CHAPTER III

PROPOSAL

Comparison of Cost-effectiveness between 9-month Isoniazid and 2-month Rifampicin plus Pyrazinamide for prevention to active tuberculosis among people living with HIV in Chiang Rai province, Thailand

3.1 Background and Rationale

Tuberculosis(TB) poses an importance public health problem worldwide and in Thailand , it is a main cause of death among communicable diseases and affects all segments of population in both urban and rural settlements.[National Epidemiology Board of Thailand, 1987] Chiang Rai is a province in Northern of country, where HIV epidemic was very intense especially in early 1990s but the recent decline in HIV incidence and prevalence is observed. However, HIV epidemic still has long-term impacts as reflected by increase of TB cases. The incidence rates of new TB case per 100,000 population were 50 in 1990 and 63 in 1997 and increased to 140 in 1999. Among TB patients on 1999, 43% were HIV positive 32% were negative and 25% were unknown.[Saisorn, 1999]

Infection with human immunodeficiency virus(HIV) is a potential risk factor

for people infected with Mycobacterium tuberculosis (Mtb) to develop active tuberculosis. The mechanisms by which HIV can affect development of acute tuberculosis can be either by reactivation of latent Mtb infection and reinfection with a new Mtb .[Rieder et al., 1989, Raviglione et al., 1997, Rieder et al., 1989] HIV negative with latent TB infection have about 5% chance of developing active TB but the chance rises to 50% in HIV infected person. Rates of progression to TB among HIV-infected persons have ranged from 35 to 162 per 1000 person-years of observation. [Cohn et al., 2000] and also, rate of rates of progression to TB among HIV-infected persons in injecting drug user(76 cases per 1000 person-years) is higher than among HIV-negative and unknown group(10 cases per 1000 person-years). [Selwyn et al., 1989] In addition, there are several surveys and surveillance data that have shown a significant proportion of tuberculosis patients have HIV infection. In developing countries shows that up to 70% of those who have co-infection of HIV and TB.[UNAIDS & WHO, 2001, www: WORLD TB DAY 2001] This burden of HIV and TB coinfections requires an urgent need for interventions, including possible implementation of preventive therapy for tuberculosis among HIV-infected individual. [WHO, 2002]

There are evidences showing that treatment HIV-infected individuals with isoniazid (INH) for 6 to 12 months reduces the risk of develop to tuberculosis. The effects are more pronounced among HIV-infected individuals with reactivity to a skin test with purified protein derivative(PPD).[Moreno et al.,1997] The effectiveness of INH as a treatment(instead of "prophylaxis") of tuberculous infection has been well established before the era of HIV infection, e.g. among household contacts. The role of

INH as a treatment of tuberculous infection in HIV epidemic has been generally accepted and recognized by public health authorities including the Division of Tuberculosis Control of the Ministry of Public Health of Thailand [TB Division 2001] Although up to 20% of individuals receiving INH may experience elevated liver enzymes (aspartate aminotransferase) and some may have peripheral neuropathy, the abnormal liver function is usually mild and requires no discontinuation of INH.[Michell et al., 1976] In addition, co-administration of pyridoxine (vitamin B6) has been shown to reduce the incidence of peripheral neuropathy [Devadatta et al., 1960]

A study in Thailand showed that 9 months of INH preventive therapy among asymptomatic HIV-infected individuals are feasible and well-tolerated (Ngamvithayapong, 1997). The completion rate the 9-month regimen is 69.4% and the adherence rate, defined as the proportion of those who took more than 80% of pills, was 67.5%. On the other hand, a study in Haiti showed the completed the 6-month INH regimen was 46.8%. [Halsey et al., 1998]

Experiments with other regimens, e.g. the ones containing rifampicin (RFP) and pyrazinamide (PZA) have been done and show the reduction of tuberculosis as well [Gordin et al., 2000, Halsey et al., 1998]. This regimen was used for only two months. However, there are precautions against rifampicin-containing regimens due to fear of *Mucobacterium tuberculosis (Mtb)* resistance to these potent drugs. However, there are not many studies on regimens containing RFP and PZA. The RFP-containing regimen has not been studied in Thailand and its feasibility and compliance are not known. However, since this regimen requires a shorter duration of treatment, the adherence to

treatment is though to be higher unless the RFP and PZA causes a high rate of drug side effects or toxicity. In addition, because of problems with adherence and toxicity with 6- to 12-month isoniazid regimen, an alternative short-course tuberculosis preventive regimes is needed to evaluate Isoniazid versus Rifampicin and Pyrazinamide for preventive tuberculosis.

In the decision making on the treatment of latent tuberculosis infection for tuberculosis preventive therapy as the health care policy, the biomedical and economic consideration should come together. In evaluating cost-effectiveness of treatment options, it is necessary to consider not only the drug prices of medications used, but also the other direct and indirect costs, costs associated with treating side effects and the effectiveness of the treatments. This study proposes to assess the cost-effectiveness in term of cost per achieving one HIV-infected person with completing treatment in two different preventive therapies for latent tuberculosis infection 2-month of Rifampicin and Pyrazinamide and 9-month of Isoniazid with the assumption of the same efficacy, that some study have been done and show the reduction of tuberculosis of Rifampicin and Pirazinamide as well as INH. For example, the Gordin 98 study in US, Mexico and Brazil, they found a daily 2-month regimen of rifampin and pyrazinamide is similar in safety and efficacy to a daily 12-month regimen of isoniazid.(Gordin et al, 2000)

3.2 Research question

Which regimens is more cost-effectiveness of treatment of latent tuberculosis infection (LTBI) for preventive tuberculosis disease between 9-month Isoniazid and 2-month Rifampin plus Pyrazinamide from both perspectives, hospital and patient (with assumption of the same efficacy) to HIV-infected person ?

3.3 Objectives

3.3.1 General objectives

To inform a new alternative health program of tuberculosis preventive therapy to health care policy maker base on information of cost-effectiveness for tuberculosis prevention programme.

3.3.2 Specific objectives

1. To measure the *costs* of implementing treatment of latent tuberculosis infection for prevention to active tuberculosis in two regimens: 9-month Isoniazid and 2-month Rifampin plus Pyrazinamide from both perspective, hospital and patient to HIV-infected person.

2. To measure the *effectiveness in term of completed treatment* of latent tuberculosis infection for prevention to active tuberculosis in two regimens: 9-month Isoniazid and 2-month Rifampin plus Pyrazinamide to HIV-infected person

3. To compare the *cost-effectiveness* of treatment of latent tuberculosis infection for prevention to active tuberculosis in two regimens (with assumption of the same efficacy): 9-month Isoniazid and 2-month Rifampin plus Pyrazinamide from both perspective, hospital and patients to HIV-infected person.

3.4 Operational definition

Terms are defined for the purpose of this study as following:

- **Tuberculin skin test(TST):** a test used to detect TB infection and Purified Protein Derivative (PPD) be used in the Mantoux skin test.[The self-study Modules on Tuberculosis, the Centers for Disease Control and Prevention (CDC), p 11]

- **Treatment of latent tuberculosis infection :** is the use of one or more anti-TB drug given to individuals with latent Mycobacterium tuberculosis infection in order to prevent the progression to active TB disease. [WHO/UNAIDS, 1998]

- **Cost:** is defined as the value of resources used to produce something, including a specific health service or a set of services which may be expressed as a monetary or non-montery value of actual expenditure for the acquisition of these goods or services.[Crease and Parker, 1994]

  Cost might be seen differently from the points of view so the cost of TB

preventive therapy can be classified in two point of view:

- hospital point of view and patient point of view

And also classification of cost can divide in two major economic categories: direct cost and indirect cost

- **Patient point of view cost:** Cost born by patients and families. The cost to patient is the amount the patient will need to pay for direct cost medical care. (Treatment, hospitalization, etc, that is the portion not covered by insurance) and direct cost for non-medical care(transportation, accommodations, support homecare workers, etc.) and the other indirect costs that might be incurred because of the illness or the treatment that make patient loss of labor productive.(absent from work).

- **Hospital point of view cost:** the cost incur by the provider (hospital) is the real cost of delivering the service, regardless of the charge to the patient (HIV–infected person) at district hospital in Chiang Rai province

- **Direct costs:** The cost of the materials and labor that go directly into production of goods or service. Direct cost are essentially transactions. This transaction may be for the purchase of medical services as well as for non-medical services. Direct medical cost include labor cost of staff at hospital, drug, laboratory test, radiological procedures, hospitalization and also the cost for treatment of drug adverse that may be occur. Direct non-medical service such as transportation, accommodations, support homecare

worker.

- **Indirect cost:** The cost of lost productivity and monetary values, are essentially those of life and livelihood. They are the cost that are incurred because of morbidity and those that are incurred because of mortality which is premature. Additionally, including the cost occur from opportunity cost due to go to hospital that makes patient absence from work.

- **Efficacy:** defines as whether or not a specific type of medical care can work. For example in a carefully designed and meticulously managed clinical trial, can a new treatment for anti-TB drug kill and treat tuberculosis sufficiently? Even if medical care might work in the idealized setting and demonstrate that it is efficacious, it still may not be effective.

- **Effectiveness**: refer not to whether medical care can work, but rather to whether medical care does work. Even if a type of medical care can work in an idealized setting, it may not be effective in a real-life setting, perhaps because of side effects of the drug, its cost, or other problems leading to poor compliance. In this study effectiveness refer to HIV infected person who success to take medication base on treatment regimen such as INH 9 months.

- **Efficiency:** asks what the service costs for what we get from it. In other word , efficiency id a measure of the degree to which the resources that are expended result in a substantial beneficial outcome.

- **Cost-effectiveness analysis (CEA):** Cost effectiveness is measured as a ratio of cost to effectiveness. In this study, it is expressed as the ratio of cost per achieving 1 patient with completing treatment of latent tuberculosis infection.

3.5 Conceptual framework (1)

Figure 3.1:

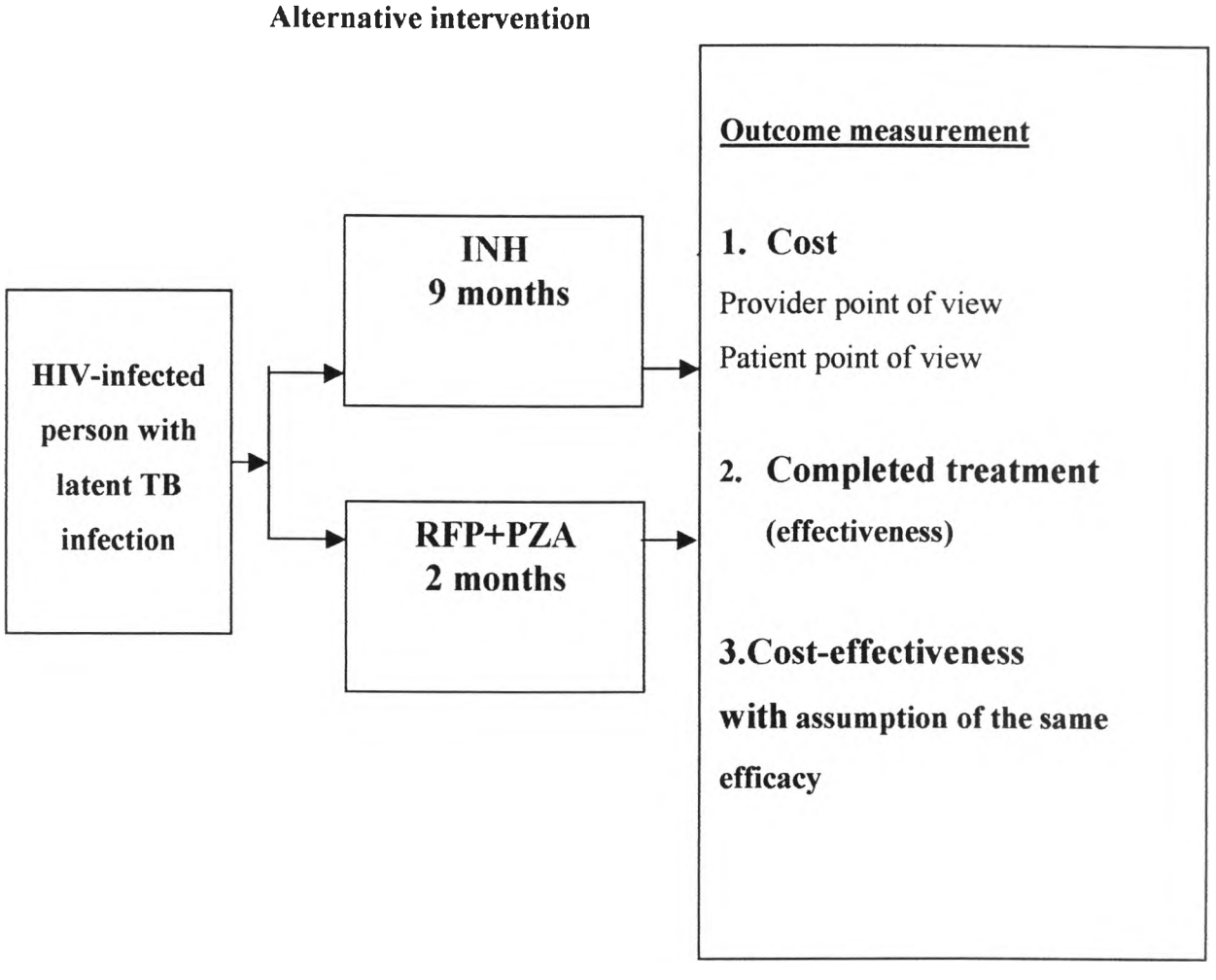
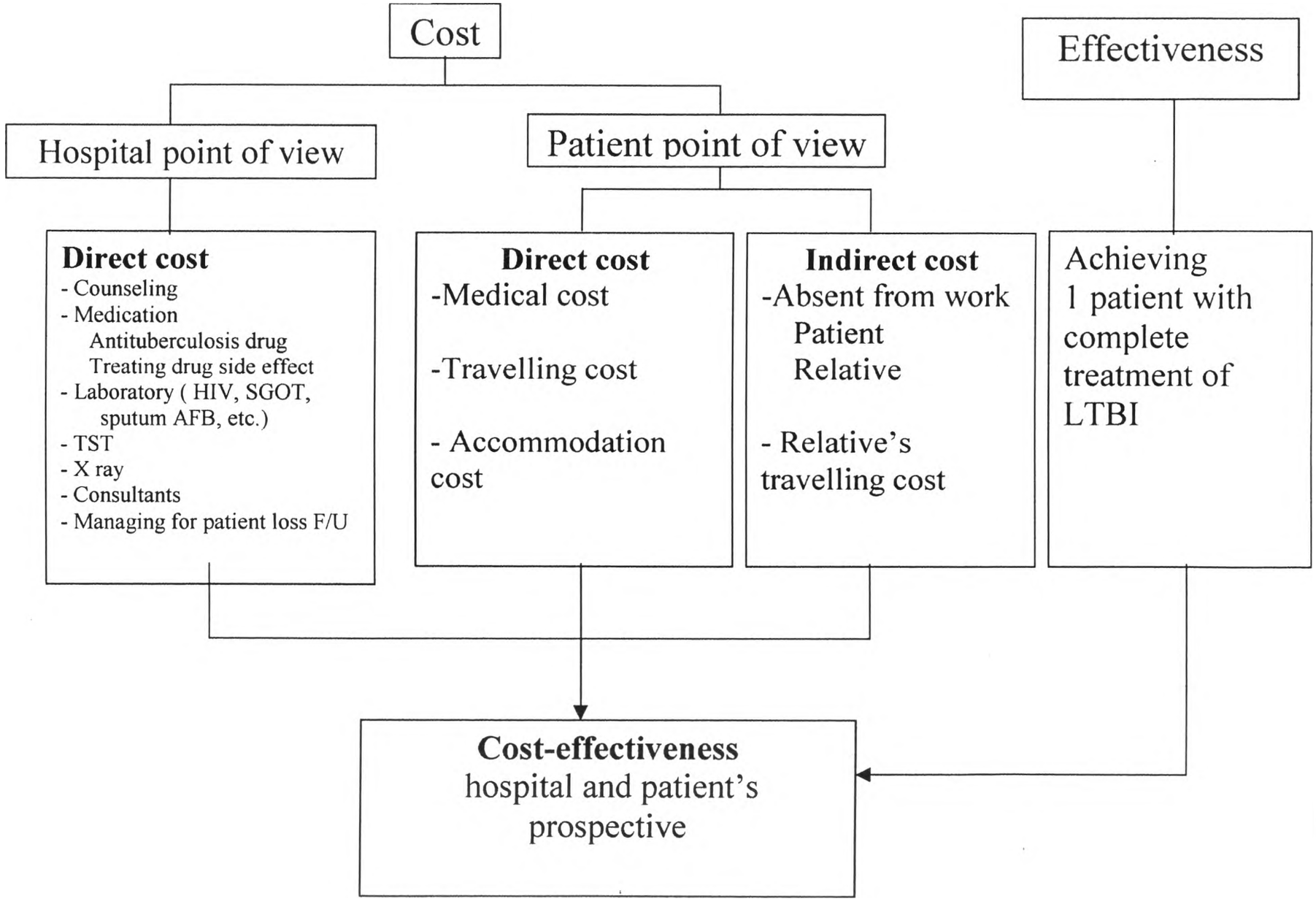


Figure 3.2 conceptual framework (2)



3.6 Research methodology

3.6.1 Study design

Multi-center randomized, two-arm, open-label controlled trial to compare cost-effectiveness of Isoniazid 9 months versus Rifampin plus Pyrazinamide 2 months for treatment of LTBI for preventing tuberculosis disease among people living with HIV.

3.6.2 Study population

Subject must be HIV-infected person and also be registered in Day Care Center(DCC; this is a hospital-based facility that provides physical, psychological, and social services to people living with HIV/AIDS) at district hospital. Subject will be recruited by follow from inclusion and exclusion criteria.

3.6.3 Inclusion criteria

1. HIV infected person.
2. PPD skin test positive $\geq$ 5 mm.
3. Signed consent form

3.6.4 Exclusion criteria

1. Age <18 and > 50 years
2. Weighing < 30 kg and > 75 kg
3. Current active tuberculosis case* (Pulmonary TB and Extra pulmonary TB)
4. Patients with a history of TB disease including history for INH preventive therapy.
5. Pregnancy woman
6. Persons with mental, behavioral or other conditions unable to give inform consent.
7. Patient with a history of non-compliance($\leq$ 80% of prescribed drugs) to any drug therapy such as antihypertensives.
8. Jaundice or have history of chronic hepatitis or active hepatitis within 6 month or other liver disease
9. Laboratory: aspartate aminotransaminase (SGOT) > 122U/L, total bilirubin $\geq$ 2 , creatinin $\geq$ 1.5 mg/dl, Hemoglobin < 6.5 gm/dl, neutrophil count < 1,000 cells/ mm^3 , platelet < 75,000mm^3
10. Karnofsky performance status** < 60 (indicating that they are not in bed > 50% of the day, do not require assistance for activities of daily living, and do not require frequent medical care)

** = ***Karnofsky performance status*** is based on the following scoring:

Table 3.1: Karnofsky performance status

Physical ability	Score
Normal	100
Independent with minimal symptoms	90
Independent with more efforts and symptomatic	80
Can do only activity of daily living	70
Partially independent	60
Partially dependent and require more medical treatment	50
Dependent with specific care	40
Totally dependent, require hospitalization, and not impending to die	30
Moribund, need hospitalization with full medical treatment	20
Comatose	10
Death	0

Source: Karnofsky and Burchenal, 1949

After enrollment, *criteria* for withdrawal from the study will be:

1. The subject's voluntary withdrawal
2. Development of active TB
3. Permanent move precluding access to the study clinic
4. Clinician's discretion for medical complications of AIDS, or suspected drug toxicity or subject who develop laboratory abnormalities that may indicate Isoniazid, Rifampin and Pyrazinamide toxicity.

3.6.5 Study sites

This study will be conducted 10 districts hospital in Chiang Rai province, Thailand. 10 district site will be selected base on tuberculosis preventive program which already established and also have higher number of PLWA in each hospital base on information in all districts in Chiang Rai province as following:

Table 3.2 Background of study population at Day Care Center in Chiang Rai province

District (Hospital bed)	Over all population	Age 20-45 years	HIV positive (total)	Death	Alive	DCC only	IPT only	DCC and IPT	Not yet IPT
Phan (120)	132061	58,512	1086	258	828	295	671	120	37
Mae Chan (90)	110028	41,238	970	307	663	537	92	341	230
Wiang Papao (60)	69155	29,570	503	93	410	440	29	34	347
Khuntan (60)	34303	16,959	323	32	291	245	65	13	213
Chiang Khong (90)	67252	29,874	308	69	239	98	105	105	29
Wiang Kan (30)	33671	12,362	183	20	163	162	0	21	142
Padad (30)	26868	12,651	154	39	115	137	5	12	98
Chiang Sean (30)	52068	22,347	300	58	242	294	4	2	236
Mae Sai (90)	80991	34,641	238	54	184	142	17	79	88
WiangChiangRung (30)	26685	12,918	116	9	107	68	15	33	59
Total	**633082**	**271,072**	**4181**	**939**	**3242**	**2418**	**1003**	**760**	**1479**

3.6.5 Study Duration

From January 2003-December 2003

Enrollment: for 3 month: January 2003- March 2003 with sample size 634 participants. Research team in 10-district hospital will enroll subject at DCC with HIV–infected person.

Follow up: 9 months for INH and 2 months for Rifampicin and Pyrazinamide

Follow up will end in December 2003.

3.6.7 Interventions:

The drug will be specifically prepared by the Government Pharmaceutical Organization or an equivalent institute or agency. The doses for Isoniazid will be 300 mg daily for the study weight range(30-75 kg). Subject who receive INH will also be provided pyridoxine(Vitamin B6) 25 mg daily. The doses for Rifampin and Pyrazinamide will be provided daily 2 months base on body weight as follows:

Weight	Rifampin	Pyrazinamide
30-39.9 kg	450 mg	1500 mg
40-49.9 kg	450 mg	2000 mg
50+ kg	600 mg	2500 mg

3.6.8 Sample size

The propose of sample size is calculated in order to have a 80% power to detect 10% difference in completion rate of Isoniazid and RFP plus PZA. The following parameters are used to estimate the sample sizes of two arm be equally allocated:

1. Completion rate of INH = 70%
2. Expected difference completion rate RFP + PZA = 10%
3. Type I error (α) = 0.5(two-side)
5. Type II error (β) = 0.2

Formula used for calculating

$$n = \frac{[\, Z_\alpha * / (2\, p1q1) + Z_\beta * /(p1q1 + p2q2)\,]^2}{[\, p1 - p2\,]^2}$$

n = sample size required

Z_α = 1.96 with two-sided significance level p= 0.05

Z_β = 0.84 (power 80%), 1.28 (power 90%) and 1.64 (power 95%)

p1 = proportion of completion rate of INH

q1 = 1- p1

p2 = proportion of completion rate of Rifampicin and Pirazinamide

q2 = 1- p2

Table 3.3 : Sample size of completion rate of treatment of LTBI requirements for comparisons of proportions

	80% power	90% power	95% power
Difference = 5 %			
	2614	3472	4274
Difference = 10%			
	634	836	1024
Difference = 15 %			
	272	354	430

Sample size in this study is 634 HIV infected person, divide to INH 317 and RFP+PZA 317 person.

3.6.9 Operational procedures

3.6.9.1 Enrollment, Randomization, and Follow-up

This study will use the randomization strategy to allocated subject into 2 group, using individual subject as a unit of randomization. To accomplish a valid randomization, an independent central study allocation unit will be set up at TB/HIV research project-Chiang Rai. This unit will be responsible for developing the randomization process and making the assignment of subject to the appropriate group. One of investigators not otherwise involve with the care or evaluation of the subject

will prepare the randomization scheme using block randomization (block size of 4) for assignment at the TB/HIV research project-Chiang Rai before the trial begins.

Day Care Center at each hospital recruit HIV-infected person member from difference resources such as blood donors, cutpatient clinic, inpatient clinic, antenatal care clinic and Prevention of Mother to Child Transmission program(PMTCT) and anonymous clinic. Almost of them were be provided pre-post HIV counselling which all hospital in Chiang Rai already have and also give them about DCC information in order to invite them to attend.

HIV-infected individual will be approached and explained about the study. If agreeing, they will undergo the procedure as follow:

Day -3: HIV-infected individuals registered at the DCCs will be approached by well-trained project staff who will explain about the objectives, benefits and risks of participation in the project and invite them to participate. If agreeing, the HIV-infected individuals will be screened by an screening and enrolment questionnaire to determine their eligibility.(Appendix 2) If eligible and willing to participate, the potential participants will be handed and asked to read a participant information sheet that explains about the entire project and they will be asked to sign (or print a thumb mark on) a consent form. .(Appendix 1) PPD skin testing, chest radiography, sputum AFB x 3 days with culture, CD4 count, complete blood count, blood chemistry including liver enzymes(SGOT and bilirubin) creatinin and pregnancy test (for women only) will be performed. The potential research participants will also be physically examined by a

physician at each site. They are appointed for coming back 2 days later for reading the result of PPD skin test.

Days 0: Chest radiograph, PPD skin test results, three AFB smears and other laboratory results will be read and the participants' eligibility will be reassessed. The participants will also be asked again to confirm whether they are still willing to participate. To minimize loss to follow-up, the participants will be asked to provide name(s) and telephone number(s) of a friend(s) or a family member(s) who is or are likely to maintain contact with them. They will also be asked whether they are willing to be contact via mail or visited at home or both in case they are late for follow-ups. If they participants are found to be unwilling or ineligible, they will be dropped from the study and referred to usual care they are entitled to before they participated in the project. If eligible and still willing, the participants will be randomized(based on block randomization) into one of the two arm;

The first arm is daily Isoniazid 9 months with pyridoxine(Vitamin B6) 25 mg and the second arm is daily Rifampin plus Pyrazinamide 2 months. The participants will be provided with 15-day supply of medicine and also be asked to do self-report for taking drug.

Day 15: The participants will be invited back for an evaluation of adverse medication effects by use follow up questionnaire (Appendix 3) and blood draw for repeat liver functions and complete blood count. If no serious toxicity and adverse events are detected, the participants will be provided with another 15-day supply of the medicine.

Day 30: The participants will be invited back for a re-evaluation of adverse events, active TB and clinical progress of HIV disease. If no serious adverse evens are detected, the participants will be provided with another 30-day supply of medicine.

Day 60: The participants will be invited back for a re-evaluation of adverse events, active TB and clinical progress of HIV disease. If no serious adverse evens are detected, the participants will be provided with another 30-day supply of medicine, of which the first arm will continue to receive Isoniazid but the second arm will be stop.

Day 90, 120,150, 180, 210, 240, : The participants will be invited back for a re-evaluation of adverse events, active TB and clinical progress of HIV disease. If no serious adverse evens are detected, the participants will be provided with another 30-day supply of medicine.

Day 270(last visit): The first arm participants will stop to receive Isoniazid and chest X ray will be obtained in last follow.

At each visit: the participants will be asked to bring self-report and left-over pill so that adherence to treatment can be detected by pill count. The subject will be asked for urinary testing for Isoniazid metabolites by random and also observe the color for check Rifampicin.

3.6.9.2 Follow up for compliance of completing treatment

To maximize compliance, all subjects will be encouraged at enrollment and at each follow-up to take all medications as prescribed.

Pill count: Subjects will be asked to bring any remaining medication to every follow-up visit. Pill counts will be done, results recorded and reasons for discrepancies will be explored, however, subject will not be told that the returned pills will be counted.

Self-report also will be check by provide daily schedule taking drug.

Urine test: In addition, the subject will be asked to provide a urine specimen that will be screened for Isoniazid metabolites and observe urine color of Rifampicin by ramdom.

Random home surprise visit: A sample of subject of both groups in the various months of program will be randomly selected to be visited for pill count.

3.6.9.3 Follow-up for drug toxicity

Drug toxicity and adverse events will be assessed by history taking, physical examination, routine laboratory evaluation, and additional investigation at the discretion of the study doctors. Participants will be removed from the study if they develop biochical hepatitis, define as a serum aspartate transaminase(AST) greater than twice normal(normal AST 5-45 IU).

3.6.9.4 Loss to follow-up

If a participant is 2-week late, the participant will be located and contacted via mail or visited at home (according to their expressed willing at the time of enrolment). Study staff who will follow-up the participants will keep records as well as reasons for loss to follow-up in a form to be developed. The reasons for loss to follow-up will include:

- Voluntary temporary withdrawal (up to two months)
- Voluntary permanent withdrawal
- Toxicity and adverse events intolerance
- Intercurrent illness without hospitalization
- Intercurrent illness with hospitalization
- Engagement with works or other businesses (too busy)
- Migration to other areas and inconvenience to come as appointed
- Imprisonment
- Death
- Undetermined (no reason given or detected)

For participants who are declared "lost to follow-up" TB Register and hospital records of each of the hospital will be reviewed on a monthly basis to see if they are hospitalized and the Provincial Death Registration will be searched on an annual basis to see if they are dead. If a participant is found to be dead, a letter will be send to his/her friend(s) or family member (according to his/her prior specification)

3.6.10 Research instrument for data collection.

Questionnaires consist of 2 part as enrollment phase and follow up phase. Items included in the *enrollment questionnaire* consist of:

- Demographic characteristics
- Costs associated with participating program (patient perspective, direct and indirect costs)
- TB screening
- Drug side effects screening
- Non compliance screening
- Physical examination
- Laboratory and tuberculin skin test

The *follow up questionnaire* consist of:

- Cost associated with program each follow up visit (patient perspective)
- Evaluation for active TB
- Evaluation for drug side effects
- Evaluation for compliance
- Evaluation for drug side effects

Data costs from hospital perspective, this is separated from patient perspective. Worksheet for costs information (See in appendix 4) will be used for data collection. Worksheet for costs information consist of:

- Cost of counselling

- Cost of consultation
- Cost of medication
- Cost of treating side effect
- Cost of laboratory, TST, X-RAY
- Cost of follow up

3.6.11 Data collection and management

This following is guideline how the data will be collected in order to answer research question.

1. Costs data of treatment of LTBI in hospital perspective will be collect retrospectively through reviewing financial records about labor cost, interviewing hospital staff that response with each costs such as pharmacologist, medical technologist administrator, nurse and physician and also observing and recording the time that caregiver spent for patient by using worksheet for costs information (See in appendix 4)

Costs data of treatment of LTBI from patient perspective will be collect by interview patient directly with questionnaire (Appendix 2,3)

2. Questionnaires for this study will be translated to Thai.

3. Pre-test of the questionnaire will be performed prior to the administration to PLWHA and necessary modification will be made.

4. Research team(hospital staff and staff from TB/HIV research project) will be informed by conduct 1 day meeting in order to explain about research program with purpose have the same practices with good system in each hospital site.

5. Training interviewer: the interviewers will be given an orientation on how to interview and how to fill up the questionnaire.
6. Collect of questionnaire back from interviewer: at each hospital, project staff will co-ordinate and also double check questionnaire before handling all form to office center.(TB/HIV research project)
7. *Quality of data* Data will carefully code by two coders to minimize error and also repeat entry for validation every month so that error can be corrected in time and the databases stay updated.

3.6.12 Plan of data analysis

Epi Info version 6.04 will be used for data entry. Data from all the forms will be transcribed and entered at TB/HIV research project. This following is plan for data analysis.

1. **Cost:** This cost is the cost of implementing treatmet of LTBI for 1 PLWA. Cost will be classified to 2 alternative regimens and from hospital and patient perspective and base on direct and indirect cost.
    - Daily INH 9 months in hospital perspective and patient perspective
    - Daily RFP and PZA 2 months in hospital perspective and patient perspective

Hospital perspective

Total cost of implementing treatment of LTBI for 1 PLWA (Direct costs)

= A+B+C+D+E+F

A = Cost of counselling

B = Cost of medication

C = Cost of treating side effect

D = Cost of laboratory, HIV, TST, X-RAY

E = Cost of consultation

F = Cost of loss follow up patient e.g. home visit, letter

Detail of each cost see in appendix (Appendix 4)

Patient perspective

Total cost of 1 patient pay for treatment of LTBI

= Direct cost + indirect cost

= **(A+B+C) + (D+E+F)**

Direct cost

A = Cost of medication

B = Cost of patient's transportation

C = Cost of accommodation

Indirect cost

D = Cost of absent from work of patient

E = Cost of absent from work of relative

F = Cost of relative's transportation

Data of patient's cost will be collected by questionnaires. (Appendix 2,3)

All cost can present by table as following:

	Hospital perspective		**Patient perspective**		
	Direct cost	**Total costs**	Direct cost	Indirect cost	**Total costs**
IHN 9 months	X	XX	x	x	XX
RFP+PZA 2 months	x	XX	x	x	XX

2. effectiveness in term of completed treatment

The INH and RFP+PZA may work in an ideal setting that is efficacious, yet it still may not be effective in a "real-life" setting because of side effect of drug regimen or long duration of treatment leading to poor adherence. The term effectiveness of this study refer to **achieving 1 case with completing treatment**

Complete treatment explain as patient who has successfully complete treatment regimen and will define as participant who;

- Receive all tablets base on regimens i.e. INH (300 mg) 270 dose and RFP+PZA 60 doses.
- Taking drugs more than 80% with self-report and pill count.
- Return to follow up within one month of taking the last dose.

Competing treatment of two regimens will be compared at the end of treatment of each regimen and also comparison during first 2 months of INH and RFP+PZA.

Then, cost effectiveness will be considered.

3. Cost-effectiveness analysis

Cost effectiveness mean cost of implementing preventive therapy per achieving 1 patient with completing treatment regimen.

$$\text{Cost-effectiveness ratio} = \frac{\text{Costs}}{\text{Effectiveness}}$$

$$= \frac{\text{Costs of implementing treatment of LTBI}}{\text{Achieving 1 case with completing treatment}}$$

For meaningful comparison, it is necessary to examine the additional costs that one service or programme imposes over another, compared with the additional effects, benefits, or utilities it delivers. Although cost-effectiveness could compare the simple ratios of costs to outcomes for the two alternatives, the correct comparison is the one of incremental costs over incremental outcomes, since this tell us how much we are paying (for each extra completing treatment)

$$\text{Incremental analysis = incremental ratio} = \frac{\text{Additional cost}}{\text{Additional effect}}$$

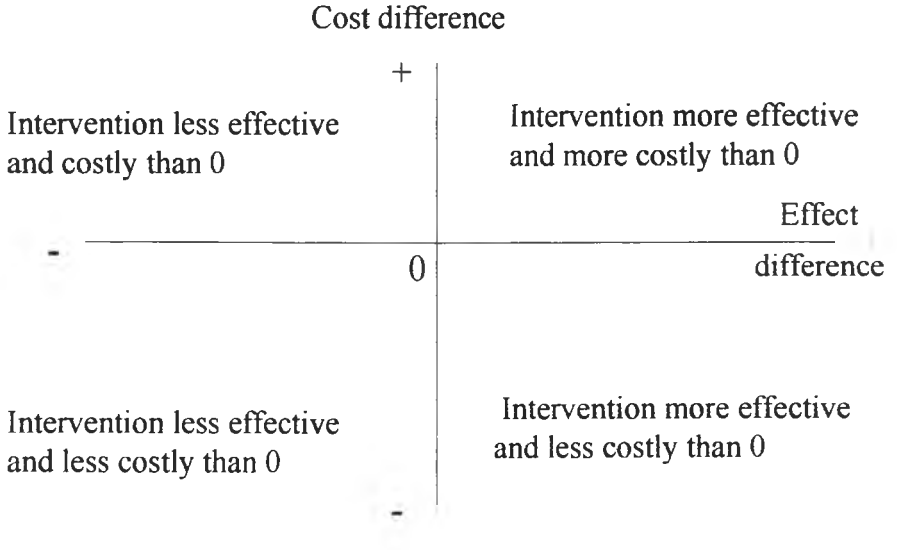
$$= \frac{\text{Cost of INH- Cost RFP+PZA}}{\text{Effectiveness INH – Effectiveness RFP+PZA}}$$

The final result of economic evaluation of tuberculosis two regimens will be present by table as following:

Drug regimens	**Costs**	**Outcome Complete treatment**	**Ratio of cost to outcome ($ per 1 achieve treatment)**
INH 9 months	A	B	A/B
RFP+PZA 2 months	C	D	C/D
Increment (of RFP+PZA over INH)	C - A	D - B	(C – A) / (D – B)

These can be illustrated graphically on a four quadrant diagram known as the cost-effectiveness plane.

The cost-effectiveness plane



In the diagram the horizontal axis represents the difference in effect between the intervention of interest(A) and the relevant alternative (0), and the vertical axis represents the difference in cost. The alternative(0) could be the status quo or a competing programme. If point A is in quadrants II or IV the choice between the programmes is clear. In quardant II the intervention of interest in both more effective and less costly than the alternative. That is, it dominates the alternative. In quadrant IV the opposite is true. In quadrants I and III the choice depend on the maximum cost-effective ratio one is willing to accept. The slope of the line OA gives the cost-effective ratio.

3.7 Ethical considerations

Benefits and risks to the research participants

Subject will be provided with active treatment for latent tuberculosis infection and also all participants will be given the TB knowledge and TB prevention. TB screening and HIV counseling will be provided. Among those who has TB signs and symptoms will be done for active TB screening, physical examination by physician, chest x-ray and sputum examination for 3 days immediately. If the participants are diagnosed active TB case by medical doctor, they will be taken TB chemotherapy and they will be taken all procedure by without charge.

Most of the risks involved in this study concern inconvenience to the participants for frequent follow-ups that require transportation (although the

participants will be compensated for their transportation expenses and losses of time). Blood draw and skin testing are additional but minimal risks that should not outweigh the benefits. Apart from minor discomfort, rare complications of venipuncture include hematoma and infection at bleeding site(s). Severe reaction to skin testing. E. g. blister formation, can also infrequently occur but responds well to supportive treatment. Since the participants will be recruited from DCCs where HIV-infected individuals already disclose their HIV status, there should be no risk associated with disclosure of HIV status. In addition, all completed forms will be stored in secure locations at the central co-ordinating office(the TB/HIV research project). All databases(at local offices and at the central co-ordinating office) will be handled(i.e. entered and edited) by a well-trained staff member who has no information on the participants' names and addresses; The databases will contain no identifying information such as names and addresses. All databases will be password-protected.

Refusal to participate: Subject can change any time to stop in study and still get normal care and treatment from hospital.

Informed consent: Written informed consent will be obtained. In accordance with current practices, if a participant is not literate, consent will be obtained verbally.

Ethical approval: The project will seek ethical approval from the Ethical Review Committee of the Ministry of Public Health and other institution review board(s) if so required.

3.8 Funding and resource

This project will be supported by TB/HIV research project-Chiang Rai.

Table 3.4 Budget plan

Item	Description	Amount (Baht)
1	Salary	
1.1	Salary for research assistance 12000 baht * 12 months	144,000
1.2	Salary for Research Coordinator 20000 baht * 12 months	240,000
2	Medical supplies	
2.1	Cost of skin test antigen	
2.1.1	PPD (634 test * 35 baht)	22190
2.1.2	Cost of needle and syringe for skin test (634 test * 5 baht)	3170
2.2	Cost of RFP+PZA(634*260.8)	165347.2
2.3	Cost of INH (634*162 baht)	102708
2.4	Cost of Vitamin B6 (634 * 21.6 baht)	13694.4
2.5	Cost of HIV testing (634 test *170 baht)	107780
2.6	Cost of CD4 testing (634test * 700 baht)	443800
2.7	Cost of SGOT testing (634* 50 baht)	31700
2.8	Cost of Bilirubin testing (634 * 50 baht)	31700
2.9	Cost of Creatinine testing (634 * 50 baht)	31700
2.10	Cost of chest x-ray (634 * 120 baht)	76080
2.11	Sputum examination (634* 60 baht)	38040
2.12	Sputum Culture (634* 100 baht)	63400

Item	Description	Amount (Baht)
3	Transportation	
3.1	Transportation for home visit	100,000
3.3	Transportation for consultant	100,000
3.4	Specimen transportation for CD4 and sputum culture	5000
4	Report Printing	50,000
5	Miscellaneous (Xerox, communication, etc)	50,000
	Total	1,820,310

3.9 Activities and schedules

Table 3.5 Activities and schedules

Activity	Timing Month, The year 2002											
	JAL	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC
1. Developed proposal and Literature review	◄	─	─	─	─►							
2. Submission to ethical review committee of Ministry of Public Health and edition from they 's comment						◄	─	─►				
3. Arrangements of administrative and organizational issues.							◄	─►				

Activity	Timing Month, The year 2002 JAN FEB MAR APR MAY JUN JUL AUG SEP OCT NOV DEC
4. Pilot of project at Mae Chan Hospital and home visit	
5.Training and further agreements with the research team and local coordinators (job description, revising the proposal according to the field situation)	

Activity	Timing Month, The year 2003 JAN FEB MAR APR MAY JUN JUL AUG SEP OCT NOV DEC
6.Starting data collection and continue Enrollment phase and continue to collect data	
9. Data analysis and Interpretation	
10. Report writing, dissemination of results.	

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