PHYSICIAN ADHERENCE TO ISONIAZID PREVENTIVE THERAPY GUIDELINES FOR HIV-INFECTED PATIENTS IN THAILAND

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Abstract. Isoniazid preventive therapy (IPT) has been shown to reduce the risk of active tuberculosis in tuberculin skin test (TST) positive human immunodeficiency virus (HIV) infected individuals. The World Health Organization has recommended IPT for HIV-infected patients since 1999. Physicians' non-adherence to the IPT guideline is one of the limitations to the wide spread use of IPT. A study of the extent to which physicians in Thailand adhere to this guideline will optimize the implementation of national IPT program. Three hundred physicians who provided medical care for HIV-infected patients were sampled by multistage cluster sampling of public hospitals according to the region and the level of health care service. Fifty-eight (19.3%) of the surveyed physicians provided IPT; 86.2% and 34.5% of physicians who provided IPT did not do the TST or screening chest radiography for active TB, respectively. Experience with HIV patient care was significantly associated with providing IPT.

INTRODUCTION

As a consequence of the human immunodeficiency virus (HIV) pandemic, the global burden of tuberculosis (TB) is increasing dramatically both in terms of morbidity and mortality in many developing countries. (Raviglione *et al*, 1992; Dolin *et al*, 1994; Joint Tuberculosis Committee, 2000; Gillini and Seita, 2002; Leonard *et al*, 2002; Williams and Dye, 2003; de Colombani *et al,* 2004; Narain and Lo, 2004).

In Thailand, the annual incidence of TB was about 90,000 cases with 18,000 death each year (Payananda, 1995; Department of Communicable Disease Control, 1999). After implementation of DOTs in 1995, the detection and cure of new TB cases all have been successfully achieved. In order to augmenting the control of TB in the country, Division of TB Prevention and Control is considering whether implementation of isoniazid preventive therapy (IPT) program should be conducted nationwide. IPT has been shown in several randomized controlled trials to reduce the risk of developing active TB in tuberculin skin test (TST) positive HIV-infected individuals (Hawken *et al,* 1997; Mwinga *et al,* 1998; Gordin *et al*, 2000; Wilkinson, 2000; Woldehanna and Volmink, 2004). In 1998, WHO and UNAIDS convened a meeting to review the data available regarding preventive therapy for TB and to make recommendations to governments that would serve to update the recommendations published by the WHO and the International Union Against TB and Lung Disease (IUATLD) in 1993 (Anonymous, 1994). From that meeting, in 1999, WHO published specific guideline addressing IPT among HIV-infected persons. (Anonymous, 1999). This guideline recommended that the following steps should be included in the delivery of IPT: (1) counseling on TB; (2) screening for active TB; (3) targeting of those most likely to benefit from IPT; (4) provision of IPT to those without active TB; (5) monitoring for adherence and toxicity of IPT; and (6) evaluation of outcome of TB. The physicians' acceptance and practice of IPT according to this guideline is a major factor for the success of IPT implementation in each country. However, studies in western countries showed that only 47-80% of physicians provided

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IPT for their HIV-infected patients according to the guideline (Sackoff *et al*, 1998; DeRiemer *et al*,1999). In Thailand, the extent that the physicians adhere to this guideline has not been studied. Understanding this issue will provide the information to optimize an effective implementation program of IPT among HIV-infected patients.

MATERIALS AND METHODS

A cross-sectional survey about the adherence to the IPT guideline, published by WHO, was done by personal interview of physicians who provided medical care for HIV-infected patients in Thailand. Because, in Thailand, physicians in specialties other than internal medicine deemed unlikely to provide medical care for HIV-infected patients, we included only the internists and general practitioners who worked in the public hospitals under the organization of the Ministry of Public Health, the Bureau of University Affairs, and the Bangkok Metropolitans Administratives as the target population for the study. We used the hospital list as the sampling frame and the physicians who provide medical care for HIV-infected patients in the hospital as the sampling element.

The multistage sampling technique was used as follow: (1) stratifying the hospitals in Thailand into 13 zones according to the geographic locations and organization structure of the Thai Ministry of Public Health; (2) from each zone, excluding Bangkok, we randomly selected the provinces ; (3) from each province, we stratified the hospitals according to the level of health service :- the medical school or regional hospitals, general hospitals, and community hospitals. We selected every medical school or regional hospitals and general hospitals in that province and randomly selected the community hospitals. For Bangkok, because there are more medical schools or regional hospitals and general hospitals than provincial area, we randomly selected them into the study.

For the number of physicians in each zone and each level of hospital, after obtaining total studied physicians from sample size calculation, we used a frequency sampling according to the ratio of the number of internists and general practitioners among each zone and each level of hospital (from the annual report of the Ministry of Public Health of Thailand in 2000) to achieve the number of physicians to be surveyed in each hospital. Each physician was then contact by telephone call explaining briefly about the project. If they agreed to participate, the visiting appointment was done. On the visiting day, after giving the informed consent, they were personally questionnaire-interviewed about their adherence to IPT guideline regarding to counseling on risk of developing TB, provision of IPT, TST screening, screening for active TB and monitoring of IPT. The survey was done by 4 well-trained research nurses. They were invited to a meeting in Bangkok prior to the interviewing process. They were informed about the objectives of the study and the questionnaire. Questions about the questionnaire and others were discussed and clarified particularly the readability and comprehension among the interviewers. Then, the interviewers pretested this questionnaire by interviewing physicians attending a training course in Critical Care Medicine in Bangkok during February 2002. Finally, the questionnaire was revised and used for interview from March to June 2002. Each interview took about 30-60 minutes.

Sample size calculation and statistical analysis

Sample size calculation was based on the following formula:

$$n = \frac{Z^2_{1-\alpha/2} P\,(1-P)}{d^2}$$

While P is a proportion of studied physicians who provide IPT. d = desired precision, $Z_{1-\alpha/2} = 1.96$ at $\alpha = 0.05$, two-tailed. Because a study of physician's practice for IPT has not been done in Thailand, so we use the number from the study in other country as a reference. Study in the USA found that 47% of physicians provide IPT to their HIV-infected patients. We assumed that the proportion of physician in Thailand who provides IPT in is 50% of that in USA. So, we used 24% as the proportion for calculating sample size. With 5% precision range of this proportion, the minimum sample size was 280 at 5% alpha level. For our study, 300 physicians

were enrolled and interviewed.

For statistical analysis, we used a median and percentage for descriptive data. The chi-square and Fischer exact test were used to examine the association between the independent and dependent variables.

RESULTS

Three hundred physicians were questionnaire-interviewed. The median age of the studied physicians was 26 years (ranged 22-64 years). One hundred and twenty-three participants were female (41%) and 216 physicians (72%) had graduated from medical school for 5 years or less. Seventeen percent of the studied physicians were working in Bangkok and 83% were working in the provincial areas. About 60% of them were working in the community hospitals (Table 1). Two-thirds had been providing care for HIV-infected patients for 1-5 years. Approximately 50% were providing care for 1-9 patients per month, while 14% were providing care for more than 50 patients per month (Table 2).

Seventy-four physicians (24.7%) provided counseling about the risks of developing TB. Fifty-eight physicians (19.3%) provided IPT to their HIV-infected patients. Among physicians who did not provide IPT, the most common reason was TST was not available in the hospital or not practical because the tested patient had to come back for test result reading 2-3 days afterwards (39.7%). Other reasons were patient's poor adherence (24.8%), IPT might induce the occurrence of isoniazid-resistant TB cases (20.2%), concern about side effect of isoniazid (12.8%), chest X rays were required prior to IPT (9.9%), and they felt that IPT was not beneficial (6.2%). Regarding to TST, 50 physicians (60.9%) provided IPT without doing TST. The reasons for

Table 1
Distribution of studied physicians according to duration of graduation from medical school, working province, and type of hospital where they were working.

	Number (300)	Percentage
Duration of graduation from medical school (year)		
< 5	216	72.0
6-10	26	8.7
11-15	24	8.0
16-20	12	4.0
>20	22	7.3
No. of physicians according to working region		
Bangkok	51	17.0
Central region	49	16.3
Eastern region	27	9.0
Western region	15	5.0
Northeastern region	82	27.3
Northern region	46	15.0
Southern region	30	10.0
No. of physicians according to the type of hospital where they were working[a]		
Community hospital	185	61.7
General hospital	57	19.0
Medical school or regional hospital	58	19.7

[a] The medical school and regional hospitals serve as teaching and training hospitals and also providing tertiary cares for the public health services. They have more than 500 beds. The general hospitals provide secondary medical cares for the public health services at the provincial level. They have 120-500 beds and located in every province. The community hospitals provide mainly primary and partly secondary medical cares for the public health services at the district level. They have less than 120 beds and locate in every district.

Table 2
Distribution of studied physicians according to duration of providing care and number of HIV-infected patients whom they provided care for during the past month.

	Number (300)	Percentage
Duration of providing care (year)		
< 1	49	16.3
1-5	212	70.7
6-10	28	9.3
>10	11	3.7
No. of physicians according to the number of HIV-infected patients whom they provided care for during the past month		
1-9	173	57.7
10-19	59	19.7
20-49	37	12.3
50-99	12	4.0
100+	19	6.3

Table 3
Reasons for not providing IPT to HIV-infected patients among 242 studied physicians[a].

Reason	Number (n = 242)	Percentage
TST is unavailable or impractical	96	39.7
Patient's poor adherence	60	24.8
May induce isoniazid-resistant TB cases	49	20.2
Increase risk of developing side effect from isoniazid	31	12.8
Need to do chest X rays prior to IPT administration	24	9.9
IPT is not beneficial	15	6.2
Others	14[b]	5.8

[a]Each subject might have more than one reasons.
[b]Did not have the information of IPT (10), not confident about the benefit of IPT (4), IPT had short term benefit (1), IPT could not increase the survival of patient (1), most of the patients had several opportunistic infections (1), INH should be used only for treatment option (1), IPT should be used only in a child with history of contact TB (1), situation of TB in Thailand was different from western countries (1).

not doing TST were: no TST available in their hospitals (60%), patients could not come back for test result reading 2-3 days after TST (48%) and concern about the reliability of the test (44%) (Table 4). Among 58 physicians who provided IPT, one-third did not do the chest radiography prior to IPT because their patients had no symptom or sign suggestive of pulmonary TB (80%), increased cost to their patients (15%), and chest radiography was neither sensitive nor specific enough for screening of active pulmonary TB (5%) (Table 4).

Forty-eight participants (82.8%) provided IPT for 6-12 months and the remaining did them lifelong. More than two-third of the physicians followed up their patients every month after providing IPT (Table 5). At follow-up, 48 physicians (82.8%) assessed the adherence to IPT. Regarding to the method of adherence assessment, forty subjects (83.3%) looked at the appointment keeping of the patients, five (10.4%) assessed the adherence by patient's self report and three

Table 4
Reasons for not doing TST and chest radiography prior to IPT among studied physicians who provided IPT.

	Number	Percentage
Reasons for not doing TST (n = 50)		
No TST available in the hospital	30	60
Patients had to come back for test result reading 48-72 hours later	24	48
Result of TST reading was not reliable	22	44
Patients refused to do it	5	10
Reasons for not doing chest radiography (n = 20)		
Patients had no symptom or sign suggestive of pulmonary TB	16	80
Increase cost to the patients	3	15
Chest radiography was neither sensitive nor specific enough for screening of active pulmonary TB	1	5

Table 5
The frequency of follow-up the HIV-infected patients for whom IPT were prescribed.

Frequency of follow-up	Number	Percentage
Every month	38	65.5
Every 2 month	13	22.4
Every 3 month	6	10.4
Every 6 month	1	1.7
Total	58	100

(6.3%) assessed by pill count. We found that183 physicians (61%) had seen WHO guidelines for providing IPT in HIV-infected patients. Our study revealed that physicians who worked in the medical school or regional hospitals significantly provided IPT more than individuals in the community hospitals. There was also a statistically significant association between providing IPT and the number of HIV-infected patients under medical care in the previous month (Table 6).

DISCUSSION

In Thailand, despite high prevalence of both HIV and *M. tuberculosis* infections and frequent dual infections, not all physicians are knowledgeable about the minimum standard of care regarding to TB preventive therapy among HIV-infected patients. Our results showed that, although more than half of studied physicians had seen the WHO guidelines for providing IPT in HIV-infected patients, the adherence to this guideline was still low. Only 25% of interviewed physicians routinely provided information to HIV-infected patients about the risks of developing TB compared to 65% in the study among physicians in USA (De Riemer *et al*, 1999) and only 20% provided IPT to TST-positive HIV-infected patients compared to 47-80% of physicians in USA (Sackoff *et al*, 1998; De Riemer *et al*, 1999). In addition, among physicians who provided IPT, 40% did not do the TST and one-third did not do the chest radiography for screening of active TB prior to administration of IPT. The operative problems of TST; including unavailability of test and patients had to return for test reading, were reported as the most common reason among physicians who did not provide IPT and who provided IPT without doing TST. Therefore, integrating IPT, including TST, into the HIV voluntary counseling and testing services with flexible hours of service in Thailand are needed before nationwide implementation of IPT.

Other major reasons for not providing IPT were poor adherence of patients and concern of inducing INH-resistant TB cases. Several studies of IPT among HIV-infected patients in Thailand actually found that most of the patients adhere to IPT and the adherence rates were 67.5- 84.5%. (Natrapan *et al*, 1996; Ngamvithayapong *et al,*

Table 6
Physicians who provided IPT and type of hospital according to the level of health care service and the number of HIV-infected patients under medical care.

	Providing IPT			p-value
	Yes (%)	No (%)	Total (%)	
Type of hospital according to the level of medical care				
Medical school hospital or Regional hospital	40 (69.0)	18 (31.0)	58 (100.0)	< 0.05
General hospital	40 (70.2)	17 (29.8)	57 (100.0)	
Community hospital	132 (82.2)	53 (17.8)	185 (100.0)	
Number of HIV-infected patients under medical care (per month)				
1-9	143 (82.7)	30 (17.3)	173 (100.0)	< 0.05
10-19	46 (78.0)	13 (22.0)	59 (100.0)	
20-49	23 (62.2)	14 (38.8)	37 (100.0)	
50-99	6 (50.0)	6 (50.0)	12 (100.0)	
≥ 100	14 (73.7)	5 (26.3)	19 (100.0)	

1997, Hiransuthikul *et al,* 2004). For HIV-infected persons who were administered IPT and subsequently develop TB, several studies suggested that IPT did not lead to drug-resistant TB (Hong Kong Chest Service/Turberculosis Research Center, Madras/British Medical Research Council, 1992; Guelar *et al*, 1993; Moreno *et al,* 1993). However, the concern that preventive therapy for TB might lead to an increased incidence and dissemination of drug-resistant TB, if they were widely implemented, is appropriate. This concern is based on the inadvertent monotherapy or dual therapy of anti-TB drugs in HIV-infected people with unrecognized TB. Our study showed that one-third of the physicians who provided IPT did not do the screening chest radiography to exclude pulmonary TB and the most common reasons were their patients had no symptom and sign suggestive of TB. While it is recognized that most people with active pulmonary TB will have symptoms such as cough, it was shown from recent study that cough alone might be inadequate for screening patients for potential tuberculosis preventive therapy, and that a chest radiography might be necessary. (Hawken *et al*, 1999). Until the validity of different screening algorithms is well established, it is still recommended that a chest radiography is indicated for every individual before providing IPT and this issue should be advised to all physicians who are providing care for HIV-infected patients. Most of the studied physicians followed up their patients every month after IPT according to the recommendation by WHO. However, most of them assessed the patients' adherence by looking at the appointment keeping which had been shown to be an unreliable method for measuring adherence to anti-TB medication (Sumartojo, 1993). Our study found that number of HIV-infected patients to whom the physicians provided care, which reflected the experience in taking care of HIV-infected patients, was significantly associated with providing IPT. This corresponds to a study in USA which found that field experience in providing care for HIV-infected patients was probably the best predictor of physician's adherence with a recommended IPT guideline (De Riemer *et al*, 1999). Physicians who worked in the medical school or general hospitals usually had more HIV-infected patients than the community hospitals, so this might explain the association between providing IPT and type of hospital according to the level of health care services.

In Thailand, physicians who just graduated from the governmental medical school are mandated to work in the general hospital during the first year and then in the community hospital during the second and third year respectively after graduation. Subsequently most of them will leave the community hospital and continue their

residency training program in the medical school hospital. This probably explained the low median age, short duration of graduation and duration of providing care for HIV-infected patients among our studied physicians.

Our study was the first to assess the physician's adherence to IPT guideline from every level of health care services in Thailand. However, a number of physicians who worked in the private sector and other organizations of public sector, such as the Ministry of Defense, were not included. Because the practice of IPT might vary among different hospital settings, generalization of the results of our study may be limited.

Decisions about nationwide IPT program require a balance between the need of the individual and those of TB control at a public health level. The challenge in resource-limited countries will be to provide voluntary HIV testing and counseling, TST, and IPT in an integrated and supervised fashion to benefit as many people as possible without jeopardizing public health through undisciplined use of anti-TB drugs, future operative researches and cost-benefit studies are needed to answer these questions.

In conclusion, the physicians' adherence to the guideline of IPT among HIV-infected patients in Thailand was still low. Nineteen percent of physicians who provided care for HIV-infected patients in Thailand administered IPT and 86 and 34% of these physicians did not do the TST and chest radiography for active pulmonary TB screening prior to IPT. The major reasons for not providing IPT were the operative problem of TST, concerns of induction of drug-resistant TB and poor adherence of patients. Experiences in providing care for HIV-infected patients were significantly associated with IPT provision. Educational and training programs for physicians who are providing medical care for HIV-infected patients in Thailand should be a priority followed by implementing IPT service in the context of integrated care, with benefits to both TB control and HIV care.

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