Declining Prevalence of Drug-Resistant Tuberculosis among HIV/Tuberculosis Co-Infected Patients Receiving Antiretroviral Therapy

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Background: *Drug-resistant tuberculosis (DR-TB) is a serious threat in developing countries where the prevalence of both HIV and TB are high. Antiretroviral therapy (ART) has been more accessible in these countries. The present study aimed to determine the impact of ART on the prevalence of DR-TB among HIV/TB co-infected patients.*
Material and Method: *A retrospective cohort study was conducted among HIV-infected patients with culture-proved TB from 1999 to 2004. Susceptibilities of Mycobacterium tuberculosis to antituberculous drugs and rate of ART use were studied.*
Results: *There were 225 patients, mean age 35.8 years, 72.4% male and median CD_4 44 cells/mm^3. Patients who had received ART increased from 18.5% in 1999 to 92.1% in 2004 ($p<0.001$). The prevalence of DR-TB in the years 1999 and 2004 were 48% and 7.9%, respectively ($p<0.001$). The prevalence of isoniazid- and rifampicin-resistance significantly declined in 2004 when compared with those in 1999 ($p<0.05$).*
Conclusion: *The declines in the prevalence of DR-TB, INH- and RFP-resistance in HIV/TB co-infected patients are possibly attributable to the use of ART. In addition to the survival benefit from ART in HIV-infected patients, increasing use of ART among HIV-infected patients may eliminate DR-TB in this population.*

Keywords: *HIV, Tuberculosis, Drug resistance, Prevalence, Antiretroviral therapy*

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Tuberculosis (TB) is the most common opportunistic infection that occurs in HIV-infected patients worldwide particularly in Africa and South Asia[1,2]. It has been estimated that global prevalence of TB is greater than one third of the estimated 36 million patients infected with HIV[3]. South Asian countries including Thailand have a high rate of overlapping HIV and TB epidemiology[4,5]. In addition, TB is still the leading cause of mortality among HIV-infected patients, accounting for one-third of deaths in AIDS worldwide[1,5-7].

The prevalence of drug-resistant TB (DR-TB) in HIV-infected patients is higher than that in HIV-uninfected patients[8-12]. Some studies have demonstrated that the prevalence of DR-TB is 2-3 folds greater in HIV-infected patients[11,12]. The problem of drug-resistant TB in an HIV-infected population is a serious threat to HIV care, particularly in developing countries where the prevalence of both HIV and TB are high. A previous study has addressed the higher mortality rate among patients with DR-TB [13]. Recently, antiretroviral

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therapy (ART) has been more accessible in developing countries. Clinical data of the impact of ART on the prevalence of DR-TB in HIV-infected population is still limited. The present study aimed to determine the effect of ART on the prevalence of DR-TB among HIV-infected patients in an area of high prevalence of HIV and TB.

Material and Method

A retrospective cohort study was conducted among HIV-infected patients with culture-proved TB at Bamrasnaradura Infectious Diseases Institute, Ministry of Public Health, Thailand between January 1999 and December 2004. Inclusion criteria were as follows: (1) HIV-infected patients > 15 years of age, (2) firstly diagnosed active tuberculosis by positive culture for *Mycobacterium tuberculosis* and (3) susceptibility testing of *M. tuberculosis* was performed.

The results of susceptibilities of *M. tuberculosis* to isoniazid (INH), rifampicin (RFP), ethambutol (ETB), and streptomycin (STR) were studied. Rate of ART use in each year was determined. Prevalence of DR-TB (at least one anti-TB drug resistance), INH-resistance, RFP-resistance, ETB-resistance, STR-resistance, and multi-drug resistance (MDR-TB) in 1999 and 2004 were compared. The present study was reviewed and approved by the institute review board.

Culture of *M. tuberculosis* was performed using Lowenstein-Jensen medium and the proportion susceptibility testing method was conducted. MDR-TB was defined as *M. tuberculosis* resistant to both INH and RFP. ART was defined as combined triple antiretroviral drugs.

Mean (± standard deviation, SD), median (interquartile range, IQR) and frequencies (%) were used to describe patients' characteristics. Chi-square test and Mann-Whitney U-test were used to compare categorical and continuous variables between the two groups, respectively. All analyses were performed using SPSS version 11.5. A *p*-value of less than 0.05 was considered statistically significant.

Results

There were 225 patients with a mean age of 35.8 ± 8.1 years, and 72.4% were males. Median (IQR) CD_4 cell count at the time of TB diagnosis was 44 (17-114) cells/mm^3. Forty percent presented with pulmonary TB; the others had extra-pulmonary TB. One fourth had a history of AIDS-defining illnesses. Table 1 shows demographics and baseline characteristics of the patients.

Of 225 patients, there were 27, 50, 43, 26, 41, and 38 patients in the years 1999, 2000, 2001, 2002, 2003, and 2004, respectively. Percentages of HIV-infected patients who had received ART from the year 1999 to 2004 were 18.5%, 14%, 41.9%, 61.5%, 61%, and 92.1%, respectively (Fig. 1). Table 2 shows the rates of ART use and the prevalence of DR-TB in the year 1999 versus 2004. Patients who had received ART increased from 18.5% in 1999 to 92.1% in 2004 ($p < 0.001$). The prevalence of DR-TB to any one drug in the years 1999 and 2004 were 48% and 7.9%, respectively ($p < 0.001$). The prevalence of isoniazid- and rifampicin-resistance significantly declined in 2004 when compared with

Table 1. Demographics and baseline characteristics of 225 patients

Characteristics	Value
Age, years, mean ± SD	35.8 ± 8.1
Male gender, number (%)	163 (72.4)
Baseline CD4 cell count, cells/mm^3, median (IQR)	44 (17-114)
Baseline CD4 percentage, median (IQR)	4 (2-8)
Baseline plasma HIV RNA, copies/mL, median (IQR)	195,500 (7,121-462,500)
History of previous major OIs, number (%)	57 (25.3)
Site of TB, number (%)	
Pulmonary	90 (40)
Cervical lymph nodes	100 (44.4)
Intra-abdominal lymph nodes	6 (2.7)
Gastrointestinal tract	5 (2.2)
Central nervous system	8 (3.6)
Disseminated infection	16 (7.1)

OIs = opportunistic infections

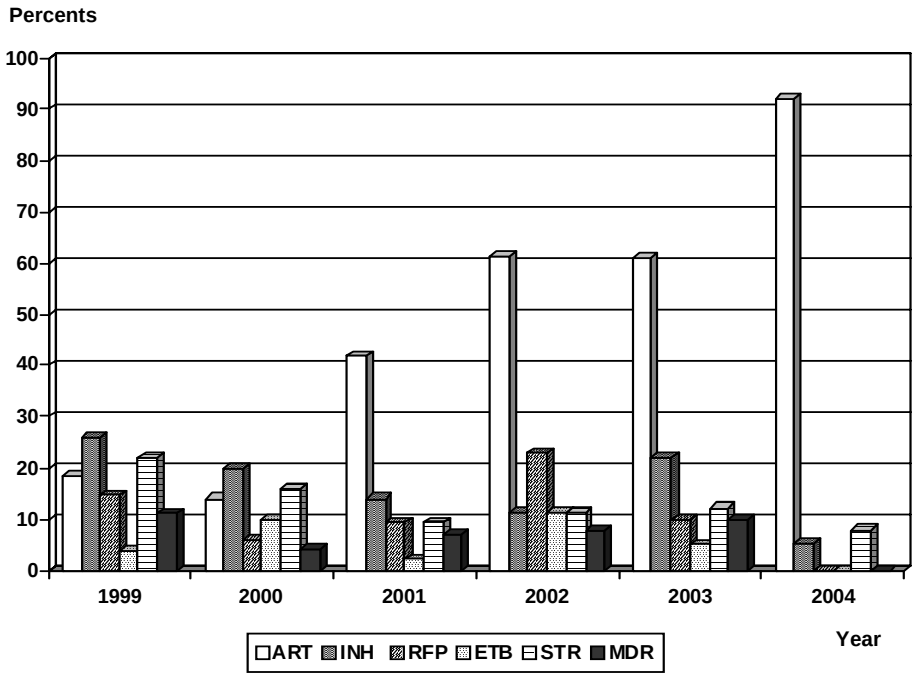

Fig. 1 Percentages of patients who had received ART and the prevalence of drug-resistant TB from the year 1999 to 2004
INH = isoniazid, RFP = rifampicin, ETB = ethambutol, STR = streptomycin

those in 1999 ($p < 0.05$). There was a trend toward a lower prevalence of MDR-TB in 2004 ($p = 0.067$).

Discussion

The results from the present study demonstrated that the prevalence of DR-TB has significantly declined from the year 1999 to the year 2004. Although many factors may contribute to this decline of the prevalence of DR-TB, the dramatically higher rate of ART use would play an important role. Since the advent of highly active antiretroviral therapy (HAART) for the treatment of HIV infection, the dramatic reductions in mortality and morbidity associated with immune reconstitution have included a marked decline in the incidence of several opportunistic infections particularly *Pneumocystis jiroveci* pneumonia[14,15]. Recent epidemiological studies suggest that ART can prevent the development of TB in HIV-infected individuals[16,17]. Kampmann B, et al has reported that mycobacterial-specific immune responses can be demonstrated in patients after commencing ART[18]. These findings may explain the findings from the present study that there was a significantly lower prevalence of DR-TB when the rate of ART use was markedly higher. Patients who had DR-TB may have a better response to treatment and may lead to a lesser spreading of DR-TB in HIV

Table 2. Use of ART and the prevalence of drug-resistant TB in the year 1999 versus 2004

ART and DR-TB	1999	2004	p-value
ART use (%)	18.5	92.1	<0.001
Drug resistance (%)			
Any one-drug resistance	48.1	7.9	<0.001
INH resistance	25.9	5.3	0.027
RFP resistance	14.8	0	0.026
ETB resistance	3.7	0	0.415
STR resistance	22.2	7.9	0.145
MDR-TB	11.1	0	0.067

population. However, further study is needed to confirm this observation.

In the year 1999, the prevalence of DR-TB (to any anti-TB drug) was almost 50%. Of these, approximately half had INH-resistance and about one-fifth was MDR-TB. The prevalence was concordant with the previous studies in Thailand in the same time period[11,12]. It brings a concern that DR-TB is a serious threat to health care in Thailand. After ART has been more accessible, the prevalence of DR-TB has declined dramatically. In addition to the established survival benefit from ART in HIV-infected patients, the results from the present warrant the importance of ART in terms of controlling DR-TB in HIV-infected population. Nevertheless, an implementation of direct observed therapy (DOT) for patients with DR-TB should be conducted in order to assure the appropriate treatment for drug-resistant TB.

The limitations of the present study included the nature of retrospective character that patients' microbiological results were missing. The authors included only patients who had cultures and susceptibilities of M. tuberculosis. This made the sample size smaller and may not be adequate to show the statistical significance of the declined prevalence of MDR-TB ($p = 0.067$). However, the sample size was adequate to demonstrate the significant declines of DR-TB including resistance to any anti-TB drug, INH-resistance and RFP-resistance.

In conclusion, the declines in the prevalence of DR-TB, INH-resistance and RFP resistance in HIV-infected patients with TB are possibly attributable to the use of ART. In addition to the survival benefit from ART in HIV-infected patients, increasing use of ART among HIV-infected patients may eliminate DR-TB in this population.

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การลดลงของความชุกวัณโรคดื้อยาในผู้ป่วยติดเชื้อเอชไอวีและวัณโรคที่ได้รับการรักษาด้วยยาต้านไวรัส

สมนึก สังฆานุภาพ, บุญช่วย เอี่ยมโภคลาภ, สุทัศน์ โชตนะพันธ์, ศุภิดา ทองเย็น, วีรวัฒน์ มโนสุทธิ

***ภูมิหลัง**: วัณโรคดื้อยาเป็นปัญหาที่สำคัญในประเทศกำลังพัฒนาที่มีความชุกของทั้งเอชไอวีและวัณโรคสูง การรักษาด้วยยาต้านไวรัสเป็นที่เข้าถึงมากขึ้นในประเทศเหล่านี้ การศึกษานี้มีจุดมุ่งหมายเพื่อกำหนดผลกระทบของการรักษาด้วยยาต้านไวรัสต่อความชุกวัณโรคดื้อยาในผู้ป่วยติดเชื้อเอชไอวีและวัณโรค*

***วัสดุและวิธีการ**: ทำการศึกษาแบบติดตามกลุ่มผู้ป่วยย้อนหลังในผู้ป่วยติดเชื้อเอชไอวีที่เป็นวัณโรคที่มีผลการเพาะเชื้อเป็นหลักฐานระหว่างปี พ.ศ. 2542-2547 ได้ศึกษาถึงความไวของเชื้อวัณโรคต่อยาต้านวัณโรคและอัตราการใช้ยาต้านไวรัส*

***ผลการศึกษา**: มีจำนวนผู้ป่วย 225 ราย อายุเฉลี่ย 35.8 ปี ร้อยละ 72.4 เป็นเพศชาย ค่ากลางของปริมาณซีดีสี่เท่ากับ 44 เซลล์/ลบ.มม. จำนวนผู้ป่วยที่ได้รับการรักษาด้วยยาต้านไวรัสเพิ่มขึ้นจากร้อยละ 18.5 ในปี พ.ศ. 2542 เป็นร้อยละ 92.1 ในปี พ.ศ. 2547 (ค่าพี < 0.001) ความชุกของวัณโรคที่ดื้อยาไอโซไนอะสิดและวัณโรคที่ดื้อยาไรแฟมปิซินในปี พ.ศ.2547 ลดลงจากปี พ.ศ. 2542 อย่างมีนัยสำคัญทางสถิติ (ค่าพี < 0.05)*

***สรุป**: การลดลงของความชุกวัณโรคดื้อยา วัณโรคที่ดื้อยาไอโซไนอะสิด และวัณโรคที่ดื้อยาไรแฟมปิซินในผู้ป่วยติดเชื้อเอชไอวีและวัณโรค ส่วนหนึ่งน่าจะเป็นผลมาจากการใช้การรักษาด้วยยาต้านไวรัสที่มากขึ้นนอกเหนือจากการที่ผู้ป่วยติดเชื้อเอชไอวีจะมีชีวิตที่ยืนยาวขึ้นจากการรักษาด้วยยาต้านไวรัสแล้วการรักษาด้วยยาต้านไวรัสที่ครอบคลุมมากขึ้นอาจจะลดปัญหาวัณโรคดื้อยาในผู้ป่วยเหล่านี้*