CHAPTER V

PRESENTATION

I presented the portfolio of my thesis on the topic " Incidence of Tuberculosis and associated factors among HIV infected persons registered for Isoniazid Preventive Therapy in Chiang Rai, Thailand" on Wednesday 3, April 2002 to the examination committee. The presentation was divided into three parts: essay, proposal and data exercise.

In essay part, I presented the background information of TB/HIV and rationale using four problems and evidences related to IPT in Thailand. In proposal part, I presented the objectives, study design, data collection process, data analysis and ethical considerations.

After the presentation, I answered some questions, which were asked by committee members. They provided important advice and recommendations. The main recommendation was to add the characteristic of TB cases stratified by gender in Data Exercise part.

The slide prepared on Microsoft Power Point are attached as follows.

Incidence of Tuberculosis and Associated Factors Among HIV-Infected Persons Registered for Isoniazid Preventive Therapy in Chiang Rai, Thailand

Kaori Hazama

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Definitions

- **BCG:** vaccination is given at birth to protect childhood tuberculosis
- **Culture:** Laboratory test to identify bacteria grown in media
- **CD 4 :** CD4+ T- lymphocyte cell counts to check immune statuse
- **Smear:** Microscope examination, used to detect bacteria in a specimen
- **Tuberculin skin test:** A test used to detect TB infection
- **TB infection: Symptom (-), Infectious (-)**
- **Active TB : Symptom (+) , Infectious (+)**

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Tuberculosis (TB) and HIV Situation in Thailand

- **About one third of the population carries the TB bacteria.**
- **Estimated 15,000 new TB cases occur in each year**
- **HIV seroprevalence in new TB patients is 15.8 % in 1998.**
- **TB is the most frequent opportunistic infection among HIV Infected Persons**

(Battle against TB, TB division)

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Risk of TB among HIV Infected Person

Incidence peryear of developing active TB

- **TB infection 0.4 % per year**
- **Co-infected with the TB and HIV 3.4 - 10 % per year**

(Dolin PJ et al (1994) Bull World Health Organ;72:213-22)

- **Co-infected with the TB and HIV in Thailand 5 % per year**

(P Akarasewi (1999) IUATLD volume 3, Number 9, Supplement 1. S23)

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Isoniazid Preventive Therapy (IPT)

- **IPT induce TB infection to dormant stage and reduces the risk of developing active TB among HIV Infected Persons around 40 %.**

(WHO and UNAIDS: Policy statement on preventive therapy against TB in people living with HIV)

- **In Thailand, estimate efficacy of active TB protection among HIV Infected Persons reported to be 78 %**

(P Akarasewi (1999) IUATLD volume 3, Number 9, Supplement 1. S23)

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PROBLEM 1.

Improper active TB screening* is related to development of active TB among HIV Infected Persons registered for IPT

Study in Northern Thailand report improper medical evaluation of active TB before IPT enrollment and inclusion of HIV infected person with advanced immunosuppression who have a higher probability to develop TB.

(Communicable disease control 10 report 2000)

* Improper active TB screening means, no tuberculin skin test or sputum smear or chest X-ray for active TB evaluation.

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PROBLEM 2.
Long term IPT efficacy is not clear

- Study in Spain; cumulative probability of active TB is less than 5 %, 3 years after IPT

(Casado J L et al (2002) Clinical Infect Dis Feb 1, 34(3): 386-91)

- Study in Northern Thailand; protective effect of IPT was decreasing after 18 month among HIV Infected Persons who have completed 9 months IPT.

(Akarasewi P, et al. CDC 10 report 2000) 7

PROBLEM 3.
Incidence of active TB is depends on TB diagnostic method

The incidence rate of TB (6 month-IPT)

1. Confirmed and presumed TB	2. Including probable TB
2.74 per 100py	4.94 per 100py

Classification

1) **Confirmed TB**; Smear or culture or histopathology prove TB.
2) **Presumed TB**; Pulmonary infiltrates and clinical symptoms or pleural or pericardial effusion without a response to antibiotic but with a response to TB treatment within 2 months
3) **Probable tuberculosis**; Radiological features and respiratory symptoms suggestive of TB, who were started TB treatment before antibiotics were given

(A Mwinga et al (1998) AIDS:12) 8

PROBLEM 4.
There is a lack of understanding the factor related the to development of active TB in Thailand

Factors which decrease TB incidence

- Age 30 years older
- Tuberculin skin test of 5 mm or greater
- Lymphocyte count of 2 X10 ^{9}/l or higher
- Hemoglobin of 10 g/dl or higher
- Presence of BCG vaccine scar

Factor which increases TB incidence

- Exposure to TB
- CD4 lymphocyte less than 20

A. Mwinga et al. (1998), Casado J L et al. (2002) 9

Implication of the Study

- To develop the optimal IPT guideline of active TB diagnostic method for HIV Infected Persons.
- Health care workers are encouraged to pay more attention for IPT participants who have a factor related to development of active TB

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Research Questions (1)

1. What is the 9-month incidence rate of active TB among HIV Infected Persons registered for 9-month IPT in Chiang Rai province?
2. What are the factors affecting the development of active TB among HIV Infected Persons who registered for 9-month IPT in Chiang Rai province ?

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Research Questions (2)

3. What is the 3-year incidence rate of active TB among HIV Infected Persons who completed 9-month IPT* in Chiang Rai province ?
4. What are the factors affecting the development of active TB among HIV Infected Persons who completed 9-month IPT in Chiang Rai province ?

* Completed 9-month IPT means, when 9-month IPT finish, the participants are followed-up, inspite of the number of Isoniazid pills, which they have taken. 12

Specific Objectives (1)

1. To determine the 9 month incidence rate of active TB among HIV Infected Persons registered for 9 month IPT in Chiang Rai province.

2. To identify the factors affecting the development of active TB among HIV Infected Persons who registered for 9-month IPT in Chiang Rai province.

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Specific Objectives (2)

3. To determine three years incidence rate of active TB among HIV Infected Persons who completed 9 months IPT in Chiang Rai province.

4. To identify the factors affecting the development of active TB among HIV Infected Persons who completed 9-month IPT in Chiang Rai province.

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Methods of the Study

- Study Design

This Study will be a prospective cohort study

- Study duration

Enrollment: From July 2002 until the sample size is reached. (Expected 3 month)

Follow-up: 9-month IPT plus 3 years follow up after 9 months.

Total 45 months for each subject

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Study Population

- For Study of 9 month incidence:
  HIV Infected Persons registered for 9-monrhs IPT in all 17 public hospitals in Chiang Rai province.

- For Study of 3 years incidence:
  HIV Infected Persons who completed 9-month IPT in all 17 public hospitals in Chiang Rai province

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Inclusion Criteria

-Asymptomatic HIV Infected Persons registered in IPT in Chiang Rai.

-Tuberculin skin test positive

- Persons who are willing to participate in this Study

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Exclusion Criteria

-Below15 and over 50 years of age
- Current active tuberculosis
- Past history of tuberculosis
- Pregnancy
- Abnormal liver enzymes
- Serious illness

* Those with antiretroviral therapy will not be excluded.

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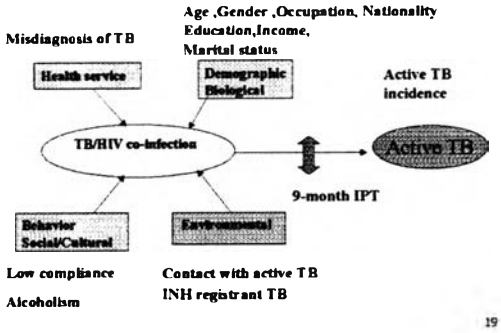
Conceptual Framework



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Dependent (Outcome) Measurement - Active TB

Definition of active TB case

1. Confirmed TB (Pulmonary TB or Extra-pulmonary TB)

- Clinical case of TB of the lung, lymph node, abdominal organ, central nervouses system, disseminated and other organs with positive acid-fast bacilli (AFB) smear and/or culture

2. Probable TB

2.1. Chest radiography consistent with active TB (infiltration or cavity) with negative AFB and culture, excluding suspected case of inactive pulmonary TB with old inactive infiltration or cavity.

2.2 Clinically diagnosed active extrapulmonary TB based on clinical evidence, e.g. cervical lymph node swelling, abdominal pain with fever, abnormal symptoms of central nervous system including lost or blurred consciousness, without positive AFB or culture.

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Independent Variable (potential factors)

- **Demographic factors**
- **Biological factors**
- **Predisposing factors for TB infection**
- **Behavior factors (compliance of INH)**
- **Health care provider's factors**

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Sample Size

Conf. Level (%)	Power of Test (%)	Screening A : B	Incidence of TB (%) Screen A	Screen B	Sample size Screen A	Screen B	Total
95	80	4 : 1	1%	4%	1648	260	1300
95	80	3 : 1	1%	4%	678	339	1017
95	80	3 : 1	1%	4%	861	287	1148
95	80	5 : 1	1%	4%	1220	244	1464
95	80	4 : 1	1%	2%	5780	1445	7225
95	80	4 : 1	1%	3%	1900	475	2375
95	80	4 : 1	1%	5%	696	174	870

Screening A: Screening B + chest X-ray and culture
Screening B: Screening using sign and symptom and smear

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Data collection Process (1)

- **Enrolment**

  Research team in each hospital will check inclusion and exclusion criteria using screening list. They will interview all IPT participants using IPT screening list.

- **Follow up 9 month**

  Research team will follow up participants every month to check symptoms and Isoniazid compliance using IPT follow up form. Also they will check blood test every 3 month

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Data collection Process (2)

- **Follow up after finish taking Isoniazid to 3 years**

  Research team will follow up participants every 6 months and they will check blood test and Chest X ray every 12 month using follow up form.

- **Active TB cases**

  Research team will find active TB case from TB registry and IPT registry. They will interview all TB cases using TB case investigation form

  All data collected by research team will be sent to TB/ HIV research project center for analysis

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Data Processing and Analysis

- Data will be transcribed into Epi-info version 6
- Incidence rate using cumulative incidence and incidence density will be calculated
- Univariate analysis: Relative risk with 95 % confidence interval will be performed to determine the strength of association between factors and outcome event (active TB).

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Ethical Considerations

1. Balance of risk and benefit: Benefit exceed risk.
   - 1.1 Benefit - More active TB screening and follow-up
     - TB education will be given to participants
   - 1.2. Risks - Inconvenience of participation
     - Side effect of Isoniazid
     - Discomfort or minor skin infection related to tuberculin skin tests and blood draw
2. Participants have freedom to refuse
3. Written informed consent will be obtained
4. Confidentiality
5. Approval to the ethical committee, Ministry of Public Health

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DATA EXERCISE

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Objective of DATA EXERCISE

1. To investigate the availability of data in routine basis, to decide whether new data need to be collected for data collecting form which will be used for prospective cohort study
2. To investigate the process of data collection for analyzing the data quality
3. To investigate the characteristics of TB cases among HIV-infected persons registered for 9 month IPT program in Chiang Rai province.

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Study Design and Population

- Design

  This Study is cross sectional descriptive study
- Population

  HIV Infected Persons who had active TB diagnosed during and after IPT in Chiang Rai.

  (Active TB was found by passive follow up of the IPT participants.)

  Passive follow up; recognizing that get TB diagnosed at hospital and some patients never return to hospital but might become TB

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Method of Data Collection (1)

- 85 active TB cases among HIV Infected Persons registered for 9 month IPT were identified by using IPT registry and TB registry database.
- The investigation of availability of data in routine basis were done by using the medical record and IPT registry in each hospitals.

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Method of Data Collection (2)

- The investigation of data collecting process was done by observation of IPT registry, TB registry and interview of health care worker.
- The investigation of characteristics of TB cases were done by using medical record, TB registry and IPT registry, during 1995 - 2001 in 6 hospitals in Chiang Rai provinces. (Khuntan, Chiang Kong, Phan, Wiang Papao, Mae Chan, Mae Sai Hospital).

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Data Analysis

- Data was entered into SPSS version 10
- Quantitative analysis used frequency of characteristics of active TB cases with stratified by gender.
- Independent samples t test.

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Findings of Objective 1.
Availability of Data

A) Available Data

- Age, Gender,Nationality, address
- Entering Day care activity
- The frequency of visit to the hospital during IPT
- Weight
- Tuberculin skin test reaction
- Blood test (Complete blood cell count)
- The use of antiretroviral drug
- IPT and TB treatment outcome
- Dead date

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B) Not Available Data or cannot collect systematically

- Socio-cultural (income, education level, occupation, marital state)
- Life style (alcohol, cigarette, intravenous drug use, History of imprisonment)
- Contact with TB patients
- Current and past disease history
- Physical exam (height, BCG scar, mumpus anergy skin test)
- TB and AIDS symptom and sign
- Laboratory test (Liver function, CD4 lymphocyte count)
- The distance from houses to the hospitals and the way to travel to the hospitals

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Findings of Objective 2
The process of Data Collection

A) The information of IPT

- Only Mae Chan hospital has individual IPT registry written by TB/HIV research project staffs. These are 3 forms, Active TB screening form and IPT follow up form during and after Isoniazid medication.
- Another hospitals have not individual IPT registry and written by hospital nurses. The form of IPT registry are different in each hospital.

B) The information of TB

- All hospitals have the same TB registry written by hospital nurses.

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c) The information collected through interview in four hospitals

- Some symptonmatic HIV infected persons were registered for IPT.
- Some active TB screening befor IPT enrollment was done without sputum smear or chest X-ray.
- All hospitals using sputum smear and chest X-ray for active TB diagnostic method for IPT participants.

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Findings of Objective 3
Characteristics of TB cases

Demographic Facter (n =85)

	Numbe	Percentage
• Gender		
Male	53	62.4
Female	32	37.6
• Nationality		
Thai	83	97.6
Hill tribe	2	2.4

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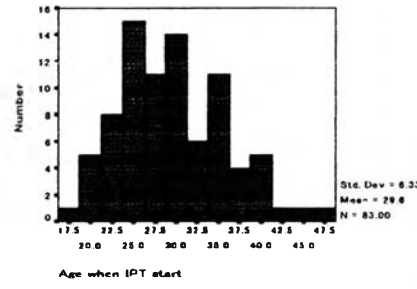
Distribution of Age When IPT Started



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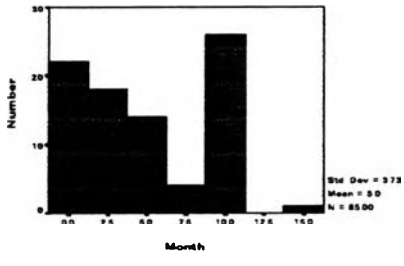
Months of Isoniazid Pill Taking



1 to 9 months 72 cases (84.7 %)
10 to 15 months 13 cases (15.3 %)

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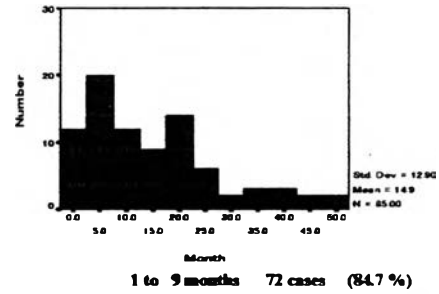
Time from Starting IPT to Become Active TB



1 to 9 months 72 cases (84.7 %)
10 to 15 months 13 cases (15.3 %)

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Description of TB Outcome
Site of TB

Site of TB	Number (%)
• Pulmonary	66 (77.6)
• Extrapulmonary	15 (17.6)
• Pulmonary & Extrapulmonary	4 (4.7)

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The Outcome of
Sputum Smear, Chest X-ray

	Number (%)
Sputum smear	
• Positive	39 (45.9)
• Negative	39 (45.9)
• Not done/ Unknown	7 (8.2)
Chest X-ray	
• Cavity	18 (21.2)
• Non cavity	23 (27.1)
• Effusion	1 (1.2)
• Missing	43 (50.6)

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The Relationship Between Sputum Smear and TB Site

Sputum outcome	Pul. TB	Extrapul. TB	Pul. and Extrapul. TB
Sputum smear Positive	34 (51.5 %)	2 (13.4 %)	3 (75 %)
Sputum smear Negative	31 (47.0 %)	7 (46.6 %)	1 (25 %)
Missing	1 (1.5 %)	6 (40 %)	0
Total	66 (100 %)	15 (100 %)	4 (100 %)

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Lessons Learned

1. Many data for prospective study could not be available.
2. Some active TB screening before IPT enrollment was done without smear or chest X-ray.
3. Compliance of IPT was low.
4. Many cases developed active TB during 9 month-IPT
   - Low number of TB after 9 months might be due to dropout from follow up system
5. Many extrapulmonary TB cases were observed in spite of sputum smear negative.
6. Nearly half of sputum smear were negative in pulmonary TB cases.

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Recommendations

1. Making deta collection forms for prospective study is needed.
2. The criteria of screening before IPT enrollment should inform to each hospitals clearly.
3. To increase IPT compliance is important.
4. More careful TB screening is needed.
5. More detail TB diagnostic guideline for extrapulmonary TB is needed.
6. Adding sputum smear, chest X ray and culture is needed for measureing TB incidence seriously.

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