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Management of TB in HIV Subjects, the Experience in Thailand

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1. Introduction

Currently, tuberculosis (TB) remains a major public health threats of humankind. It has been occurred since antiquity and is the second communicable-disease cause of death after the human immunodeficiency virus (HIV)/ acquired immunodeficiency syndrome (AIDS). Of the mycobacterial diseases, TB is by far the most important because of its most virulence. Most of the disease and nearly all of the deaths occurs in the developing countries. Co-infection with HIV/AIDS and TB represents a public health crisis worldwide. An estimated 2 billion people worldwide carry latent infection and more than 8 million persons develop active TB each year. Approximately, 3 million people per year die from TB (WHO, 2010). Various comorbidities, especially the immunocompromised statuses will accelerate the TB sickness and deaths. The prevalence of primary drug- (Jiang et al., 2011) and multidrug-resistant (MDR) (Wells, 2010) pulmonary TB among the immunocompromised populations is globally increased. In Thailand, total-estimated TB cases is more than 140,000, now ranking 18 of the 22 high-burden countries of the world (WHO, 2010). The clinical features of active TB are very highly variable, depend on the immune status of the host and the site and extent of disease. New diagnostic, therapeutic, preventive and control strategies for TB are heavily investigated throughout the world. How we can rapidly diagnose TB within few hours and how we can shorten the treatment regimens to weeks or days. World elimination of TB is expected to occur in 2050 when the incidence is 1 patient per 1 million populations per year (WHO, 2010).

2. Epidemiology

While HIV/AIDS has continued to pose greater threats to the public health system worldwide which is a major risk of double increasing within the first year after *Mycobacterium tuberculosis* exposure and 10% per year for developing TB (Barnes et al., 1991, as cited in Silva et al., 2010 & Sonnenberg et al., 2001, as cited in Nachega & Maartens, 2009). Now it is clear that non-communicable comorbidities such as diabetes mellitus, especially type 2 (Goldhaber-Fiebert et

al., 2011), malignancies, chronic renal failure, immunosuppressive drug uses as well as biological modifiers such as rituximab and infliximab are undoubtedly adding to the multiple burdens the people suffer. A previous study in The Philippines demonstrated 37.4% of central nervous system TB among patients with systemic lupus erythematosus (SLE) (Vargas et al., 2009). Multiple immune system abnormalities contribute to high prevalence of TB with SLE (Prabu & Agrawal, 2010). Fatal tuberculous myositis at the left thigh was also reported in a 55-old-male patient with primary Sjögren's syndrome (Huang et al., 2010). TB patients with diabetes type 2 have lower antimicrobial peptides gene expression that contribute to enhance the TB-reactivation risk (Gonzalez-Curiel et al., 2011). A recent study conducted in India showed the ranks of risk factors for developing of TB disease as the following: diabetes (30.9%), smoking (16.9%), alcoholism (12.6%), HIV/AIDS (10.6%), malignancies (5.8%), chronic hepatic diseases (3.9%), history of TB contact (3.4%), chronic corticosteroid therapy (2.9%), chronic renal diseases and malnourishment (1.5%) (Gupta et al., 2011). No evidence was found that TB increases the risk of diabetes (Young et al., 2010). There has been a recent evidence of increased risk of lung malignancies among pulmonary TB patients and may increase further with coexisting chronic obstructive pulmonary disease (COPD) (Yu et al., 2011). A annual TB report of the fiscal year 2009 demonstrated that TB patients in northern Thailand who had COPD, HIV/AIDS, hypertension and diabetes mellitus ranked 1 to 4 of the specific causes of death (10th Zonal Tuberculosis and Chest Disease Centre, Chiang Mai, Thailand and the 10th Office of Disease Prevention and Control, Chiang Mai, Thailand, 2009 Tuberculosis annual report). A study in Brazil revealed that among the non-HIV-infected immunocompromised patients with TB, the only factor statistically related to mortality was the need for mechanical ventilation (Silva et al., 2010). In 2009, a total of 300,000 HIV-positive TB patients were enrolled on co-trimoxazole preventive therapy, and almost 140,000 were enrolled on antiretroviral therapy. In 2006 northern Thailand survey, only 69.6% and 63.1% of the HIV- infected/AIDS patients received co-trimoxazole prophylaxis therapy and antiretroviral therapy, respectively (10th Zonal Tuberculosis and Chest Disease Centre, Chiang Mai, Thailand and the 10th Office of Disease Prevention and Control, Chiang Mai, Thailand, 2006 Tuberculosis annual report). Almost 80,000 persons living with HIV were provided with isoniazid preventive therapy. This represents less than 1% of estimated number of HIV- infected persons worldwide. The 2015 targets are HIV testing of 100% of TB patients, enrolment of 100% of HIV-infected TB patients on antiretroviral therapy and co-trimoxazole preventive therapy while in 2009 revealed only 26%, 75% and 37%, respectively (WHO, 2010).

In northern Thailand, TB is the most common opportunistic infection among HIV-infected/AIDS individuals (38.9%) (Cheepsattayakorn et al., 2009). The highest prevalence of TB co-infected with HIV/AIDS in northern Thailand appeared in 1999 which was 48.8% of the total registered TB cases in the same year compared to 12.2% of the country (10th Zonal Tuberculosis and Chest Disease Centre, Chiang Mai, Thailand and the 10th Office of Disease Prevention and Control, Chiang Mai, Thailand, 2005 Tuberculosis annual report, Figure 1). In 2004 northern Thailand survey revealed that the extrapulmonary site of TB among HIV-infected/AIDS cases was accounted for 18.7% of the total TB cases, especially TB of the jugular lymph nodes (Cheepsattayakorn & Cheepsattayakorn, 2009). A recent study of extrapulmonary TB in a Caucasian population demonstrated that the proportion of extrapulmaonry TB has been increased while the overall incidence of TB has been reduced (Garcia-Rodriguez et al., 2011). This could be explained by an increase of life expectancy. There is no statistically significant difference between the development of pulmonary and

extrapulmonary TB among diabetic persons (Young et al,. 2010). A recent study in the United States and Mexico revealed high diabetes prevalence among newly-diagnosed TB cases which was 39% in Texas and 36% in Mexico, respectively (Restrepo et al., 2011). A recent study on TB among end-stage renal disease (ESRD) patients in Taiwan showed that the independent risk factors for TB infection in ESRD are male gender, old age, chronic obstructive pulmonary disease (COPD), and silicosis (Li et al., 2011). A survey between 2001-2007 in northern Thailand showed the highest incidence of TB among the populations with more than 64 years of age (10th Zonal Tuberculosis and Chest Disease Centre, Chiang Mai, Thailand and the 10th Office of Disease Prevention and Control, Chiang Mai, Thailand, 2007 Tuberculosis annual report, Figure 2).

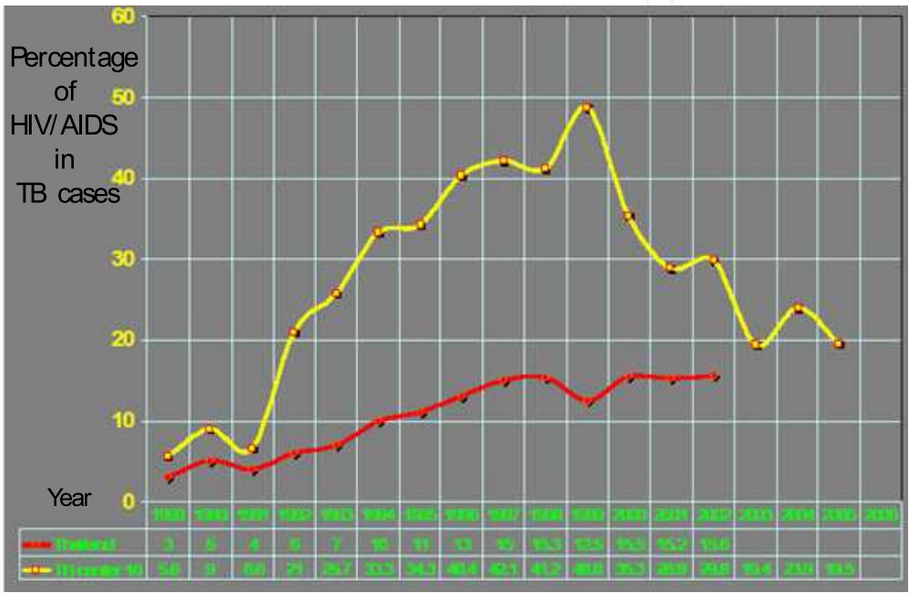


Fig. 1. TB/HIV/AIDS sentinel surveillance in northern Thailand between 1989-2005.

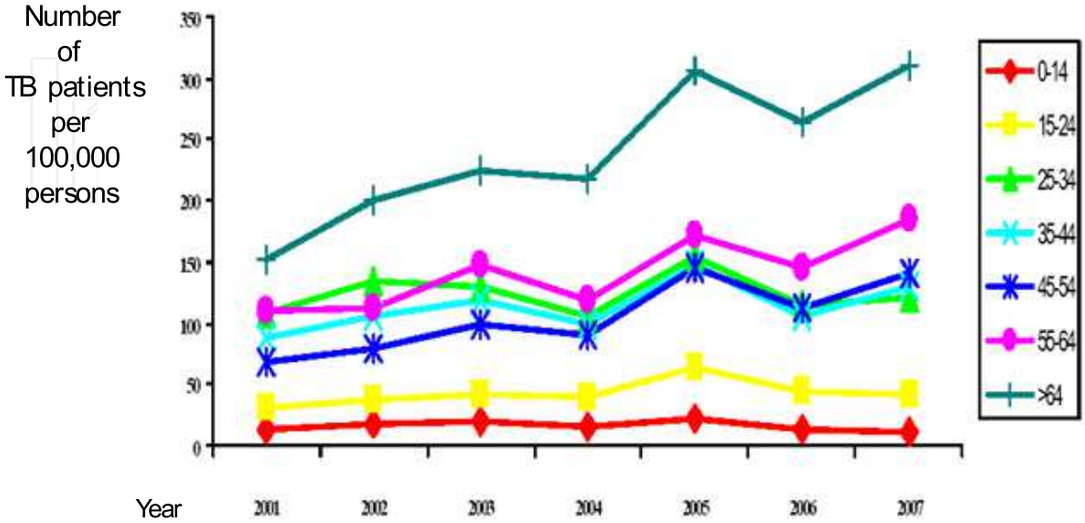


Fig. 2. Incidence of TB patients by ages in northern Thailand between 2001-2007.

3.Tuberculosis investigations in immunocompromised patients

3.1 Acid-Fast Bacilli (AFB) smear and culture

The finding of AFB on stained specimens is the only reliable and affordable rapid diagnostic method of TB which has lower yield (40%-70%) compared to the mycobacterial culture (75-90%) (Nachega & Maartens, 2009).

3.2 Interferon-gamma release assays

Since 2001, development of interferon-gamma release assays (IGRAs) for the detection of TB infection has been initiated in addition to the tuberculin skin test (TST). It detects sensitization to *Mycobacterium tuberculosis* by measuring interferon-gamma release in response to *Mycobacterium tuberculosis* complex antigens (Converse et al., 1997, Rothel et al., 1990 & Streeton et al., 1998, as cited in Mazulek et al., 2010 & Walsh et al., 2011). QuantiFERON-TB test (QFT) (Cellestis Limited, Carnegie, Victoria, Australia) was the first assay approved by the Food and Drug Administration (FDA) in 2001 (FDA, 2010 & Mazurek & Villarino, 2003, as cited in Mazulek et al., 2010). The QuantiFERON-TB Gold test (GFT-G) (Cellestis Limited, Carnegie, Victoria, Australia) was the second IGRA approved by FDA in 2005 (FDA, 2010 & Mazulek et al., 2005, as cited in Mazulek et al., 2010). The United States Centers for Disease Control and Prevention (CDC) published guidelines for using QFT and QFT-G in 2003 and 2005, respectively (Mazurek & Villarino, 2003, Mazulek et al., 2005, as cited in Mazulek et al., 2010). The CDC recommended that a positive interferon-gamma release test should be confirmed with a TST (Mazurek & Villarino, 2003, as cited in Hopewell, 2005). A recent study compared the sensitivity of QFT- G to enzyme-linked immunospot (ELISPOT) among pulmonary TB including HIV - negative immunocompromised patients and demonstrated the superiority of ELISPOT over QFT-G at the low lymphocyte count conditions, not depending on gender, age, and nutritional status (Komiya et al., 2010).

Many studies have been shown that these new assays are useful for diagnosis of active TB in both immunocompromised patients and immunocompetent ones such as HIV/AIDS, diabetes mellitus, systemic immunosuppressant administration, malignant diseases and chronic renal failure (Ito et al., 2011, Nachega & Maartens, 2009, Tan et al., 2010 & Walsh et al., 2011). The sensitivity of the interferon-gamma release assays are not compromised by serum glucose levels in TB patients with diabetes (Walsh et al., 2011) including other immunocompromised TB patients (Ito et al., 2011). A study demonstrated that, unlike the tuberculin skin test, the sensitivity of these assays are less interfered by moderately advanced HIV status (Rangaka et al., 2007, as cited in Nachega & Maartens, 2009). The QFT-G assay has higher detection rate of the latent TB infection than the TST. It may has lower sensitivity among the immunocompromised persons but requires shorter turnaround time than the TST (Baboolal et al., 2010). A previous study of QuantiFERON-TB Gold In-Tube (QFT-GIT) showed 33.4% of indeterminate results among HIV-infected/AIDS patients with CD4-T cell count below 200 cells/μL and the TST has higher degree of agreement than QFT-GIT in patients with immune-mediated inflammatory diseases. This study results indicated that the performance of QFT-GIT varied between different types of immunocompromised patients (Sauzullo et al., 2010). The CDC do not recommend the blood interferon-gamma release assay for pregnant women, individuals with HIV/AIDS, individuals with increased

risk of TB, screening children younger than 17 years old, contacts with an infectious case of TB, or individuals being evaluated for suspected TB (Mazurek & Villarino, 2003, as cited in Hopewell, 2005).

3.3 Imaging

Several chest roengenographic pictures plays a critical role in the diagnosis of TB in HIV-infected/AIDS patients, however, the degree of immunosuppression is a core determinant of the roentgenographic appearance. Most notably the presence of bilateral hilar lymphadenopathy is highly suggestive of TB, but is not diagnostic (Nachega & Maartens, 2009, Figure 3). When a CD4+ T-cell count is higher than 200 cells/μL, the pulmonary infiltrates are characteristic adult picture with cavitation and upper lobe predominance. But when a CD4+ T-cell count is below 200 cells/μL, the pulmonary infiltrates shift toward atypical patterns for adults: hilar or mediastinal adenopathy, and mid- ,lower-zone or military infiltrates (Nachega & Maartens, 2009, Figure 4). Pleural effusion can occur with any CD4+ T-cell count (Havlir & Barnes, 1999, as cited in Nachega & Maartens, 2009, Post et al., 1995, Long et al., 1991, as cited in Nachega & Maartens, 2009, Perlman et al., 1997, Wendel & Sterling, 2002, as cited in Nachega & Maartens, 2009, Figure 5). There is no statistically significant pulmonary shadowing among old patients with TB (Toure' et al., 2010).

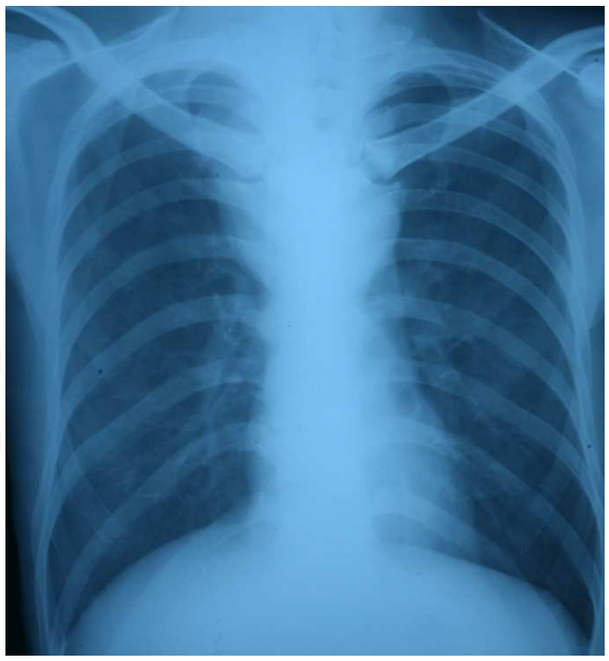


Fig. 3. Chest roentgenogram from the initial presentation of a 34-year-old Thai male with HIV-infection/AIDS who attended the tenth Zonal Tuberculosis and Chest Disease Centre, Chiang Mai, Thailand showing bilateral hilar adenopathy. The sputum smears for AFB and cultures revealed positive results. Diagnosis of pulmonary TB was made.

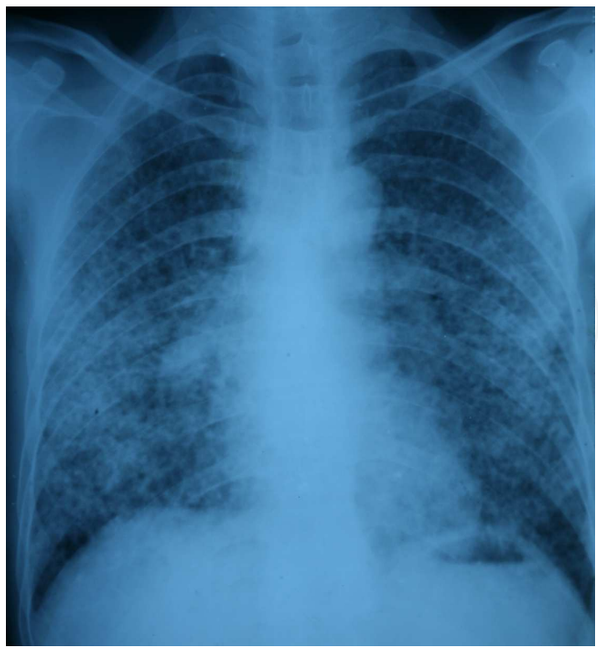


Fig. 4. Chest roentgenogram from initial presentation of a 44-year-old Thai female with chronic smoking who attended the tenth Zonal Tuberculosis and Chest Disease Centre, Chiang Mai, Thailand showing military infiltrates. Her three consecutive sputum smears for AFB and cultures revealed negative results. After completeness of anti-TB chemotherapy her chest roentgenogram completely resoluted.

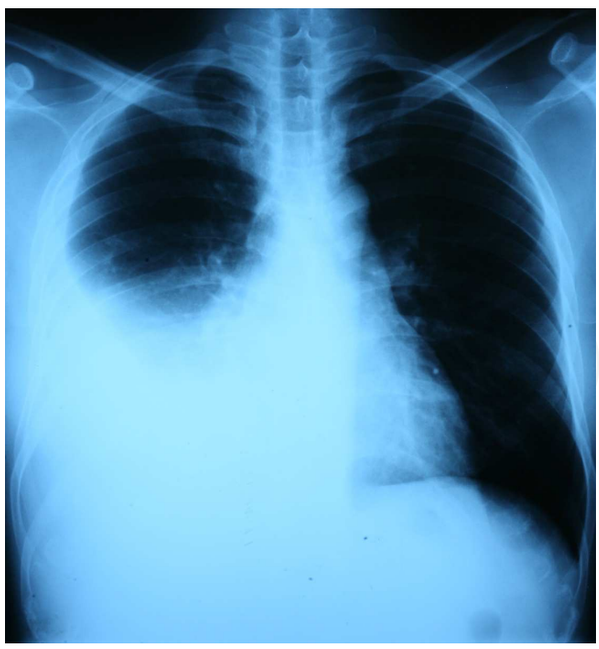
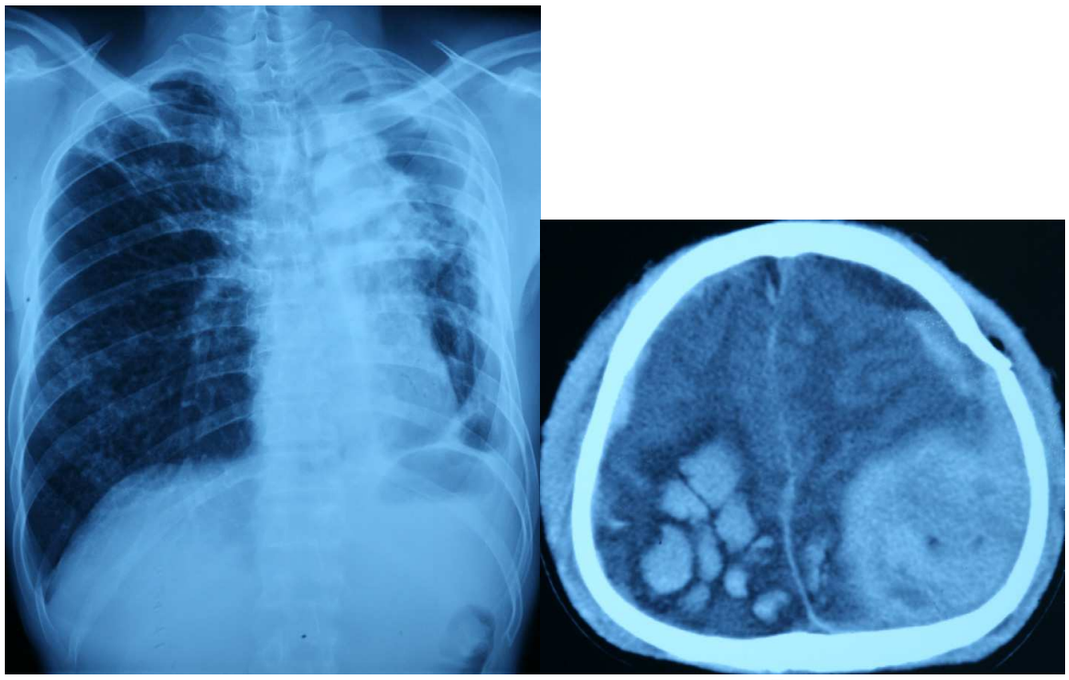


Fig. 5. Chest roentgenogram from initial presentation of another 34-year-old Thai male with HIV-infection/AIDS who attended the tenth Zonal Tuberculosis and Chest Disease Centre, Chiang Mai, Thailand showing a right massive pleural effusion. His pleural biopsy revealed tuberculous pleurisy.

A recent study of TB patients with diabetes conducted in India revealed that lower lung field involvement was predominant (84%) as compared to upper lung field. Cavitation was predominantly confined to the lower lung field (80%) while nodular lesions were found in 36% and exudative lesions were found in 22% (Patel et al.,2011). A previous report in 2000 also demonstrated a higher lower-lung field involvement (Perez-Guzman et al., 2000, as cited in Patel et al.,2011). Some investigators have demonstrated no major differences of the roentgenographic pictures (Bacakoglu et al., 2001, as cited in Patel et al.,2011) while other previous studies have reported more common multiple cavities among diabetic patients (Sen et al., 2009, as cited in Patel et al.,2011). There are not clear reasons for atypical images in TB patients with diabetes.

Alveolar infiltration which indicates tuberculous pneumonia mostly occurs in the upper lung fields is frequently found in HIV-infected/AIDS (20%) and diabetes (15%) patients (Moreira et al., 2011).

Other imaging techniques may be helpful depending on localization of the clinical manifestations. Magnetic resonance imaging (MRI) or computed tomography (CT) scans are specifically detection of TB of the central nervous system (Figure 6 A & B) while ultrasonography can detect intraperitoneal TB such as splenic microabscesses, mesenteric lymphadenopathy and hepatic tuberculous granulomas. CT of the chest is superior to chest roentgenogram to demonstrate latent TB infiltrate in patient with hepatic transplantation (Lyu et al., 2011).



A B

Fig. 6. A: Chest roentgenogram from initial presentation of a 46-year-old Thai male with HIV-infection/AIDS who attended the tenth Zonal Tuberculosis and Chest Disease Centre, Chiang Mai, Thailand showing bilaterally diffuse reticulo-nodular infiltrates with left pleural effusion. His three consecutive sputum smears for AFB and cultures revealed positive results. B: Computed tomography of the brain from initial presentation of the same

patient in Figure 6 A showing multiple tuberculous granulomas with various sizes throughout both parietal lobes.

3.4 Tuberculin skin test

The tuberculin skin test is now the standard technique to detect the latent TB infection. The sensitivity and specificity of the TST in immunocompromised persons with TB infection are very low. A study on latent TB infection during renal replacement therapy in India demonstrated that TST was insensitive and nonspecific to detect latent TB infection (Bhowmik et al., 2010). The TST in HIV-infected/AIDS patients is more likely to be negative due to the declines of the CD4+ T-cell count (Markowitz et al., 1993, as cited in Nachega & Maartens, 2009). More than 5 mm. induration on the Mantoux test in HIV-infected/AIDS patients is a positive result but this has been challenged by a previous study with sensitivity of 64.3% at a cutoff value of 10 mm. and of 71.2% at a cutoff value of 5 mm. and after adjustment for tuberculosis-specific anergy, the sensitivity was 67.6% and 74.5%, respectively (Cobelens et al., 2006, as cited in Nachega & Maartens, 2009). The sensitivity and specificity of TST for diagnosis of latent TB infection in patients on renal replacement therapy were only 20% and 9%, respectively, showed in a previous study (Agarwal et al., 2010). The only benefit and effectiveness of the positive-result TST is TB preventive therapy (Woldehanna & Volmink, 2004, as cited in Nachega & Maartens, 2009).

3.5 Tissue aspiration, excision and biopsy

Aspiration of lymph node with macroscopic tuberculous caseation demonstrates positive results 40.8% of cases (Bem et al., 1993, as cited in Nachega & Maartens, 2009, Pithie & Chicksen, 1992, as cited in Nachega & Maartens, 2009). Patients with negative-result aspiration should be performed needle-core biopsy or excisional biopsy. First needle-core biopsy made a definite diagnosis in 85% of cases (Wilson et al., 2005, as cited in Nachega & Maartens, 2009).

3.6 Mycobacterial molecular identification modalities

3.6.1 Amplicor Polymerase Chain Reaction (PCR)

A previous study in Kenya showed that the sensitivity and specificity of this technique were 93% and 94%, respectively and did not affected by the HIV status (Kivihya-Ndugga et al., 2004, as cited in Cheepsattayakorn & Cheepsattayakorn, 2006).

3.6.2 IS6110-PCR

The sensitivity of this technique was 100% in smear-positive, 81.8% in smear- negative, 66.7% in extrapulmonary, and 42.9% in blood specimens of HIV-infected/AIDS patients as demonstrated in a study (Schijman et al., 2004, as cited in Cheepsattayakorn & Cheepsattayakorn, 2006).

3.6.3 Nested PCR

This technique was studied in urine specimens of the HIV-infected/AIDS participants and revealed the sensitivity of 40.5% in smear-positive, 66.7% in smear-negative, and 57.1% in

extrapulmonary cases. The overall specificity was 98.2%. This study results were different in the non-HIV-infected/AIDS and HIV-infected/AIDS patients (Torrea et al., 2005, as cited in Cheepsattayakorn & Cheepsattayakorn, 2006).

3.6.4 GeneXpert MTB/RIF test

This test is based on nucleic acid amplification and detection of an *Mycobacterium tuberculosis*-specific region of the *rpoB* gene, use real-time PCR with molecular beacons. It also detects mutation associated with rifampicin resistance. It is fully automated system which integrates sputum processing, deoxy-ribonucleic acid extraction, and amplification to diagnose TB. Its results are available within 90 minutes. It is minimized biosafety and contamination because of its closed system (Lockman, 2011). A clinical study conducted in Azerbaijan, India, Peru and South Africa showed the sensitivity of this test for only one sputum specimen examination was 92.2% for all positive-culture, 98.2% for positive AFB smear and positive culture, and 72.5% for negative AFB smear and positive culture cases with a specificity of 99.2%. When 3 specimens were tested the sensitivity was 97.6%, 99.8%, and 90.2% with a specificity of 98.1%, respectively (Boehme et al., 2010, as cited in Lockman, 2011). This test would increase case finding by 30% (replacing or adding to the conventional sputum AFB smear) and MDR case finding by 3-fold (replacing sputum culture and conventional drug-susceptibility testing) (Boehme et al., 2011, as cited in Lockman, 2011). The WHO stated in 2010 that this test should be used as the initial diagnostic test in persons suspected of being HIV/AIDS-associated TB or MDR-TB and it may be used as a follow-on test in smear-negative specimens where HIV/AIDS and/or MDR are of lesser concern (WHO, 2010, as cited in Lockman, 2011). Thailand will soon start using 4 GeneXpert MTB/RIF units in collaboration with the United States CDC.

4. Diagnosis of pulmonary tuberculosis (Sociedade Brasileira de Pneumologia e Tisiologia, 2004 & WHO, 2010)

The diagnosis of pulmonary TB is based on meeting one or more the following criteria: 3.1 detection by two positive sputum smear examinations 3.2 detection by one positive sputum smear examination and positive sputum culture 3.3 detection by one positive sputum smear examination and roentgenographic pictures consistent TB positive sputum culture or 3.4 clinical manifestations, epidemiological findings and roentgenographic pictures consistent TB, together with a favorable response to anti-TB drugs.

5. Antituberculous chemotherapy

There have been substantial studies from both prospective and retrospective demonstrated that standard 6-month rifampicin and isoniazid-contained regimens supplemented by pyrazinamide and ethambutol are effective for cure in treating HIV-seropositive patients with TB (Hopewell & Chaisson, 2000). The WHO recommends standard regimen (2HRZE/4HR, H=isoniazid, R=rifampicin, Z=pyrazinamide, E=ethambutol) for new TB patients with seropositive-HIV and all TB patients living in HIV-prevalent settings should receive daily antituberculous therapy at least during the intensive phase (Khan et al., 2010, as cited in WHO, 2010). Co-trimoxazole preventive therapy should be started as soon as possible and prescribed throughout antituberculous therapy (International Standards for

Tuberculosis Care (ISTC), 2009, as cited in WHO, 2010) which substantially reduces mortality among these patients (Harries et al., 2009, as cited in WHO, 2010 & WHO, 2006). The standard 6-month regimen is currently recommended for treating TB of any site, excepts of the central nervous system, which is recommended 2HRZE/7HR or 2HRZE/10HR (Nachega & Maartens, 2009). Recurrent rates of pulmonary TB among patients with and without HIV/AIDS have varied among various studies, mostly of 5% or less (Kassim et al., 1995, as cited in Nachega & Maartens, 2009, Chaisson et al., 1996, as cited in Nachega & Maartens, 2009, el-Sadr et al.,1998, as cited in Nachega & Maartens, 2009, Connolly et al.,1999, as cited in Nachega & Maartens, 2009 & Sterling et al., 1999, as cited in Nachega & Maartens, 2009). The recurrent rates of TB among HIV-infected/AIDS patients were associated with the duration of rifampicin-based regimens which rifampicin durations of 2-3, 5-6, and more than 7 months were associated with rates of 4, 2, and 1.4 cases per 100 person-years, respectively (Korenromp et al., 2003, as cited in Nachega & Maartens, 2009). WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD) recommends a standardized 6-month rifampicin-based regimen with directly observed treatment for highly TB/HIV-endemic, low- income countries for at least the first 2 months for all positive-sputum smear cases (Korenromp et al., 2003, as cited in Nachega & Maartens, 2009). The IUATLD recommends an 8-month regimen (2HRZE/6HE) for negative-smear HIV-infected/AIDS cases but this regimen is related to high relapse rates (Korenromp et al., 2003, as cited in Nachega & Maartens, 2009). A study in Zaire among HIV-infected/AIDS-related TB patients demonstrated that additional 3 months in the continuation phase (2HRZE/7HR) of the standardized 6- month short-course regimen (2HRZE/4HR) resulted in 1% versus 8% of relapse rates, respectively but the survival rates were no different in patients given extended regimen (Perriens et al., 1995, as cited in Hopewell & Chaisson, 2000). Other studies revealed relapse rates of TB with various treatment regimens among HIV-infected/AIDS patients between 2%-7% (Kassim et al., 1995, as cited in Hopewell & Chaisson, 2000, Chaisson et al., 1996, as cited in Hopewell & Chaisson, 2000, el-Sadr et al., 1998, as cited in Hopewell & Chaisson, 2000). The United States CDC , the American Thoracic Society (ATS) and the Infectious Disease Society of America (IDSA) recommend the extension of the continuation phase from 6 to 9 months of the standardized 6-month rifampicin-based regimen for patients with positive cultures and cavitary TB, regardless of the HIV status (Chaisson & Nachega, 2010). Acquired- rifampicin resistance has been occurred among HIV-infected with advanced immune suppression treated with twice weekly rifampicin-based or rifabutin-based regimens (Chaisson & Nachega, 2010). The continuation phase of isoniazid plus rifapentine once weekly is contraindicated in HIV-infected/AIDS patients because of acquired resistance to rifamycins and unacceptably high rate of relapse (Chaisson & Nachega, 2010). Patients with CD4-T cell count < 100 cells/μL should receive daily or three-times weekly regimens (Chaisson & Nachega, 2010). WHO recommends the same regimens for extrapulmonary and pulmonary TB excepts longer treatment for TB of bone or joint and TB of meninges (WHO, 2010). Progress against TB is being made on several fronts. Several new drugs are being studied for TB therapy, including nitroimidazopyrans (e.g., PA-824), quinolone (moxifloxacin & gatifloxacin), oxazolidinones (e.g., PNU-100480, linezolid), macrolides (e.g., clarithromycin, azithromycin), ring-substituted imidazoles, and diamines (e.g., SQ109). Finally, new TB vaccines is being directed toward developing and should be ready for human testing within a few years.

6. Empirical antituberculous therapy

Empirical therapy will often initiated pending culture results in areas where mycobacterial culture is available, especially in areas of high proportion of sputum smear-negative cases and relatively rapid disease progression of HIV-related TB. Three consecutive-negative smear results, a compatible chest roentgenogram, and no response to a 2-week trial of antibiotics for pneumonitis is the common case definition for negative-smear pulmonary TB used in resource-poor settings (WHO, 2010, Figure 7). This case definition has been modified by WHO to include consideration of acutely-ill patients (especially with Pneumocystis pneumonia). If there has been a clinical response with negative-culture results, the empirical therapy should be continued. A previous study of case definitions in South Africa demonstrated high positive predictive value for a modified case definition of negative-smear pulmonary TB and case definitions of extrapulmonary TB and found that improvement of symptoms, Karnosky performance score, and serum C-reactive protein level were very sensitive to evaluation of the empirical therapy, excepted improvement of body weight and hemoglobin level (Wilson et al., 2006, as cited in Nachega & Maartens, 2009). The specificity of case definitions cannot be 100% so patients who have no response to empirical therapy within 2-8 weeks need to be investigated for alternative diagnoses discontinuation of their empirical therapy (Nachega & Maartens, 2009). In developing countries, the national TB control programs and the international agencies discourage the clinical trials of antituberculous therapy.

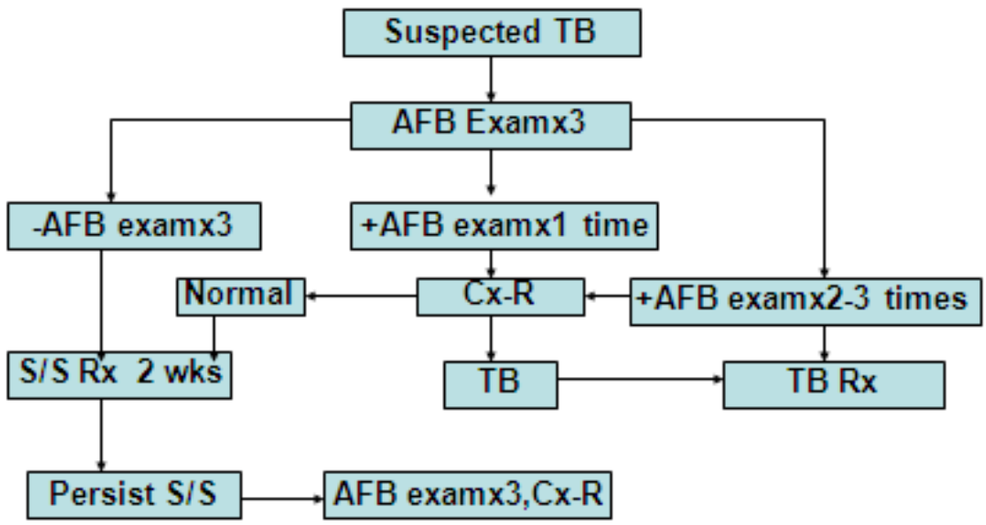


Fig. 7. TB case management (WHO, 2010)

7. Antiretroviral therapy

TB patients with advanced HIV disease/AIDS indicates antiretroviral therapy (ART) which improves survival (Harries et al., 2009, as cited in WHO, 2010), reduces TB disease rates by 60% at a population level, by up to 90% at personal level and reduces TB recurrence rates by 50% (Lawn & Churchyard, 2009, as cited in WHO, 2010 & Golub et al., 2008, as cited in WHO, 2010). Patients co-administered ART and antituberculous therapy may increase risk

of adverse drug reactions, especially hepatitis (McIlleron et al., 2007, as cited in Nachega & Maartens, 2009). Around 25%-40% of these patients develop the so-called immune reconstitute inflammatory syndrome (IRIS) which paradoxically deteriorate TB disease (Lawn et al., 2005, as cited in Nachega & Maartens, 2009). Factors related to an increased risk of TB-IRIS include rapidly decreasing viral loads, lower CD4+ T-cell count and more shorter intervals between starting of antituberculous therapy and ART (Lawn et al., 2005, as cited in Nachega & Maartens, 2009). These worsening clinical manifestations should be excluded notably poor compliance to antituberculous therapy, systemic drug hypersensitivity reactions, MDR-TB, and new opportunistic infections. The most common manifestation of TB-IRIS is enlarging lymphadenopathy with caseous necrosis. The optimal timing of starting ART in relation to starting antituberculous therapy is unclear but TB treatment should always be initiated first, and waits at least until the patient is tolerating the antituberculous therapy before initiating ART as soon as possible and within the first 8 weeks of initiating antituberculous therapy (Nachega & Maartens, 2009 & WHO, 2010). All active-TB patients living with HIV should be initiated ART irrespective of CD4+ T-cell count (WHO, 2009, as cited in WHO, 2010). In 2010 Thailand's guidelines, starting ART when CD4 T-cell count is below 350 cells/μL. Patients who are already receiving an ART regimen, ART should be continued (Nachega & Maartens, 2009). WHO recommends the first-line ART regimens contain two nucleoside reverse transcriptase inhibitors (NRTIs-zidovudine (AZT) or tenofovir disproxil fumarate (TDF) plus lamivudine (3TC) or emtricitabine (FTC)) plus one non-nucleoside reverse transcriptase inhibitors (NNRTI-efavirenz (EFV) or nevirapine (NVP)) (WHO, 2010). In Thailand, the available regimens are stavudine plus lamivudine plus efavifenz or stavudine plus lamivudine plus nevirapine or stavudine plus lamivudine plus indinavir or ritonavir (Cheepsattayakorn & Cheepsattayakorn, 2009).

8. Adjunctive glucocorticoids in TB patients with HIV-infection/AIDS

There is lacking of evidence base for adjunctive glucocorticoids among these patients. There is likely to be a mortality benefit when used in HIV-infected/AIDS patients with tuberculous meningitis and pericarditis, but more larger studies are needed (Nachega & Maartens, 2009).

9. Adjuvant immunotherapy

A previous study demonstrated that immunization with killed *Mycobacterium vaccae* had ability to modify immune response to TB, but failed to showed clinical benefit in HIV-infected/AIDS patients (Mwinga et al., 2002, as cited in Nachega & Maartens, 2009).

10. Monitoring during antituberculous therapy

Sputum-smear examinations at the completion of the intensive phase of treatment course is a conditional, rather than a strong WHO recommendation (WHO, 2010). The evidence of a positive smear at this stage has a very poor ability to predict relapse or pretreatment isoniazid resistance (WHO, 2010). A positive-sputum smear at the end of the intensive phase among new patients should trigger sputum-smear examinations at the end of the third month and if it is positive, sputum culture and antituberculous-drug susceptibility testing should be done (WHO, 2010). There is no longer recommends to extend the intensive phase

for patients have a positive-sputum smear at the end of the second month of treatment course (WHO, 2010).

11. Antituberculous therapy in non-HIV-infected immunocompromised patients

Regimens used in these patients are the same as used in HIV-infected/AIDS patients except regimens used in military TB, TB of bone or joint, and meninges which are more longer than 6 months, usually at least 8 months (WHO, 2010).

12. Treatment of latent TB infection

The IUATLD conducted a study in Eastern Europe and revealed that 3 months of isoniazid therapy reduced the TB incidence by 20%, 66% for 6 months, and 75% for 12 months (Chaisson & Nachega, 2010). This study also resulted in 92% reduction in TB risk for patients completing 12 months of isoniazid compared to 69% decrease for patients completing the standard-6 month regimen. A recent study in Alaskan populations revealed that the optimal duration of isoniazid therapy was 9 months therefore, the new ATS/CDC recommendation is 9 months of isoniazid as the preferred regimen, and the alternative regimen is 6 months (Chaisson & Nachega, 2010). A previous study in northern Thailand showed that 78% of HIV-infected/AIDS patients did not have TB disease at the end of 24 months after completion of 9 months of isoniazid therapy (Cheepsattayakorn, 1998, as cited in Cheepsattayakorn & Cheepsattayakorn, 2009).

13. Bacille Calmette-Gue'rin (BCG) vaccination

The protective benefit of BCG for active TB disease and death is about 50% (Chaisson & Nachega, 2010). It decrease hematogenous dissemination of primary TB infection and so reduces the incidence of military TB and childhood tuberculous meningitis (Chaisson & Nachega, 2010). BCG should not be given to immunocompromised individuals, including those with HIV-infection/AIDS, or to pregnant women (Hopewell, 2005).

14. Further research areas

It demonstrates that the WHO's DOTS strategy for case finding and effectively treating cases is not sufficient to eliminate TB, particularly in countries with HIV epidemics. Neither combination ART nor treatment of latent TB infection has a significant impact on community TB incidence. The most effective measures are reduced HIV incidence and improved TB case finding and treatment success rates. A better understanding of natural immunity to TB and its pathogenesis may contribute to the development of a new more effective vaccine. The genome sequencing of *Mycobacterium tuberculosis* promises to produce a new generation of TB control research.

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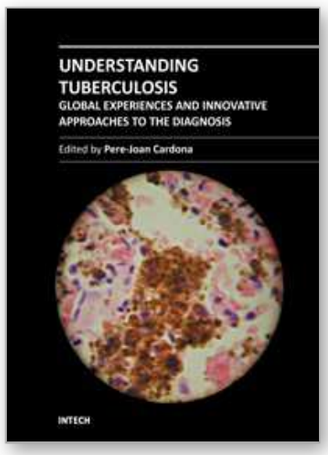

Understanding Tuberculosis - Global Experiences and Innovative Approaches to the Diagnosis

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Mycobacterium tuberculosis is a disease that is transmitted through aerosol. This is the reason why it is estimated that a third of humankind is already infected by Mycobacterium tuberculosis. The vast majority of the infected do not know about their status. Mycobacterium tuberculosis is a silent pathogen, causing no symptomatology at all during the infection. In addition, infected people cannot cause further infections. Unfortunately, an estimated 10 per cent of the infected population has the probability to develop the disease, making it very difficult to eradicate. Once in this stage, the bacilli can be transmitted to other persons and the development of clinical symptoms is very progressive. Therefore the diagnosis, especially the discrimination between infection and disease, is a real challenge. In this book, we present the experience of worldwide specialists on the diagnosis, along with its lights and shadows.

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