CHAPTER II

ESSAY

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

2.1. Introduction

2.1.1 Global TB burden

Someone in the world is newly infected with TB every second. As estimated 30-60 % of adults in developing countries have TB infection and 7 to 8 million people around the world become sick with active TB. Active TB kills about 2 million people each year. The rate of active TB increase about 3 % year on average. (WHO, 2000)

The 23 highest-incidence countries are Afghanistan, Bangladisesh, Brazil, Cambodia, China, DR Congo, Ethiopia, India, Indonesia, Kenya, Mozambique, Myanmar, Nigeria, Pakistan, Peru, Philippines, Russia, South Africa, Tanzania, Thailand, Uganda, Viet nam, Zimbabwe. These 23 countries accounted for 80 % of all new cases in the world and

estimated numbers of new cases are 6.7 million. In Thailand, the global rank was reported 16. (WHO, 2001)

2.1.2 TB situation in Thailand

In Thailand, the prevalence and the incidence of active TB started to decline around 1985 due mainly to the implementation of short course active TB treatment regimens and improved therapeutic coverage and efficacy. The prevalence (per 100,000 population) dropped from 150 in 1985 to 76 in 1991.But, it appeared to revert to a new trend of increase started with 2 % average annual rise in the rates of new activ TB cases during 1992-1997. In 1999, estimated incidence was 141 per 10,000 population . (TB division, 1999)

2.1.3. Global HIV situation

According to the UNAIDS report (2000), the estimated number of adults and children newly infected with HIV during 2000 worldwide is 5.3 million and the estimated number of HIV infected persons is 36.1 million. In South East Asia, 78,000 people were newly infected with HIV during 2000 and the number of HIV infected persons is 5.8 million. Average adult prevalence rate is 0.56 % in South East Asia, but in Cambodia, Myanmar and Thailand, adult prevalence rate is exceeds 1%.

2.1.4. HIV situation in Thailand

From 1984, when the first AIDS cases was identified in the country, until 1999, there were cummulatively 740,000 HIV infected cases, 106,350 AIDS cases and 66,000 AIDS death were reported. Adult HIV prevalence was 2.15 %. (UNAIDS,2000)

2.2. Burden of TB and HIV co-epidemic

2.2.1. Global HIV /TB problem

The association between active TB and HIV presents as immediate and grave public health and socioeconomic thereat, particularly in the developing world. About a third of the world's population (around 2 billion) carries the TB bacteria and, about 11 million people are co-infected with TB and HIV in world wide.

Seventy percent of all TB cases are concentrated in Asia and between 56 and 80 % of AIDS patients in the South East Asia are co-infected with TB. (UNAIDS, 2000)

2.2.2 Burden of HIV/TB in Thailand

For TB patients in Thailand, HIV co-infection rate was 15.3 percent in 1998. (Ministry of Public Health, 2000) The study of 1091 patients with bacteriologically confirmed active TB in Central Chest Hospital, Bangkok, HIV seroprevalence was 22 % (Punnotok J. et al., 2000). Also active TB is the most frequent opportunistic infection among HIV infected

persons. The study of 88 HIV infected persons in Srinagarined Hospital from 1992 – 1994, 37.2 % of HIV infected persons had active TB. (Mootsikapun P et al.,1996)

2.2.3. HIV/TB situation in Chiang Rai

Chiang Rai Province is in the northern area of Thailand. The population was about 1.2 million in 1996.The first case of AIDS in Chiang Rai was reported in 1998 and there was an explosive epidemic among intravenous drug users and female commercial sex workers. The active TB case rate in the province has increased from 50 cases per 100,000 populations in 1990 to 140 cases per 100,000 in 1999, and about half of all active TB cases are co-infected by HIV. (Ngamvithayapong J.et al., 2001)

2.3. *Mycobacterium tuberculosis* transmission

2.3.1. TB transmission

"The bacteria are transmitted through the air. When a person with active TB in their lungs coughs or sneezes, they exhale droplets of moisture which contain bacteria. The very tiny droplets can remain suspended in the air for long periods of time. In another person inhales these droplets deep into the their lungs then they can become infected. Only people with active TB are infectious. Those with TB infection are not." (Cegielski J.P.)

2.3.2. TB infection versus active TB

The TB infection means that TB bacteria is under control by the immune system, the person perceives no symptoms of being sick, and there is no active disease. The person is not infectious to others at this stage. TB infection is shown by a positive reaction to tuberculosis skin test. Table 2.1 shows the comparison of TB infection and active TB.

Table 2.1 Comparison of TB infection and Active TB

	TB infection	**Active TB**
Symptoms	No	Yes
Tuberculin skin test	Positive	Positive
Chest X-ray	Stable	Worsening
M. tuberculosis	Dormant	Rapid growth
Infctiousness	No	Yes
Effective treatment	One drug (INH)	Multiple drugs

(Cegielski J.P.)

2.3.3. Conditions that increase the risk of active TB

"Anyone whose immune system is weak from any reason that comes into contact with active TB cases is at much higher risk of developing the active disease. People with HIV

infection are at the highest risk of developing active TB, but many other conditions also increase the risk of active TB. (Substance abuse, recent infection with *Mycobacterium tuberculosis*, prior active TB not adequately treated, diabetes mellitus, silicosis, low body weight, certain kinds of cancers, kidney failure, intestinal bypass surgery or removal of the stomach, chronic intestinal malabsorption, immunosuppressive drugs such as steroids, pregnancy, extremes of age)" (Cegielski J.P)

2.3.4. Risk of active TB among HIV infected person

In high TB prevalence countries, between 2.4 and 7.5 % of HIV infected adults may develop active TB each year. In those with a positive tuberculin test, the rate rises to between 3.4 and 10 % per year (WHO and UNAIDS, 1998). Study in Thailand shows HIV infected persons are at risk of getting active TB at a rate of approximately 5 % per year and more than 30 % - 40 % during their life-time. (TB division, 2000)

2.4. Diagnosis of TB

2.4.1 Diagnosis of TB infection and active TB

"The diagnosis of active TB is established first of all by a careful medical history, finding out about symptoms, any possibility of exposure of TB bacteria, and risk factors. Next a careful physical examination may reveal clues to the presence of active TB. Then

tuberculin skin test and chest X-ray may provide strong evidence for or against the presence of TB infection or active TB. " (Cegielski J.P.)

But definitive diagnosis is confirmed by the isolation and identification of *mycobacterium tuberculosis* from the sputum or other body fluids and tissue specimens in the laboratory.

The six TB diagnostic methods is described below.

1. The medical history

- Been exposed to a person who has infectious TB.
- Had TB infection or active TB before.
- Risk factors for developing active TB.

2. Symptoms of TB

- Symptoms of active TB: Pulmonary TB have coughing, pain in the chest when breathing or coughing, cough up sputum or blood.
- Pulmonary and extrapulmonary active TB have weight loss, fatigue, malaise, fever, night sweats.

3. The tuberculin skin test

- The tuberculin skin test is used to determine whether a person has TB infection.
- False positive reactions can be caused by infection with nontuberculous mycobacteria or vaccination with BCG.

- False negative reactions can be caused by anergy, recent TB infection (within the pat 10 weeks), very young age (younger than 6 months old).

4. The chest X-ray

- CXR are useful for diagnosing activre TB because about 85 % of active TB cases have pulmonary TB

5. Sputum smear

- Sputum specimen are smeared onto a glass slide and stained and examined for acid-fast bacilli (AFB) under a microscope.

6. Sputum culture

- Growing mycobacteria on media, substances that contain nutrients in the laboratory and it takes as long as 2 to 8 weeks.

2.4.2. The definition of pulmonary and Extrapulmonary TB

The main categories of active TB by anatomical site of disease are pulmonary and extrapulmonary TB.

Pulmonary TB

Pulmonary TB refers to disease affecting the lung parenchyma. Tuberculosis intrathoracic lymph nodes (mediastinal and hilar) or tuberculosis pleural effusion.

- **Pulmonary TB, Smear positive**

a) A patient with at least two sputum specimens positive for acid-fast bacilli by microscopy (AFB+ve).

b) A patient with at least one AFB+ve and chest X-ray suggestive of active Pulmonary TB (PTB);and decision by a physician to treat with a full curative course of anti-TB chemotherapy.

c) A patient with at least one AFB+ve, which is culture –positive.

- **Pulmonary TB, Smear negative**

a) A patient with at two AFB - ve and chest X-ray suggestive of PTB, and a lack of clinical response despite one week of a broad-spectrum antibiotics. Also a decision by a physician to treat with a full curative course of antituberculosis chemotherapy.

b) A patient with severely ill at two AFB - ve and chest X-ray suggestive of extensive PTB (interstitial or miliary). Also a decision by a physician to treat with a full curative course of antituberculosis chemotherapy.

c) A patient whose initial sputum smears were negative, who had sputum sent for culture initially, and whose subsequent sputum culture result is positive.

Extrapulmonary TB

Extrapulmonary TB is much less common than pulmonary TB. The commonest forms are the following: lymphadenopathy, pleural effusion, pericardial disease, miliary disease, meningitis.

a) A patient with AFB+ve or culture in one examination from extrapulmonary specimens.

b) A patient with microbiological and clinical evidence of active TB and decision to give full treatment has been made by physician.

(WHO, 1997)

2.5. TB diagnosis among HIV infected persons in disease endemic countries

Active TB is a common disease for HIV infected persons and early diagnosis is very important. But the active TB diagnostic method is insufficient in disease endemic countries including Thailand. In disease endemic countries, the sputum smear test retains its primary role in active TB diagnosis. National guidelines of active TB screening test in Thailand requires 2 positive sputum smear out of 3-sputum specimen to diagnose pulmonary TB.

2.5.1. High prevalence of sputum negative TB among HIV infected persons

WHO reports sputum smears are less sensitive to detect active TB for HIV infected persons. Studies in Zambia show 43% of HIV positive pulmonary TB patients are smears negative (WHO, 1994). Study of Samb B (1999) in West African Senegal shows that, AFB-negative smears were found in 14/40 (35.0%) of the HIV-seropositive patients with pulmonary TB compared with 71/410 (17.3%) of the seronegative patients. HIV

seropositive pulmonary tuberculosis patients are more likely to have negative sputum smears.

2.5.2. Transmission of *M. tuberculosis* from smear negative patients.

The study in San Francisco, US, using molecular fingerprinting techniques demonstrated that 17 percent of active TB transmissions were attributable to sputum smear negative cases, and that the relative transmission rate from smear negative compared to smear positive active TB was 0.22, or roughly one fifth of all transmission. Also in a study done in Spain the relative risk of active TB in contacts of smear negative patients can be calculated as 0.47. The relative transmission rate of smear negative culture positive patients has important implications for the management of TB control programmes in developed and developing countries. (Behr M.A.,1999)

2.5.3. Difficulty of diagnosing smear negative TB among HIV infected persons

Study in Uganda recommends sputum culture for active TB screening for HIV infected persons. Negative and paucibacillary (very scanty or scanty) sputum acid fast bacilli smears were more frequent in HIV infected persons presenting with pulmonary TB. (Johnson J. et al.,1998)

2.5.4. High prevalence of extrapulmonary TB among HIV infected persons

Extrapulmonary TB is seen in only about 15 % of cases in immunocompromised individuals, but it occurs with greater frequency in those infected with HIV. (Lee B. Reichman and Earl S. Hershfield.)

The study in northern Thailand shows that 7 cases become active TB from 324 IPT participants and 2 cases were pulmonary TB and 5 cases were extrapulmonary TB. (Akarasewi P, et al, 1999) Another study of active TB among HIV infected persons in Bamrasnaradura hospital in Thailand shows that, extrapulmonary TB (58%) was more common than pure pulmonary involvement (42%). (Tansuphaswadikul S et al, 1998)

2.5.5 Difficulty of diagnosing extrapulmonary TB among HIV infected persons

Active TB patients usually have constitutional features (fever, night sweats, weight loss) and local features related to the site of disease. Definitive diagnosis of extrapulmonary TB is often difficult. Diagnosis maybe presumptive provided physician could exclude other conditions. (WHO,1996)

2.6. Isoniazid preventive therapy (IPT)

Preventive therapy is medication that is given to people who have TB infection to prevent them from developing active TB. Some groups of people are at higher risk for active TB

than others should receive preventive therapy. These groups are either more likely to be exposed to or infected with *M. tuberculosis*, or more likely to develop active TB once infected. HIV infected persons are one of higher risk group and HIV infected persons should be given high priority for preventive therapy if they have a positive tuberculin skin test reaction. (CDC, 1995)

2.6.1. Guideline of medical evaluation for IPT in Thailand

All people being considered for IPT should receive a medical evaluation to exclude active TB. The guideline of medical evaluation for IPT in Thailand is described below.

Indication

1. Asymptomatic HIV infection and
2. No symptoms and signs of active TB and
3. Normal chest X-ray and
4. History of contact to active pulmonary TB or
5. Positive tuberculin skin testing (over 5mm) by intradermal administration of 5-TU (Mantoux method)

2.6.2. The IPT regimen in Thailand

Isoniazid 300 mg taken orally once daily for 9 months

(Ministry of public health Thailand, 2000)

2.6.3. Efficacy of IPT

There are several prospective, randomized controlled trials of IPT among HIV infected persons. In the first study, 12 months of daily Isoniazid in Haiti resulted in 83 % active TB protection among tuberculin skin test positive persons. 6 month of daily Isoniazid provided significant level of protection in Uganda (68 %) but did not provide significant level of protection in Kenya (40 %). (CDC MMWR. ,2000)

Moreno S et al. (1997) reports the incidence of active TB was higher among HIV infected persons with no-IPT (9.4 6 per100 patients-years) than HIV infected persons completed 9 – to 12- month IPT (1.6 per100 patients-years).

A meta-analysis of seven randomized controlled trials shows the relative risk of IPT versus non-IPT among HIV infected persons was 0.4 in tuberculin positive and 0.84 in tuberculin negative. They conclude IPT reduces the risk of active TB in persons with HIV infection, but the effect is restricted to tuberculin test positive persons. (Bucher et al., 1999)

2.6.4. Situation of active TB among HIV infected person with IPT in Chiang Rai

The study of 412 HIV infected persons in Mae Chan Hospital, Chang Rai from 1995 to1999, showed active TB incidence among HIV infected persons who completed 9-month IPT was 1.8 per 100 person-years, incomplete IPT was 4.5 per 100 person-years

and no-IPT was 8.2 per 100 person-years. In addition to 9 (2.2 %) cases become active TB during 9-month IPT, an additional 8 (1.9 %) cases become active TB after IPT. Total 17 active TB cases were observed and incidence rate was 2.5 per 100 person-years. There were 7 cases of smear-positive pulmonary TB, 9 cases of smear-negative pulmonary TB, and 1 case of extrapulmonary TB. (Piyaworawong.S., 2000)

2.6.5 Side effect of Isoniazid

Common Isoniazid drug toxicitities are peripheral neuropathy * and hepatitis*. Rare Isoniazid drug toxicitities are convulsions, pellagra, joint pains, agranulocytosis, lupoid reactions, skin rash.

***Peripheral neuropathy** – damage to the sensory nerves of the hands and feet, causing a tingling sensation or a weakened sense of touch in the hands and feet.

***Hepatitis** – damage to the liver, causing symptoms such as nausea, vomiting, abdominal pain, fatigue, and dark urine.

Isoniazid can cause hepatitis in anyone. In fact, as many as 20 % of people treated with Isoniazid have some abnormality of liver function tests during treatment with Isoniazid. In most people, these test results return to normal even when Isoniazid treatment is continued.

Nolan C. M. et al (1999) reported that 0.15 % those who completed IPT had hepatotoxic reactions to Isoniazid during IPT. The rate of hepatotoxicity in persons receiving IPT increased with increasing age and there were trends toward increased rates in women.

2.7. Factors affecting the development of active TB among HIV Infected Persons registered for IPT

Some factors might be related to development of active TB were described below.

1. Age

Halsey et al. (1998) showed that aged 30 years or older were somewhat, but not significantly, more likely to develop active TB than younger IPT participants.

2. BCG scar

About 20- 50 % of BCG vaccine recipients have no scar. The status of BCG vaccine on the basis of post vaccination scare is that the range of efficacy of the BCG vaccine was 50-60 %. Halsey et al. (1998) showed no BCG scar was related to development of TB but not significant.

3. Exposure of TB

The study of Casado J L et.al. (2002), from 131 HIV infected persons who received over 9 months of IPT, 8 patients develop TB (6 %; 0.61 cases per 100 patient-years). Only the

persistence of risk factors for exposure to TB (Prison admission, Drug addiction) was statistically associated with development of active TB.

4. Complete blood count

The effect of preventive therapy was greater in those with a lymphocyte count of 2 $X10^{9}$/ l or higher, and in those with hemoglobin of 10 g/dl or higher. (A. Mwinga et al.,1998)

5. Baseline percentage CD4 lymphocyte

The study of HIV infected persons with 6 month IPT showed that baseline percentage CD4 lymphocytes less than 20 were associated with the subsequent development of active TB. (Halsey Neal A et al, 1998)

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