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Review article

WHO'S DOTS AND TUBERCULOSIS INFECTION IN DEVELOPING COUNTRIES WITH AN HIV EPIDEMIC

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How HIV affects tuberculosis

There are three ways how human immunodeficiency virus (HIV) infection has an impact on the epidemiology of tuberculosis (TB). They are as follows: endogenous reactivation of Mycobacterium tuberculosis pre-existing infection in people who later become infected with HIV; progression from Mycobacterium tuberculosis infection to TB in pre- existing HIV infected people; or TB patients, who have developed TB because of HIV infection, and transmit tubercle bacilli to the general population. The threat is serious in countries that are affected by the HIV pandemic and currently poor TB control programs.[1] There were approximately 1.4 million TB cases per year expected by the year 2000 past that could be attributed to HIV infection.[2] The incidence of HIV-associated TB will hamper poor developing countries in the future. Multidrug-resistant strains (MDR) of Mycobacterium tuberculosis also worsen the TB situation.[3] The increased risk of TB due to HIV infection in each country may vary according to the stage of the HIV epidemic, TB prevalence, and the age groups of those affected.[4]

Magnitude of the problem

According to a report from the World Health Organization (WHO), the Disability-adjusted Life Year (DALY) measures the burden of disease and expresses life lost in years to premature death and time suffered in years from a of a disability, accounted for a severity. Data from selected countries under surveillance of the WHO showed that maternal condition, HIV/AIDS, and TB were the three major causes of disease burden. They accounted for 7% of DALYs in 1998. The large proportion of the deaths that occurried among the age group 15 to 59 years old could be attributed to HIV and TB. A category of communicable diseases, maternal and perinatal conditions, and nutritional deficiencies accounted for 40.9% of DALYs. In this category, infectious and

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parasitic diseases accounted for 23.4% of DALYs, of which TB contributed 2.0% and HIV/AIDS 5.1%. However, proportions varied between high, low and middle income countries, with more burden among the latter two.[5]

In Thailand, there was an increase in HIV-related TB, particularly in the northern region. The incidence of reported TB declined from 1982 through 1991 and then increased rapidly after 1991. Data from the tuberculosis registry of Chiang Rai Provincial Hospital showed that the proportion of HIV-seropositive patients increased from 1.5% of all TB patients in 1990 to 45.5% in 1994.[6] McDonald LC *et al.* performed a prospective blood-culture survey in a hospital and found that mycobacterium tuberculosis bacteraemia might go unrecognized among febrile in-patients in Thailand, where both TB and HIV infections are high. As a consequence, Mycobacterium tuberculosis bacteraemia might cause nosocomial transmission of TB if patients were admitted.[7]

Control and prevention strategies

To improve the cure rate, early diagnosis and prompt treatment of TB patients are essential. In addition, Bacille Calmette Guerin (BCG) vaccination and prophylaxis among HIV–infected individuals are two other strategies needed.[8] Comstock GW reviewed the isoniazid recommendation for the prevention of TB and reported that among immunocompetent adults, a 9–10 month duration seemed to be appropriate.[9]

The Directly Observed Treatment, short-course strategy (DOTS), which is one of the key elements of the WHO guidelines, was introduced in the early 1990s and is accepted currently as a standard approach in over 100 countries. The aim of these guidelines is to improve the patient's adherence to treatment. This strategy seems to work, as it has achieved a high cure rate and treated over 1 million patients since 1990.[5] The WHO Global Tuberculosis Program has encouraged national TB programs to strengthen the DOTS program and conduct close monitoring of treatment outcomes. The WHO also conducted program reviews from 12 selected countries. Some of the main lessons learned from these reviews were that a program review was a useful tool to secure government commitment, and program success was related to a centralized direction, which supported decentralized implementation through the primary health care services also, control targets could be difficult to achieve if private and social security patients were left outside the scope of the program.[10] Evidence supported the success of the DOTS strategy, as in Bangladesh,[11] Caucasian countries,[12] and China.[13] Dye C *et al*. developed an age-structured mathematical model for forecasting the effect of improved case finding and a cure for TB epidemics in each of the six WHO regions. Results showed that the DOTS had a current effect on TB in several developing countries, more than it had in such

regions 50 years ago, and 48 million cases of TB would be prevented by 2020.[14] Nevertheless, the question of whether the DOTS works in developing countries with a high rate of HIV infection has been raised. Despite successful implementation in several African countries, TB case rates increase continuously where HIV prevalence is high. The DOTS can limit the development and spreading of drug resistance. However, it alone is less likely to control TB in sub-Saharan Africa.[15] The effectiveness of direct observation (DO), which was a part of the DOTS, was tested in a randomized controlled trial in South Africa. Zwarenstein M compared clinic-nurse DO with self-supervision to determine the effect of each on the success of TB treatment, and found that at high rates of treatment interruption, self-supervision achieved an equivalent outcome to clinical DO at a lower cost.[16] This trial brought about much attention and controversial issues, such as the following comments: the authors could not conclude a nullifying effect on the DOTS because a small proportion of subjects in each arm completed the treatment, and the authors could not rule out management and resource problems. Policy makers should consider self-administered therapy as one option for TB management;[17] and the authors did not mention other provisions of measures to promote adherence besides supervised swallowing.[18] There was another study conducted in Botswana during HIV and TB epidemics in sub-Saharan Africa. The results showed that the DOTS might aid in controlling drug-resistant TB, but might not stop the increasing TB case rate.[19] The DOTS might reduce the transmission of secondary infection, but might not prevent reactivation of latent TB HIV-related TB cases.[20] In most countries, the DOTS has been implemented within the framework of the national TB control program that is run by the ministries of health. Thus, their activities are emphasized on the public sector. In many countries, TB patients use publicly run health services as a last resort, therefore, the DOTS might not work as efficiently as it should.[21]

Major issues concerning the strategy of controlling TB are feasibility,[22] compliance,[23-24] and drug resistance.[25] Hawken MP recommended conducting a feasibility study before TB preventive therapy could be implemented on a large scale in developing countries.[22] Heifets LB suggested it essential that centralized laboratory services for drug susceptibility testing were reliable, practical, and affordable.[25]

Application in Thailand

In Thailand, the national tuberculosis control program (NTP) was introduced and it has been integrated with the provincial general health service since 1967. BCG was successfully implemented from the beginning, however, case findings and chemotherapy have been achieved since the late seventies after the establishment of hospitals at the

district level. The three national surveys in 1962, 1977 and 1991 showed a declining disease trend morbidity rate, infectious case rate, and annual risk of infection among children aged 0 to 14 years old. In 1985, short-course chemotherapy had been introduced and it covered all patients by 1991. This improved the treatment success rate from less than 50% when using the old standard to 70–80%.[26] Isoniazid prophy laxis treatment also decreased the incidence of active TB among HIV-infected people compared to those who did not use it.[27] During the HIV epidemic era, declining TB case rates were converted to increasing ones.[6] MDR-TB also increased. The rapid diagnosis and susceptibility patterns of MDR-TB are needed to improve treatment outcomes.[28] The WHO reviewed the TB control program in Thailand in 1995 and found low cure rates (17–68%). The Ministry of Public Health re-launched NTP with a new strategy that was implemented in pilot provinces in 1996. The new strategy directly observed short-course treatment by trained and supervised family members. The effectiveness of this strategy was evaluated in a pilot province in the northeast region and it was found that the cure rate was 85% among new sputum smear-positive pulmonary TB patients.[29] This result cannot be applied generally to the northern region where HIV infection is very high, since the infrastructure of the health care system and communication between areas are better in the northeast than in those of the northern region. More diverse ethnic groups in some provinces of the northern region and mountainous geographical areas that are hard to reach make the accessibility of health care services more difficult. The adherence study in northern Thailand showed that the isoniazid prophylaxis was feasible. Nevertheless, the selection of participants, enrollment process, and follow-up system among HIV-infected individuals needed to be adjusted.[30] Similar results of compliance problems could be observed in the central region.[31] The dual infections of HIV and TB were made worse by the recent economic crisis in Southeast Asia. The DOTS strategy is not designed to handle this kind of situation.[15] However, it could limit the development and spreading of drug resistant strains of tuberculosis and affect the transmission of new infections. In a limited government budget, the private sector, non-government organizations, and religious institutes should be more involve in the prevention program.[25,32] The NTP needed to be reviewed and its activities adjusted for each particular region or province. The major activities to be emphasized on are active case finding and preventive therapy via a modified standard approach, DOTS, and health care reform. The traditional standard approach recommended by the International Union Against Tuberculosis and Lung Disease has been disadvantaged by the heavy workload of smear examinations,

complexities of drug regimens used, and low completion therapy rates. An improvement to the drug regimen could be achieved by using a lower number of drugs in as short a period of time as possible.[33] Reducing laboratory investigations (*i.e.* two sample of sputum for screening TB suspects) and setting a sentinel site for drug resistance may be appropriate in Thailand.[34] The experience in rural South Africa showed that a community-based DOTS using an intermittent drug regimen and volunteers as supervisors could achieve high treatment completion rates.[35] This strategy may be applied in areas hard to reach in Thailand, where a family member option is not available. For health care reform, results from a feasibility study the integration of TB diagnosis and treatment into a district health system using the horizontal team, as in rural South Africa, should be applied. In addition, there is the possibility of a collaboration of HIV/AIDS programs in this kind of health care reformed, while pure vertical programs are less. [36]

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โครงการ DOTs ขององค์การอนามัยโลกกับวัณโรคในประเทศกำลังพัฒนาที่มีปัญหาการระบาดของโรคเอดส์

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บทคัดย่อ เชื้อไวรัสเอดส์ (HIV/AIDS) มีผลกระทบทางด้านระบาดวิทยาของวัณโรค โดยเฉพาะอย่างยิ่งประเทศที่มีการแพร่ระบาดของเอดส์อย่างหนักร่วมกับการมีโครงการควบคุมป้องกันวัณโรคที่ค่อนข้างแย่ องค์การอนามัยโลกเริ่มใช้มาตรการ Directly Observed Treatment Short-course (DOTS) ในต้นทศวรรษที่ 1990 และเป็นที่ยอมรับให้เป็นวิธีการมาตรฐานในปัจจุบัน เป้าประสงค์หลักของ DOTS คือทำให้ผู้ป่วยรับการรักษาอย่างต่อเนื่องจนครบกำหนด ทั้งนี้ปรากฏหลักฐานสนับสนุนความสำเร็จของมาตรการนี้จากหลายๆ ประเทศ

ประเทศไทยก่อตั้งแผนงานการควบคุมวัณโรคแห่งชาติตั้งแต่ พ.ศ. 2510 โดยผสมผสานไปกับการบริการสาธารณสุขระดับจังหวัด ในปี พ.ศ. 2528 มีการนำเอาโครงการการรักษาที่ใช้ระยะเวลาสั้นลงมาใช้ ซึ่งทำให้อัตราการรักษาที่ประสบผลสำเร็จเพิ่มขึ้น ต่อมาในยุคของการระบาดของเชื้อไวรัสเอดส์กลับพบว่าอัตราป่วยกลับเพิ่มขึ้น อีกทั้งเชื้อวัณโรคที่ดื้อยาก็เพิ่มขึ้นด้วย การทบทวนโครงการควบคุมวัณโรคของไทยในปี พ.ศ. 2538 พบว่าอัตราการรักษาหายค่อนข้างต่ำ ใน พ.ศ. 2539 กระทรวงสาธารณสุขได้ดำเนินปรับแผนงานควบคุมวัณโรคแห่งชาติโดยใช้กลวิธีการรักษา DOTs ผลการประเมินประสิทธิผลในจังหวัดนำร่องซึ่งอยู่ในเขตภาคตะวันออกเฉียงเหนือพบว่าอัตราการรักษาหายสูงขึ้นถึงร้อยละ 85 ในกลุ่มผู้ป่วยวัณโรคปอดที่มีผลตรวจเสมหะพบเชื้อ แต่ผลการศึกษานี้มิอาจจะนำไปใช้ในพื้นที่ภาคเหนือซึ่งมีการแพร่ระบาดของเชื้อไวรัสเอดส์ได้อย่างสมบูรณ์ เนื่องจากโครงสร้างพื้นฐานของระบบสาธารณสุขและการคมนาคมระหว่างพื้นที่ต่างๆ แย่กว่าในภาคตะวันออกเฉียงเหนือ นอกจากนี้ความแตกต่างทางด้านเชื้อชาติ ภาษา วัฒนะธรรมของชนเผ่าต่างๆ และภูมิประเทศที่เป็นเทือกเขาทำให้เข้าถึงการบริการได้ยากยิ่งขึ้น รวมทั้งปัญหาวิกฤติเศรษฐกิจเข้ามาซ้ำเติม มาตรการ DOTs ไม่ได้ถูกออกแบบมาเพื่อจัดการกับสถานการณ์เช่นนี้ ดังนั้นจึงจำเป็นต้องมีการทบทวนและปรับกิจกรรมต่างๆ ของโครงการควบคุมวัณโรคแห่งชาติที่สำคัญ คือ การค้นหาผู้ป่วยรายใหม่ การรักษาเพื่อป้องกันการติดเชื้อโรคโดยผ่านมาตรการที่ปรับเปลี่ยนให้เหมาะสม รวมถึง DOTs ที่ปรับให้เหมาะกับพื้นที่ การปฏิรูประบบสาธารณสุขที่คำนึงถึงการผสมผสานการวินิจฉัยโรคและการรักษาในระดับพื้นที่ โดยใช้บุคลากรส่วนต่างๆ ในพื้นที่ดำเนินเป็นหลัก **เชียงใหม่เวชสาร 2546;42(1):45-51.**