Tipaht, 2008; Wintachai, 1995). The reasons quoted for non-medication adherence among the PTB patients included 35.6% not being told to take treatment regularly (Bam et al., 2006), 25.4-28.6% feeling better and misunderstanding that the disease was cured (Bam et al., 2006; Wattanatorn, 2002), 21.7% forgetting to take medicine (Tipaht, 2008), and 21.4% having conditions that did not improve (Wattanatorn, 2002). Knowledge about TB and its treatment had an independent effect on improving adherence among the PTB patients (OR=1.32) (Bam et al., 2006). In addition, Thai PTB patients who perceived susceptibility, severity, benefits, and motivation had significant positive correlations with medication compliance in terms of taking the right dose, regularly, and at the right time (Duangkaew, 1995; Meesattayanan, 1991).

1.2) Psychological and emotional characteristics. Psychological and emotional characteristics of PTB patients were strongly linked to treatment non-adherence. A large proportion of non-adherent patients characterized their mood as generally being unstable or bad (Jakubowiak et al., 2008). The pessimistic emotional state of PTB patients may also negatively affect both patients' attitudes toward treatment and the quality of communication between patients and medical staff, thus contributing to patients' non-adherence. Altered mental states of some PTB patients caused by substance abuse, depression, and/or psychological stress may also play a role in their adherence behavior. A multivariate analysis found that depression is a factor related to PTB treatment adherence (OR=1.83) (Punta, 2008).

1.3) Underlying illness conditions. Underlying chronic illness conditions among PTB patients were significantly associated with non-adherence, including co-morbid conditions associated with side-effects (Gelmanova et al., 2007) and HIV infection (Chindasub, 2007; Kanchanapangka, 2002; Pablos-Mendez et al., 1997). A history of previous treatment among TB patients was associated with higher default rates (OR=2.8) (Santha et al., 2002) and treatment completion (OR=0.85) (Wang & Shen, 2009). The studies by Jakubowiak, Bogorodskaya, Borisov, Danilova, and Kourbatova (2007) and Dodor (2004) found that patients with smear-positive sputum had significantly higher default rates than those who had smear-negative sputum. This may be the effect of faster improvement in health conditions among smear-positive patients. Improvements in health may be mistaken by patients to mean cure, leading to default from treatment. However, this finding was inconsistent with the study by Wang and Shen (2009), which found that PTB patients who had smear-positive sputum had higher treatment completion rate than those who had smear-negative sputum (OR=2.08).

1.4) Substance abuse. In a multivariate model, any substance abuse was a factor that was strongly associated with non-adherence (OR=7.30); substance abuse was also strongly associated with default, with an odds ratio of 11.20 among PTB patients (Gelmanova et al., 2007). Similarly, a study in South Africa found that higher default rates were significantly associated with alcoholism among PTB patients (OR= 2.2, p<.01) (Peltzer et al., 2002). These results were supported by the study of Tipaht (2008) in Thailand, who found that PTB patients who abstained from drinking alcohol and smoking during TB treatment were 19.28 and 19.62 times, respectively, more likely to have success of PTB treatment.

2) Outside factors. The important outside factors which influence medication adherence among newly diagnosed PTB patients include supportive relationships between the health provider and the patient, regimen complexity, pattern of health care delivery, and economic and structure factors.

2.1) Supportive relationships between the health provider and the patient. Patient satisfaction with their main provider of health care is considered to be an important determinant of adherence (Lewin, Skea, Entwistle, Zwarenstein, & Dick, 2009). Aspects of the patient provider relationship including trust, consistency and continued interaction have been identified as being particularly important factor influencing adherence to treatment. In addition, patient adherence to medications has been found to be enhanced when providers give clear explanations and provide full disclosure of potential adverse events, as well as encouragement, reassurance and support (Reynolds, 2003). A study in South Africa by Peltzer et al. (2002) among new PTB patients with smear-positive sputum found that high quality health practitioner-patient interactions were significantly associated with more compliant behaviors. Similarly, a study in Brazil found that the strongest predictor of defaulting from TB treatment was the patient not feeling comfortable with his/her doctor (Salles et al., 2004). A multivariate logistic regression analysis indicated that poor-grade communication (OR=11.2) and fair-grade communication (OR=2.7) between the PTB patients and dispensers were significantly associated with non-adherence (Mishra, Hansen, Sabroe, & Kafle, 2006).

2.2) Regimen complexity. Tuberculosis drugs are usually taken daily. The number of tablets that need to be taken, as well as their toxicity and other side-effects associated with their use, may act as a deterrent to continuing treatment (WHO, 2003). Approximately, 10-35.7% of non-medication adherence PTB patients quoted that having an adverse drug reaction (Bam et al., 2006; Burakorn, 2004; Tipaht, 2008; Wattanatorn, 2002). A study in Hong Kong found that treatment side effects were a risk factor for defaulting from anti-TB treatment (OR=13.30) (Chang, Leung, & Tam, 2004). Similarly, a study in China found that adverse reaction to anti-TB drugs was significantly associated with treatment completion rate (OR=0.47) (Wang & Shen, 2009) and a study by Tekle, Mariam, and Ali (2002) indicated that adverse reaction to anti-TB drugs was significantly associated with defaulting (OR=4.21). Additionally, some patients were not satisfied with taking medication because of the large number of medicine tablets to take each time (Kowatanakul et al., 2001).

2.3) Pattern of health care delivery. The cure for TB relies on the patient receiving a full, uninterrupted course of treatment, which can only be achieved if the patient and the health service work together. A system needs to be in place to trace patients who miss their appointments for treatment. The best success will be achieved through the use of flexible, innovative and individualized approaches in the health service system. The treatment and care provided to the patient in the intensive phase will inevitably have an impact on his or her willingness to attend in the continuous phase. The organization of clinical services including availability of expertise, links with patient support systems, and flexibility in the hours of operation also affects adherence to treatment (Williams et al., 2008a; 2008b). Availability of daily health education has a large independent effect on improving adherence among new smear-positive PTB patients (OR=6.27) (Bam et al., 2006). A study in Thailand by Tipaht (2008) found that the PTB patients with high satisfaction in their service system were 8.62 times more likely to have successful TB treatment. In addition, a study in Southern Ethiopia found that a walking distance to the nearest treatment center of over 2 hours and public transportation to get medicine were associated with default from TB treatment (HR=2.97 and HR=1.59, respectively) (Shargie & Lindtjorn, 2007). Approximately, 28.4% of non-medication adherence PTB patients quoted that the TB clinic was too far from home (Shargie & Lindtjorn, 2007), 16% being unable to dispense medicine at the appropriate time (Arkaravichien et al., 2003) and 1.4-3.4% experienced dissatisfaction with the care provided (Bam et al., 2006; Shargie & Lindtjorn, 2007)

2.4) Economic and structural factors. Tuberculosis usually affects people who are hard to reach, such as the homeless, the unemployed, and the poor. Lack of effective social support networks and unstable living circumstances are additional factors that create an unfavorable environment for ensuring adherence to treatment (WHO, 2003). Social support may enhance adherence both because the presence of another individual helps to shape an illness representation more consonant with a desire to adhere and because it offers a reminder function. Thus social support may be a form of cognitive collaboration that provides event-based prospective cues to take medication. Further, ongoing social support may help patients overcome negative illness-related events that interfere with adherence (Reynolds, 2003). Tipaht's (2008) study among new smear-positive PTB patients in Thailand using multiple logistic analyses found that those who were unemployed with workplace commutation or who had low travel costs to the TB clinic were 6.0 and 7.01 times, respectively, more likely to have successful TB treatment (p=.001 and 0.009, respectively). Additionally, this study showed that DOT by supporters increased success of TB treatment (OR=5, p= .003). Similarly, a study by Ariyothai et al. (2005) among Thai newly smear-positive PTB patients found that the factors significantly associated with default on TB treatment were unemployment (OR=3.77, p=.01) and debt for treatment or transportation costs (OR=2.20, p=.02). In addition, the patients who lack of income had more defaulting on TB treatment than those who had monthly income ≥ 5,000 bath (OR=3.64, p=.006). These results were supported by a study in Russian regions among new PTB patients, using multivariate analysis, that risk factors associated with default outcome included unemployment (OR=4.44, p<.001) and homelessness (OR=3.49, p=.01). Additionally, this study also found that social support reduced the default outcome among these patients (OR=0.13, p<.001) (Jakubowiak et al., 2007).

In conclusion, adherence to TB treatment is a complex and dynamic phenomenon with a wide range of factors impacting medication-taking behavior. However, the most important factors are patient-related factors; most of them cannot be changed. Cognitive function is a patient-related factor, which can improve and predict accurate medication adherence. Therefore, incorporating the appropriate outside factors to enhance or facilitate cognitive function and improve the inner cognitive process of PTB patients is needed for enhancing medication adherence behavior.

2.4 Improving medication adherence

There are several effective interventions used to enhance medication adherence among newly diagnosed PTB patients. The interventions enhancing medication adherence can be organized following four domains; directly observed treatment, educational intervention, behavioral intervention, and combined intervention. Details of each intervention are described as follow:

2.4.1 Directly observed treatment

Directly observed treatment is defined as ingestion of medication where a healthcare worker, a community member, or a family member who was trained to do this, directly supervises or watches the patient swallow their tablets. DOT is one certain way to ensure patient adherence to TB treatment recommended by WHO (WHO, 2004). Recently, a systematic review by Suwannakeeree and Picheansathian (2014) indicated the beneficial effects of DOT in increasing medication adherence in terms of cure rate and success rate. In addition, a study in USA demonstrated that tuberculosis patients treated by DOT also had lower rates of tuberculosis-related mortality (Jasmer et al., 2004). This finding is similar to a review conducted by Parent (1999), which indicated that DOT was effective in promoting adherence to and completion of TB treatment. Systematic review evidence in USA and Canada demonstrated that no single intervention has been consistently effective in improving adherence to treatment for latent tuberculosis infection, including DOT (Hirsch-Moverman et al., 2008). Moreover, a second review by Volmink and Garner (2007) found that no assurance that the routine use of DOT in low- and middle-income countries improves cure or treatment completion in people requiring treatment for clinically active tuberculosis or prevention of active disease.

A reviews conducted by Volmink and Garner (2007) indicated that there is no evidence showing that one form of direct observation is better than another. Nevertheless, two RCTs (Kamolratanakul et al., 1999; Newell, Baral, Pande, Bam, & Malla, 2006) found that the success rates of PTB patients receiving DOT by a family member were significantly higher than that by a community member. In addition, the findings of three other studies (Akkslip, Rasmithat, Maher, & Sawert, 1999; Newell et al., 2006; Zwarenstein, Schoeman, Vandule, Lombard, & Tatley, 2000) showed that both family member DOT and/or community DOT strategies could reach the WHO target for treatment success. This strategy may be suitable for hard-to-access areas where tuberculosis patients are becoming increasingly overloaded and in areas where there are many different health programmes requiring healthcare workers' effort and time. Providing PTB patients with a choice of a DOT supporter who is convenient and accessible may have contributed to the comparatively favourable results in improving adherence to treatment. A study of Zvavamwe and Ehlers (2009) found that a family member was the most convenient, acceptable and accessible DOT supervisor for 72.8% of the participants and indicated that the major advantage of this strategy included the ability to continue with one's daily activities during treatment and the saving of time and money. Facilitation of the supporter's role in DOT which involved training by healthcare workers, as well as close supervision through frequent home visits by health facility staff are effective strategies to support medication adherence among PTB patients (Newell et al., 2006; Zwarenstein et al., 2000).

2.4.2 Educational interventions

Educational interventions are defined as any intervention given with the intent of improving a person's ability to manage his or her disease (Brown, 1990). In order for education interventions to be effective, they should be tailored to the patient's needs and situation. Psycho-educational programs, which are common in clinical practice, are typically ineffective (Zygmunt, Olfson, Boyer, & Mechanic, 2002); education strategies alone are not sufficient for promoting sustained medication adherence behavior (Haynes, Wang, & Goales, 1987; Haynes et al., 2002). Educating patients in concrete problem solving with booster sessions and motivational techniques are useful in increasing medication adherence in schizophrenics (Zygmunt et al., 2002). Additionally, hypertension education showed a large effect on knowledge (effect size = 0.98) within two weeks after the treatment, but declined to a medium effect (effect size = 0.46) when measured at four weeks or more after the treatment (Devine & Reifschneider, 1995). These results were supported by Pradier et al.'s finding (2003) that educational interventions that included intensive multi-session counseling showed a significant effectiveness for treatment adherence to highly active antiretroviral therapy. Dolder, Lacro, Leckband, and Jeste (2003) also found that interventions reporting an improvement in adherence to antipsychotic medication had a median of eight sessions, while interventions without gains in adherence had a median of three sessions. These results were supported by a systematic review among chronic medical conditions, which found that six sessions of informational interventions that provided educational counseling over a few sessions and addressed self-care issues improved medication adherence (Kripalani et al., 2007).

There are three theoretical approaches underlying different forms of educational interventions to improve a person's ability to manage his or her disease: communication perspective, cognitive perspective, and self-regulation perspective (Leventhal & Gameron, 1987; Van Dulmen et al., 2007). A review study of Van Dulmen et al. (2007)

has not clarified whether the three theoretical approaches are equally powerful, or powerless, in improving adherence. The communication perspective emphasizes conveying a message by trusted and affective components and concerns aspects of the provider-patient relationship such as empathy, friendliness, attentiveness, care, concern, and support. The patients should be informed adequately which means that patients understand and retain the message. Additional conditions are required for the communication to be effective in changing patient's attitudes and motivations to adhere to the treatment regimen. Patients should believe in the message as well as the messenger. They should accept the information regarding the treatment regimen and the benefits of adherence behavior. Additional information can also facilitate behavioral change, such as information about ways to incorporate the behavior into the patient's daily routines. The cognitive perspective concentrates on changing patients' dysfunctional ideas and perceptions or beliefs as motivating factors for behavior. Motivation is also determined by perceived social or group norms, and the social consequences regarding the behavior and its acceptability. The self-regulation perspective emphasizes that patients themselves are active problem solvers. Patients try to close the gap between their current health status and the goal (Van Dulmen et al., 2007). In the self-regulation perspective, behavior is considerably influenced by patients' subjective experiences, emotions and social environments (Bandura, 1991).

Educational intervention is the most important strategy to improve cognitive function of patients, which is a strong factor influencing TB medication adherence. There are different methods and theoretical approaches underlying effective educational interventions to improve patients' ability to adhere to medication regimens. However, interventions should be tailored to the patient's needs and situations. Education showed a large effect size on knowledge; however, its effect declined with time. Therefore, effective educational interventions need boosters or multiple sessions and should be combined with other strategies because education strategies alone are not sufficient in promoting sustained medication adherence behavior over a long period of time.

2.4.3 Behavioral interventions

Behavioral interventions are strategies designed to influence behavior through shaping, reminding, or rewarding desired behavior. These interventions include simplification of dosage and packaging, reminder, financial incentives, and late patient tracers.

1) Simplification of dosage and packaging. The most common and effective forms of behavioral intervention to enhance medication adherence were simplification of dosage and packaging (Haynes et al., 2008; Kripalani et al., 2007; Van Dulmen et al., 2007). These interventions are aimed either at reducing the number of doses per day or at reducing the number of different drugs in the regimen. Adherence appeared to decline as the number of daily doses increased. A systematic review by Kripalani et al. (2007) among chronic medical conditions showed that dosage simplification demonstrated an improvement in long-term medication adherence: whether switching from two doses to one dose per day or from four to two, the effect sizes were 0.89-1.20. Similarly, a systematic review by Buring, Winner, Hatton, and Doering (1999) on adherence to antibiotic regimens for peptic ulcers showed that adherence rates were higher with regimens containing three or fewer doses per day, than those with four to six doses per day ($p=0.001$), seven to eleven ($p=0.009$), or 12 or more ($p<0.0001$). These results were supported by a systematic review among various disorders indicated that adherence to one dose was 79%, two doses 69%, three doses 65%, and four doses 51% (Claxton, Cramer, & Pierce, 2001).

Additionally, a meta-analysis that included patients with chronic illnesses such as TB demonstrated that fixed-dose combinations drugs resulted in a 26% decrease in the risk of non-compliance compared with a free-drug component regimen (Bangalore et al., 2007). These results were supported by a systematic review involving treatment for chronic illness conditions including TB patients, which found that a fixed-dose combination of pills and unit-of-use packaging (pre-packaging of medications for each dose) are likely to improve medication adherence in a range of settings (Connor et al., 2004). Focusing on TB patients, WHO suggested that fixed-dose combination drugs should be recommended wherever they are available when direct observation is not fully guaranteed (WHO, 2004). Medication reminder packaging, which incorporates a date or time for medication to be taken in the packaging, can act as a reminder system to improve adherence. A systematic review among various disorders in which patients were administered medication by themselves or a family member or supporter for an individual (no active participation of a healthcare professional), demonstrated that packaging of medications with reminder systems for the day and/or time of the week showed a significant increase in the percentage of pills taken (Heneghan, Glasziou, & Perera, 2008).

2) Reminder. Mailed reminders and telephone prompts were consistently useful for reducing the number of missed clinical appointments for the supervised administration of medical care. A review study indicated that mailed reminders and telephone calls a few days prior to the appointment to remind patients of the pending appointment were consistently useful in improving patient compliance (Macharia, Leon, Rowe, Stephenson, & Haynes, 1992). Similarly, a systematic review of 153 studies among chronic disease patients indicated that written or mailed reminders (effect size = 0.21) were as effective as telephone reminders (effect size = 0.19) in keeping appointments (Roter et al., 1998). These results were supported by a systematic review of Van Eijken, Tsang, Wensing, De Smet, and Grol (2003) who found that a telephone-linked reminder system increased medication adherence among elderly people.

Focusing on TB patients, a systematic review of five RCTs indicated that reminder cards sent to patients who defaulted on treatment was an effective strategy to promote adherence to TB treatment (Volmink & Garner, 1997). Similarly, a systematic review by Liu et al. (2008) indicated that both reminder systems and late patient tracers by home visits and letters, which routinely reminded patients to keep an appointment, and actions taken when patients failed to keep an appointment showed benefits of the intervention in increasing adherence to TB treatment. Recently, Mahmud, Rodriguez and Nesbit (2010) reported that mobile health interventions conducted by healthcare workers supplied with cell phones to bridge communicative and geographic barriers had benefits for TB patient adherence, appointment reminders, and physician queries. At the end of the study, the hospital saved approximately 2,048 hours of worker time, $2,750 net ($3,000 in fuel saving minus $250 in operational cost), and double the capacity of the TB treatment program. The advantages of mobile phones for TB patients and nurses were that they provided access to each other for timely communications and that the communications were empowering for both. Patients also indicated they now felt someone cared for them, and they felt more optimistic for being cured. Nurses indicated that mobile phones provided a mechanism for providing a higher level of care and timely, proactive interventions to address real-time needs such as medication side effects or counselling against compliance default (Hoffman et al., 2010).

3) Financial incentives. Financial incentives including cash, vouchers, lottery tickets, gifts, food, clothing, books, or transportation, can improve patient adherence. The reason for using incentives is to motivate the patients to complete treatment. On the other hand, financial incentives may have negative consequences and may affect other aspects of the patient's behavior. Patients may also feel that the health care worker is trying to bribe them into accepting treatment. This is more likely to happen if the health care worker has not gained the patient's trust, and has offered incentives before getting to know him or her. When incentives are used with an attitude of caring and concern for the patient, the patient will be less inclined question the health care worker's motives. However, incentives are not a substitute for a high-quality relationship with patients based on trust, effective communication, and mutual respect (Centers for Disease Control and Prevention: CDC, 1999).

A systematic review (Giuffrida & Torgerson, 1997) showed that various disorder patients who were paid for adherence in cash, food, gifts or vouchers improved adherence, although it remained unknown whether a cash payment or payment in kind was more effective. The incentives in this study ranged from relatively small amount of money ($5) up to gifts worth nearly $1,000. Focusing on tuberculosis patients, a study by Pilote et al. (1996) found that a monetary incentive of a $5 payment to homeless people was more significant effective in improving adherence than peer health support (OR=1.8) and usual care (OR=4.7). Additionally, a systematic review by Parent (1999) showed that the effect size of incentives and the education services combined with incentives in increasing TB treatment adherence were 3.7 and 2, respectively. These incentive components consisted of money, food, clothing, books, and transportation. Similarly, the result of a systematic review from 1966 to 1996 indicated that monetary incentives improved adherence to tuberculosis treatment (Volmink & Garner, 1997). On the other hand, a RCT by Martins, Morris, and Kelly (2009) indicated that food incentives had no significant beneficial or harmful impact on the completion of treatment among newly diagnosed PTB patients but did lead to improved weight gain at the end of treatment.

4) Late patient tracers. Late patient tracers are undertaken when patients fail to keep an appointment, generally to attempt to make contact with the patient, sometimes to find out why they did not attend, and to help patients understand the need to attend treatment and overcome barriers to attending for treatment. A systematic review by Liu et al. (2008) reported that late patient tracers showed benefits of the intervention in increasing adherence to tuberculosis treatment and suggested that late patient tracers may be particularly effective when used in combination with additional education or information for patients. This result was supported by the study of Thomson, Cheti, and Reid (2011) which reported that an active defaulter tracing system is feasible in a resource poor setting, solicits feedback from patients, retains a mobile population of patients in care, and reduces loss to follow-up among TB patients. Active tracing serves several functions; as a primary prevention tool and intervening soon after a patient misses an appointment but before they may default entirely. It also contributes to improve care and treatment of TB patients, mitigate default rates, and improves treatment outcomes (Bronner et al., 2012). Because this system is patient-centered, information gathered during tracing activities enables clinic staff to modify an individual patient's treatment or social support plan immediately based-on their unique circumstances and mitigate barriers to clinic attendance (Thomson et al., 2011).

In conclusion, there are several behavioral interventions that affect medication adherence. The most effective strategies are simplification of dosage and packaging. Telephone-linked reminders, monitoring, and counseling have a beneficial impact on both patients and health care workers in terms of on keeping appointments as well as improving medication adherence and clinical outcomes. Providing incentives for the patients have both positive and negative consequences on patients and health service, they are not a substitute for a high-quality relationship with patients. Late patient tracers are feasible to reduce loss to follow-up and benefit in increasing adherence to treatment. Therefore, effective behavioral interventions for enhancing medication adherence should be combined with other strategies, especially educational interventions.

2.4.4 Combined intervention

Multi-component intervention approaches are more effective in enhancing long-term medication adherence (Haynes, 2002; Roter et al., 1998; Wright, 2000). The strategies are designed to improve medication adherence behavior, most usually combining behavioral with cognitive or educational interventions. A systematic review among chronic medical conditions found that successful behavioral interventions to enhance medication adherence were based on monitoring and feedback, and that the most successful combined interventions included various elements, such as self-management plans, reinforcement, and occasional rewards (Kripalani et al., 2007). These results are supported by a systemic review of Haynes's finding (Haynes et al., 2008) that indicated the combined interventions that could improve long-term medication adherence and health outcomes include more convenient care, information, counseling, reminders, self-monitoring, reinforcement, family therapy, psychological therapy, mailed communications, crisis intervention, and manual telephone follow-up.

A systematic review by Volmink and Garner (1997) found that a combination of patient education and incentives was an effective strategy to promote adherence to curative or preventive TB treatments. A recent systematic review by Suwannakeeree and Picheansathian (2014) found that there were three effective combined interventions for improving medication adherence and clinical outcomes among newly diagnosed PTB patients including case management with DOT; the intensive triad-model program; and intervention package. Case management with DOT is effective when in-hospital education is combined with DOT during the first two months and one home visit per week. The intensive triad-model program emphasised on roles and interaction of a healthcare provider, a TB patient, and a treatment supporter, is combined with comprehensive health education and home visit once a month. The intervention package is based on improved patient counselling and communication, along with decentralization of treatment, patient choice of their DOT supporter, and reinforcement of TB clinic staffs.

In conclusion, the consensus is that combined intervention is mostly effective for enhancing medication adherence and clinical outcomes. Therefore, the interventions for enhancing medication adherence along course of treatment among newly diagnosed

PTB patients should be the combined interventions because there are multiple factors influencing medication adherence behaviors and several pieces of evidence supporting the idea that combined interventions are more effective than single intervention in enhancing medication adherence and clinical outcomes. However, it is unclear whether such interventions are equally, more or less powerful in improving adherence. Therefore, the interventions should consist of educational and behavioral interventions combined with providing other facilitators tailored to individual patients and their local contexts and circumstances.

2.5 Social cognitive theory

In the social cognitive theory view, people are neither driven by inner forces nor automatically shaped and controlled by external stimuli. Rather, human functioning is explained in terms of a model of triadic reciprocality. In this model of reciprocal determinism, behavior, cognitive and other personal factors, and environmental influences all operate interactively as determinants of each other (Figure 2.1) (Bandura, 1986)

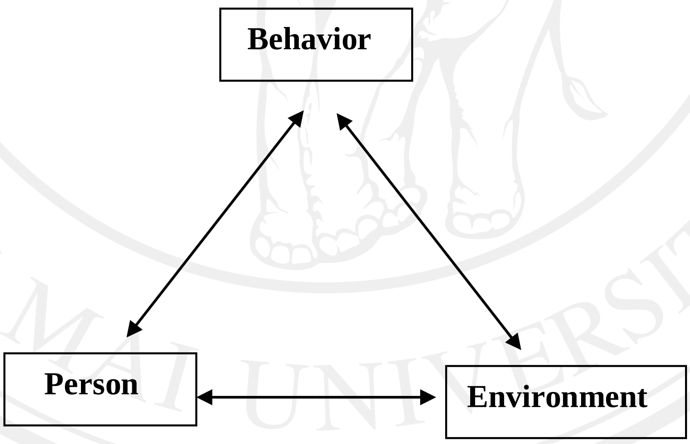

Figure 2.1 The Relations between the Three Classes of Determinants in Triadic Reciprocal Causation.

Note. Adapted from social foundations of thought and action: a social cognitive theory (p. 24), by A. Bandura, 1986, New Jersey: Prentice-Hall.

Bandura (1986) formulated a number of SCT constructs that are important to understand and intervene in health behaviors. These constructs include nature of human, environment, behavioral capability, self-efficacy, self-regulation, and reinforcement.

2.5.1 Nature of human

Human nature is characterized by direct and observational experience into a variety of forms within biological limits. Most patterns of human behavior are organized by individual experience and retained in neural codes, rather than being provided ready-made by inborn programming. The systems for processing, retaining, and using coded information provide the capability to vary characteristics including symbolizing capability, forethought capability, vicarious capability, self-regulatory capability, and self-reflective capability.

1) Symbolizing capability. The remarkable capacity to use symbols provides people with a powerful means of altering and adapting to their environment. Through symbols people process and transform transient experiences into internal models that serve as guides for future action. An advanced cognitive capability coupled with the remarkable flexibility of symbolization enables people to create ideas that transcend their sensory experiences. Through the medium of symbols, they can communicate with others at almost any distance in time and space (Bandura, 1986).

2) Forethought capability. People do not simply react to their immediate environment, nor are they steered by implants from their past. Most of their behavior, being purposive, is regulated by forethought. People anticipate the likely consequences of their perspective actions, they set goals for themselves, and they otherwise plan courses of action for cognized futures. Forethought is translated into action through the aid of self-regulating mechanisms (Bandura, 1986).

3) Vicarious capability. The capability to learn by observation enables people to acquire rules for generating and regulating behavioral patterns without having to form them by trial and error. A person can learn from other people not only by receiving reinforcements from them, but also by observing them. Observational learning occurs when a person watches the actions of another person and the reinforcements that the person receives. In observational learning, the observer does not need to engage in the time-consuming, trial-and-error process in uncertain circumstances. Instead, the

learner discovers rules that account for the behavior of others by observing the behavior and the reinforcements received for their behavior (Bandura, 1986; 1997).

4) Self-regulatory capability. Much of people behavior is motivated and regulated by internal standards and self-evaluative reactions to their own actions. After personal standards have been adopted, discrepancies between a performance and the standard against which it is measured activate evaluative self-reactions, which serve to influence subsequent behavior. Self-directedness is exercised by wielding influence over the external environmental as well as enlisting self-regulatory functions. Thus, by arranging facilitative environmental conditions, requiting cognitive guides, and creating incentives for their own efforts, people make causal contribution to their own motivation and actions. Self-regulatory functions are fashioned from, and occasionally supported by external influences (Bandura, 1986).

5) Self-reflective capability. Self-reflective capability is the capability for reflective self-consciousness. This enables people to analyze their experiences and to think about their own thought processes. By reflecting on their varied experiences and on what they know, they can derive generic knowledge about themselves and the world around them. People not only gain understanding through reflection, they evaluate and alter their own thinking. In verifying thought through self-reflection means, they monitor their ideas, act on them or predict occurrences from them, judge the adequacy of their thoughts from the results, and change them accordingly (Bandura, 1986).

2.5.2 Environment

Environment refers to the objective or physically external factors that can affect a person’s behavior. Social environment include family members, friends, or co-workers. Environment has been increasingly recognized as important in health behavior change (Baranowski, Perry, & Parcel, 2002). It is easier for patients to change a behavior if they perceive the availability of environmental support in the behavior change processes. Environmental support during early periods of behavior change and maintenance increases long-term success (Bandura, 2004).

2.5.3 Behavioral capability

The concept of behavioral capability maintains that if a person needs to perform a particular behavior, he or she must know both what the behavior is or knowledge of the behavior and how to perform it or skill. The concept of behavioral capacity distinguishes between learning and performance, because a task can be learned and not performed. Performance presumes learning (Bandura, 1986; 1997).

2.5.4 Self-efficacy

Self-efficacy is the confidence a person feels about performing a particular activity, including confidence in overcoming the barrier to performing that activity. Bandura (1986; 1997) proposed that self-efficacy is the most important prerequisite for behavior change because it affects both how much effort is invested in a given task and what level of performance is attained. Perceived self-efficacy influences all aspects of behavior, including initiation and cessation. Further perceptions of self-efficacy affect the amount of effort people spend on a task, and the amount of time they will persist at a task while facing obstacles. Self-efficacy is specific to a given situation and does not refer to a personality characteristic or trait. A person’s self-efficacy may vary depending on a specific task and context (Bandura, 1997).

Efficacy beliefs vary on several dimensions, including level, generality, and strength. Firstly, efficacy beliefs differ in different people: if the specific activity is easy to perform and there is no obstacle against performance, a person will have high perceived self-efficacy. Secondly, efficacy beliefs also differ in generality, including the degree of similarity of activities, the modality of capabilities (behavioral, cognitive, and affective), qualitative features of situations, and personal characteristics. Finally, efficacy beliefs vary in strength. People who have a strong belief in their capabilities will persevere in their efforts even if they meet innumerable difficulties and obstacles. Furthermore, concern about results from action, and belief in their capabilities encourages people to perform deliberate actions (Bandura, 1997).

Bandura (1986; 1997) divided self-efficacy into two components: self-efficacy expectation and outcome expectation. Both self-efficacy expectation and outcome expectation are significant factors in predicting health behavior (Maddux & Stanley, 1986). Self-efficacy expectation is one's judgment about his or her individual ability to achieve a task. This component is important in developing an individual's decision to participate in a specific behavior when they believe in their capabilities. Outcome expectations are the anticipated aspects of behavior that Bandura (1977; 1986) called antecedent determinants of behavior. Outcome expectations may play the greatest role in influencing initial motivation and decisions to change a health behavior (Bandura, 1997). A person learns that certain events are likely to occur in response to that person's behavior in a particular situation, and then expects them to occur when the situation recurs. The sources of self-efficacy include four ways (Bandura, 1986; 1997).

1) Mastery experience. Mastery experience refers to achieving mastery over a certain task through personal experience. Mastery experiences gained through personal experience are the strongest sources of self-efficacy since the person has developed and refined their skills through practice. Successful performance will enhance self-efficacy if it is attributed to one's own skill and ability, rather than chance or external or temporary factors.

2) Vicarious experience or modeling. Vicarious experience is a strategy that includes observing another's success. Seeing other people have success similar to one's own can raise an observer's belief that he/she too possesses the capabilities to master comparable activities in a specific behavior (Keller et al., 1999).

3) Verbal persuasion. Verbal persuasion refers to the use of strong verbal encouragement regarding the benefits of the behavior, as well as the progress the individual makes in achieving the behavior. Receiving positive language or verbal persuasion from others increases self-efficacy.

4) Physiological and emotional arousal. Physiological and emotional arousal is the strategy that includes feedback to an individual concerning how he/she is responding to the effects of the behavior. One's physiological and emotional responses provide information feedback. Stress, anxiety, and depression are interpreted as signs of personal physical inefficacy and will weaken one's self-confidence and undermine one's implementation efficacy; conversely, positive physical and emotional feedback enhances perceived self-efficacy (Bandura, 1997).

2.5.5 Self-regulation

Self-regulation refers to self-generated thoughts, feelings, and actions that are planned and cyclically adapted to the attainment of personal goals. Contextually related self-processes, such as self-efficacy, have been shown to be well- suited to explaining variations in personal motivation to self-regulate one's performance (Bandura, 1997). Self-regulation involves three classes of sub-processes: self-observation, self-judgment, and self-reaction. These performance-related sub-processes are assumed to interact with each other in a reciprocal fashion (Bandura, 1986).

Self-regulation is described as cyclical because feedback from prior performance is used to make adjustment during current efforts. Such adjustment is necessary because personal, behavioral, and environmental factors are constantly changing during the course of learning and performance, and must be observed or monitored using three self-oriented feedback loops; behavioral self-regulation, environmental self-regulation, and covert self-regulation. Behavioral self-regulation involves self-observing and strategically adjusting performance processes, such as method of learning, whereas environmental self-regulation refers to observing and adjusting environmental conditions or outcomes. Covert self-regulation involves monitoring and adjusting cognitive and affective states, such as imagery for remembering or relaxing (Zimmerman, 1989). The accuracy and consistency of learners' self-monitoring of these triadic sources of self-control directly influence the effectiveness of their strategic adjustments and the nature of their self-beliefs. Self-regulation processes and accompanying beliefs fall into three cyclical phases: forethought, performance or volitional control, and self-reflection process. Forethought refers to influential processes that precede efforts to act and set the stage for action. Performance or volitional control involves processes that occur during motoric effects and affect attention and action. Self-reflection involves processes that occur after performance efforts and influence a person's response to that experience. These self-reflections, in turn, influence forethought regarding subsequent motoric efforts, thus completing a self-regulatory cycle. The processes of self-regulation are proactive as well as reactively adapted for the attainment of personal goals (Zimmerman, 2000).

Effective self-regulation depends on feeling self-efficacious for using skills to achieve mastery (Bandura, 1986; 1993). Self-efficacy operates during all phases of self-regulation. Skillful self-regulators enter learning situations with specific goals and a strong sense of self-efficacy for attaining them. As they work on tasks, they monitor their performance and compare their attainment with their goals to determine progress. Self-perceptions of progress enhance self-efficacy, motivation, and continued use of effective strategies (Ertmer, Newby, & MacDougall, 1996). During periods of self-reflection, they evaluate their progress and decide whether adaptations in self-regulatory processes are necessary. High self-efficacy for learning in the forethought phase (goals, outcome expectations, and perceived values) becomes realized as self-efficacy for continued progress in the performance phase (self-monitoring, self-perceptions of progress, strategy use and motivation) and self-efficacy for achievement in the self-reflection phase (goals, self-evaluations and adaptation of self-regulatory processes). The latter also sets the stage for modifying goals or setting new ones (Schunk & Ertmer, 2000).

2.5.6 Reinforcement

Positive reinforcement, or reward, is a response to a person's behavior that increases the likelihood that the behavior will be repeated. Negative reinforcement also increases the likelihood of behavior is performed. Social cognitive theory incorporates three types of reinforcement: direct reinforcement (as in operant conditioning), vicarious reinforcement (as in observation learning), and self-reinforcement (as in self-control). Additionally, these types of reinforcement are categorized into external (or extrinsic) and internal (or intrinsic) reinforcement (Lepper & Cordova, 1992). External reinforcement is the occurrence of an event or act that is known to have a predictable reinforcement value. Internal reinforcement is a person's own experience or perception that an event had some value (Baranowski et al., 2002).

2.5.7 The useful intervention based on self-efficacy and self-regulation concepts of social cognitive theory on medication adherence and clinical outcomes

Social cognitive theory is a health behavior theory suggested for driving interventions for increasing long-term adherence to medication or prescribed practice

(Munro et al., 2007; Ruppar, 2010; Sirus et al., 2009). There were several quasi-experimental studies focused on newly diagnosed PTB patients and the interventions developed based on self-efficacy or self-regulation concept. These interventions had significantly increased in patients' knowledge, self-efficacy, outcome expectations, and compliance or adherence behaviors or appointments (Boonpendecha, 2001; Chuldeja, 1997; Dick & Lombard, 1997; Katmanee, 2004; Suksawat, 2002; Tansakul, et al., 2003; Ungcharoensup, 2000), as well as attitudes towards TB treatment, and sputum conversion in the 2nd month of treatment (Tansakul et al., 2003). Moreover, there were some rigorous studies among other chronic illness patients and the interventions developed based on self-efficacy and/or self-regulation concepts. These interventions had significantly improved short- (Barnason et al., 2010; Chen et al., 2010; Smith et al., 2003) and long-term medication adherence (Tuldra et al., 2000; Weber et al., 2004) and clinical outcomes (Barnason et al., 2010; Tuldra et al., 2000).

In conclusion, SCT is a health behavior theory useful for developing interventions to enhance medication adherence behaviors and clinical outcomes among PTB patients and other chronically ill patients. However, no rigorous evidence exists to support the notion that interventions based on SCT improve long-term medication adherence behaviors and clinical outcomes among newly diagnosed PTB patients. Currently, there is some rigorous evidence to support the idea that interventions based on self-efficacy and self-regulation concepts of SCT improve medication adherence behaviors and clinical outcomes among other chronically ill patients. Therefore, modification of the concepts for developing effective interventions to enhance medication adherence along course of treatment and clinical outcomes among newly diagnosed PTB patients is needed to examine and support the rigorous evidence.

2.6 Theoretical framework

Self-efficacy and self-regulation concepts of SCT (Bandura, 1986) are used as the study framework. Within SCT, behavior is depicted as dynamic, depending on aspects of both the environment and the person, all of which influence each other simultaneously. Self-regulation is the continuous process of self-generated thoughts, feelings, and actions that are planned and cyclically adapted to the attainment of personal goals. Self-regulation also encompasses the self-efficacy mechanism, which plays a central role of personal agency by its strong impact on thought, motivation, and action (Bandura, 1991). Self-efficacy is conceptualized as an individual's perception or judgment of one's capabilities to organize and execute the courses of action required to attain a specific health behavior. Self-efficacy operates during all phases of self-regulation, which include goals setting, self-monitoring, and self-reflecting. Therefore, self-efficacy promotes self-regulation capability that is needed for enhancing TB medication adherence throughout the full course of treatment. These continuous processes will directly encourage patients to tailor the problem-solving strategies appropriate to their needs and to increase self-efficacy for self-regulation along the course of the TB treatment, then sustain medication adherence behavior achieving the full course of treatment. In addition, it is easier for patients to change a behavior if they perceive the availability of environmental supports in the behavior change processes.

In order to increase self-efficacy for self-regulation to adhere to medication throughout the full course of treatment among newly PTB patients, strategies to promote participants' perception of the level of confidence in an individual's capability to perform specific actions will be provided. These strategies include putting individuals into a specific environment where they can practice the actual activity; providing knowledge, promoting mastery, using a role model, verbal persuasion, and physiological and emotional arousal for raising specific abilities; and encouraging individuals to set goals, monitor, reflect, and to have incentives during the behavior change and maintenance phases.

The combined interventions of this study were planned to provide a medication adherence enhancement program including two main components. The first component was planned to provide knowledge and activities for enhancing self-efficacy for self-regulation behaviors, including self-efficacy in: 1) goals setting and outcome expectations; 2) monitoring, using strategies to adhere to medication and adapting self-regulation processes; and 3) reflecting and incentive. This component would improve patients' cognitive function, the most important personal factor predicting TB medication adherence. Along with this component, the participants were provided with appropriate environmental components to facilitate and support these behavior changes. This environmental component consists of providing choice of family supporter, and telephone reminder and counseling. These environmental supports are factors strongly related with TB medication adherence.

Newly diagnosed PTB patients who participate in this study were provided with knowledge, activities to raise self-efficacy for self-regulation, and appropriate environmental supports. These components might enhance continuous change processes of medication adherence behaviors (goals setting, monitoring, and reflecting) and sustain throughout the full course of treatment, resulting in increased medication adherence and treatment success (Figure 2.2).

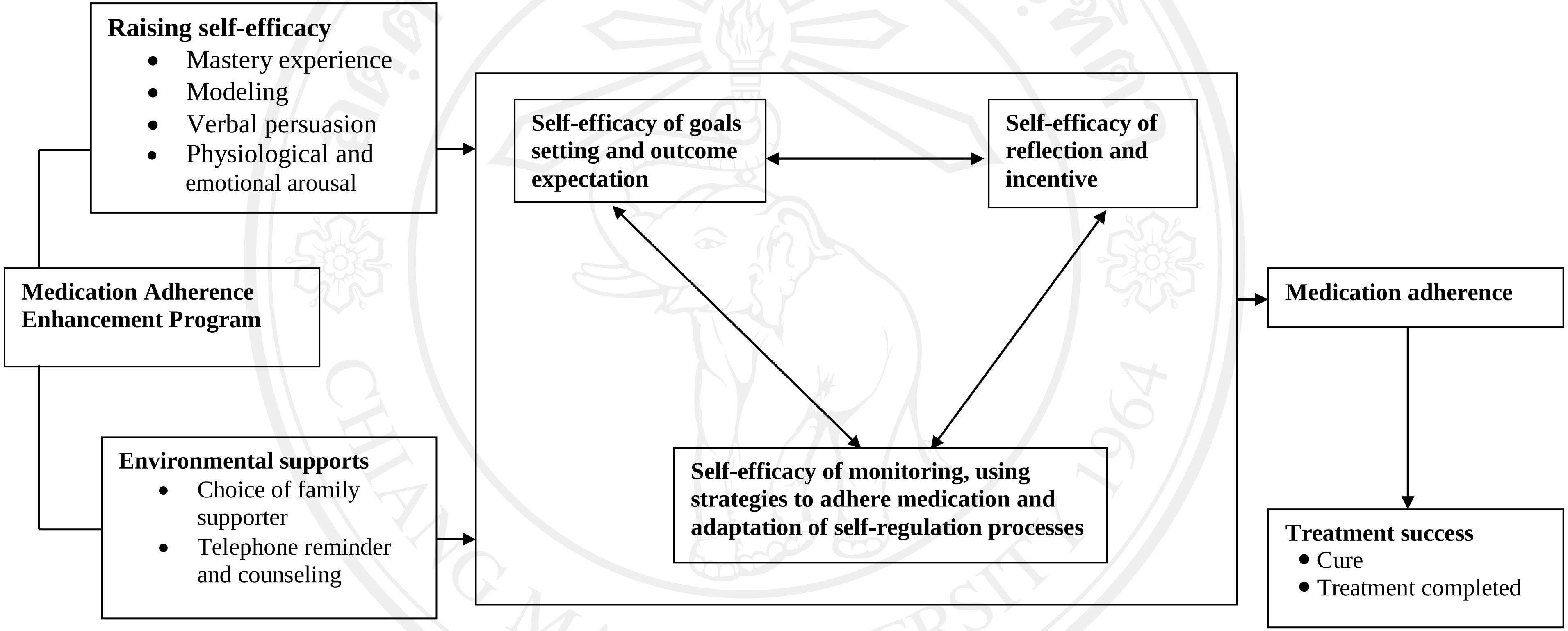

Figure 2.2 The Conceptual Model of the Study