Am. J. Trop. Med. Hyg., 80(4), 2009, pp. 675–677

Short Report: Impact of HAART Therapy on Co-Infection of Tuberculosis and HIV Cases for 9 Years in Taiwan

Shu-Hui Tseng, Donald Dah-Shyong Jiang, Hao-Seong Hoi, Shiang-Lin Yang, and Kao-Pin Hwang*

Graduate Institute of Clinical Medical Sciences, College of Medicine, Chang Gung University, Taiwan; Centers for Disease Control, Department of Health, Taiwan; Department of Pediatrics, Chang Gung Memorial Hospital - Kaohsiung Medical Center, Chang Gung University College of Medicine, Taiwan

Abstract. Free highly active antiretroviral therapy (HAART) was made available by The Department of Health since April 1997. As a result, the incidence rate of tuberculosis (TB)/human immunodeficiency virus (HIV) co-infection among HIV cases rose from 1.90% to 3.82% during 1993 to 1998 and decreased from 3.82% to 0.94% during 1998 to 2006. The incidence rate of TB/HIV co-infection among HIV cases reached its peak in 1998 and then started to reverse, although the next year the TB disease burden (incidence rate: 62.7 cases per 100,000 persons) remained consistently high, and this continued in the following years. The survival rate of TB/HIV co-infection cases was 62.16% during the period 1993–1996 (pre-free HAART era) and increased to 86.60% during the period 1998–2006 ($P < 0.0001$) (post-free HAART era). Highly active antiretroviral therapy decreased the incidence rate of new TB/HIV co-infection cases among HIV cases and increased the survival rate of TB/HIV co-infection cases.

The World Health Organization (WHO) claimed that the most threatened and severe infectious diseases were thought to be human immunodeficiency virus (HIV), tuberculosis (TB), and malaria. The number of people living with HIV was 33.2 million in 2007.[1] Estimation was made that around one-third of the world population have been infected at least one time with tuberulosis.[2] In 2005, there were 2 billion latent infection and 8.8 million new cases of TB.[1] For an infected TB person, there is approximately a 5–10% chance of development of TB disease.[2–4] Around 9% of TB cases in the world's population occur simultaneously with HIV.[4,5] In Africa, the simultaneous occurrence of TB and HIV once increased to 31%,[4,5] and this co-infection relationship has existed for years.[4,6] One of the leading causes of death in HIV patients was a result of the opportunistic infection by tuberculosis.[7,8] Highly active antiretroviral therapy (HAART) is thought to be a tool for improving HIV patients survival probability.[9–12] Our study analyzed the impact of HAART on the co-infection of TB and HIV cases by comparing the pre-era and post-era of implementing free HAART after 9 years in Taiwan.

We analyzed data collected from the nationwide database of TB cases during the period 1993–2006 and HIV patients during the period 1984–2006 from Centers for Disease Control, Department of Health, Taiwan. The definition of a TB case is either of the following: sputum smear-positive or sputum-culture positive or clinical diagnosis. Persons with a positive Western blot test were defined as HIV cases. The HIV infected case with diagnosis as a TB infectious case in a later stage was recognized as a TB/HIV co-infection case in this study. Figure 1 shows the estimated incidence rate of TB, HIV, and of TB/HIV co-infection. The incidence rate of TB was defined as the new TB cases in the same year divided by the total number of general population in the mid-year. The rate of HIV was defined as the number of HIV cases divided by the total number of general population in the mid-year. The incidence rate of new TB/HIV co-infection was the number of new TB/HIV co-infection cases divided by the number of HIV cases in the same year.

A total of 189,827 TB cases during the period 1993–2006 and 13,120 HIV cases during the period 1984–2006 were selected for analysis. The incidence rates of TB in Taiwan fell from 48 cases to 64 cases per 100,000 persons during 1993–2006. The rate of HIV continuously increased from 0.002% to 0.05% during 1993–2006, whereas the rate of new TB/HIV co-infection cases increased from 1.90% to 3.82% during 1993–1998 and then decreased from 3.82% to 0.94% during 1998–2006. The incidence rate of new TB/HIV co-infection was thought to be 15-fold to the general public in 2006.

The Kaplan-Meier method was used to calculate the survival probability of HAART in TB/HIV co-infection cases after onset of 1 year. To evaluate the impact of HAART, the survival probability from two different time intervals (1993–1996 and 1998–2006) were involved for comparison. The reason why we use these two periods is that free HAART was started in April 1997 in Taiwan. At the initial stage, health care workers and patients did not completely understand the policies and relative implementation during the first year. Thus, the consideration was made mainly at the beginning year of HAART which allowed health care workers to have a period for adjustment of the regulation. The results showed that the survival rate of TB/HIV co-infection cases were 62.16% during the period 1993–1996 (pre-free HAART era) and 86.60% during the period 1998–2006 (post-free HAART era) with a significant difference between the periods ($P < 0.0001$) (Figure 2).

Taiwan implemented a national health insurance system in 1995, allowing civilians to be accessible to the medical treatment, which included HAART. The rate of TB/HIV co-infection reached its peak in 1998 and started to reverse the next year, and even the TB disease burden (incidence rate: 62.7 cases per 100,000 persons) remained consistently high in the following years. This indicated that the risk of original latent TB infection transfers into an active type or acquisition of new TB infection highly increased for those HIV+ cases.[13] Therefore, HAART was thought to decrease the incidence rate of new TB/HIV co-infection cases among HIV cases and increase the survival rate of TB/HIV co-infection cases in Taiwan.

Many studies show that the highly concentrated HIV virus is thought to lower the function of the immune system, leading to activation of latent TB and increasing the risk of infection.[14] The HAART can effectively lower the opportunity infections, such as TB of HIV patients.[15–18] The anti-HIV drug is thought to be

* Address correspondence to Kao-Pin Hwang, Department of Pediatrics, Chang Gung Memorial Hospital-Kaohsiung Medical Center, No. 123, Ta-Pei Rd., Niao-Sung Hsiang, Kaohsiung County, Taiwan, 83301. E-mail: kapihw@adm.cgmh.org.tw

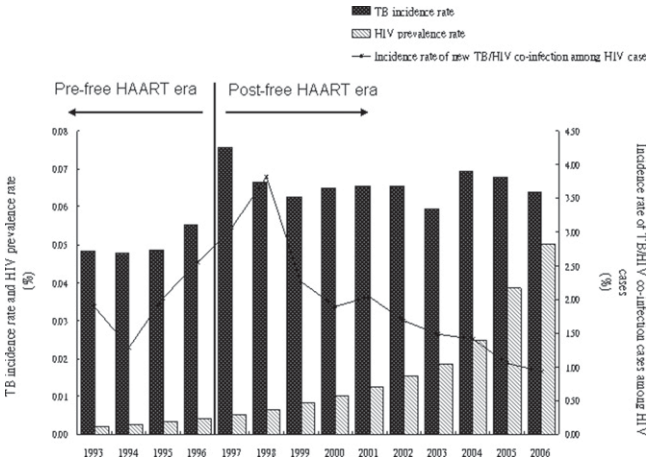

FIGURE 1. Tuberculosis (TB) incidence rate, human immunodeficiency virus (HIV) prevalence rate, and the incidence rate of new TB/HIV among HIV cases in Taiwan, 1993–2006.

one of the best methods to suppress the viral activity. Once the virus is completely suppressed, the immune system can be self-constructed, which lowers the chance of activating latent TB or opportunity infection. The key element of reducing TB/HIV co-infection is based on the complete suppression of viral activity. In Taiwan, the treatment comprising only one or two anti-HIV drugs were not very effective before April 1997, because the frequency of anti-drug resistance is relatively higher due to its complexity and variation, such as mutagenic gene. The introduction of HAART has totally changed the situation since April 1997.

Our study has some limitations because the data of CD4 count and viral load is not complete in the data warehouse. However, according to Dr. Huang's study[24] in Taiwan, HAART was thought to effectively increase the amounts of CD4 lymphocyte and lower the plasma viral load and virologic and immunologic response.[19,20] The HAART can completely suppress most of the HIV viral activity of infected patients, which lowers the viral load to the bottom. Thus, it is thought to be an effective treatment. Many researchers have also shown that HAART can cause immune system self-reconstruction, lower viral load, recover the immunity of HIV patients, and increase survival rate.[21,22] Moreover, it can lower the chance of activating latent TB or opportunity infection of TB, and decrease the incidence of TB/HIV co-infection and increase the survival probability of TB/HIV co-infection in Taiwan.

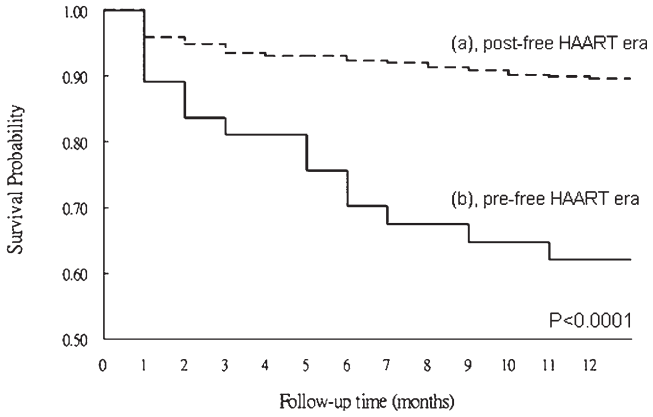

FIGURE 2. Kaplan-Meier is used to analyze the survival probability of tubercolisis (TB)/human immunodeficiency virus (HIV) co-infection in two different periods. The TB/HIV patients were divided into 2 groups: (A) survival probability of the period of post-free HAART (1998–2006) is 86.60%; (B) survival probability of the period of pre-free HAART (1993–1996) is 62.16%. There was a significant difference in survival probability of TB/HIV co-infection cases between pre-free HAART era and post-free HAART era, $P < 0.0001$.

However, there are many factors that can decrease the incidence rate of new TB/HIV co-infection cases among HIV cases and increase the survival rate of TB/HIV co-infection cases in Taiwan, such as Directly Observed Treatment, Short course (DOTS), prevention of opportunity infection, attitude and knowledge of health care workers, promotion of health education, initiation of antimicrobial prophylaxis, accumulation of clinical experience in the management of AIDS-OIs, adverse effects of antiretroviral therapy, disease reporting and management system.[23,24] The HAART is not solely responsible for the difference in Figure 1 and Figure 2. According to our data, HAART may have had an impact on the incidence rate of new TB/HIV co-infection cases among HIV cases and survival probability of TB/HIV co-infection cases, but the size of the impact is hard to determine.

Received October 22, 2008. Accepted for publication December 14, 2008.

Acknowledgments: We thank all the medical and public health staff in both local and federal authority to report HIV and tuberculosis cases to Taiwan CDC surveillance system and close follow-up those HIV and TB cases in Taiwan. We also thank director general Dr. Kuo of Taiwan CDC to supervise this research.

Financial support: This study was supported by the Centers for Disease Control, Taiwan (Taiwan CDC).

Disclosure: Shu-Hui Tseng is the deputy director of the division of surveillance and nosocomial infection control in Taiwan CDC. Her research interests focus on co-infection of HIV and tuberculosis.

Authors' addresses: Shu-Hui Tseng, Graduate Institute of Clinical Medical Sciences, College of Medicine, Chang Gung University, No. 123, Ta-Pei Rd., Niao-Sung Hsiang, Kaohsiung County, Taiwan, 83301; Centers for Disease Control, Department of Health, Taiwan, No. 6 LinShen S. Rd., Taipei, Taiwan, 10050. Donald Dah-Shyong Jiang, Hao-Seong Hoi, and Shiang-Lin Yang, Centers for Disease Control, Department of Health, Taiwan, No. 6 LinShen S. Rd., Taipei, Taiwan, 10050. Kao-Pin Hwang, Department of Pediatrics, Chang Gung Memorial Hospital-Kaohsiung Medical Center, No. 123, Ta-Pei Rd., Niao-Sung Hsiang, Kaohsiung County, Taiwan, 83301, Tel: 886-7-7317123 # 8713, Fax: 886-7-7321481, E-mail: kapihw@adm.cgmh.org.tw.

REFERENCES

1. WHO-UNAIDS, 2007. *AIDS Epidemic Update: December 2007*. Geneva, Switzerland: WHO. Available at: http://data.unaids.org/pub/EPISlides/2007/2007_epiupdate_en.pdf.
2. WHO, 2008. Tuberculosis. Global Tuberculosis Control Report 2008. Available at: http://www.who.int/mediacentre/factsheets/fs104/en/.
3. Narain JP, Lo YR, 2004. Epidemiology of HIV-TB in Asia. *Indian J Med Res 120:* 277–289.
4. Sharma SK, Mohan A, Kadhiravan T, 2005. HIV-TB co-infection: epidemiology, diagnosis and management. *Indian J Med Res 121:* 550–567.
5. Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MC, Dye C, 2003. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch Intern Med 63:* 1009–1021.

6. Vermund SH, Yamamoto N, 2007. Co-infection with human immunodeficiency virus and tuberculosis in Asia. *Tuberculosis* (*Edinb*) *87 (Suppl 1):* S18–S25.
7. Steinbrook R, 2007. Tuberculosis and HIV in India. *N Engl J Med 356:* 1198–1199.
8. WHO, 2008. Global Tuberculosis Control: Surveillance, Planning, Financing: WHO Report 2008. Geneva, Switzerland: WHO. Available at: http://www.who.int/tb/publications/global_report/2008/pdf/fullreport.pdf.
9. Lim HJ, Okwera A, Mayanja-Kizza H, Ellner JJ, Mugerwa RD, Whalen CC, 2006. Effect of tuberculosis preventive therapy on HIV disease progression and survival in HIV-infected adults. *HIV Clin Trials 7:* 172–183.
10. Muga R, Ferreros I, Langohr K, de Olalla PG, Del Romero J, Quintana M, Alastrue I, Belda J, Tor J, Pérez-Hoyos S, Del Amo J; Spanish Multicenter Study Group of Seroconverters (GEMES), 2007. Changes in the incidence of tuberculosis in a cohort of HIV-seroconverters before and after the introduction of HAART. *AIDS 21:* 2521–2527.
11. Girardi E, Sabin CA, d'Arminio Monforte A, Hogg B, Phillips AN, Gill MJ, Dabis F, Reiss P, Kirk O, Bernasconi E, Grabar S, Justice A, Staszewski S, Fätkenheuer G, Sterne JA; Antiretroviral Therapy Cohort Collaboration, 2005. Incidence of tuberculosis among HIV-infected patients receiving highly active antiretroviral therapy in Europe and North America. *Clin Infect Dis 41:* 1772–1782.
12. Girardi E, Palmieri F, Cingolani A, Ammassari A, Petrosillo N, Gillini L, Zinzi D, De Luca A, Antinori A, Ippolito G, 2001. Changing clinical presentation and survival in HIV-associated tuberculosis after highly active antiretroviral therapy. *J Acquir Immune Defic Syndr 26:* 326–331.
13. MMWR, 2007. Reported HIV status of tuberculosis patients–United States, 1993–2005. *CDC MMWR Weekly 56:* 1103–1106.
14. Selwyn PA, Hartel D, Lewis VA, Schoenbaum EE, Vermund SH, Klein RS, Walker AT, Friedland GH, 1989. A prospective study of the risk of tuberculosis among intravenous drug users with HIV infection. *N Engl J Med 320:* 545–550.
15. Girardi E, Antonucci G, Vanacore P, Libanore M, Errante I, Matteelli A, Ippolito G, Gruppo Italiano di Studio Tubercolosi e AIDS (GISTA), 2000. Impact of combination antiretroviral therapy on the risk of tuberculosis among persons with HIV infection. *AIDS 14:* 1985–1991.
16. Jones JL, Hanson DL, Dworkin MS, DeCock KM, 2000. HIV-associated tuberculosis in the era of highly active antiretroviral therapy. *Int J Tuberc Lung Dis 4:* 1026–1031.
17. Santoro-Lopes G, de Pinho AM, Harrison LH, Schechter M, 2002. Reduced risk of tuberculosis among Brazilian patients with advanced human immunodeficiency virus infection treated with highly active antiretroviral therapy. *Clin Infect Dis 34:* 543–546.
18. Badri M, Wilson D, Wood R, 2002. Effect of highly active antiretroviral therapy on incidence of tuberculosis in South Africa: a cohort study. *Lancet 359:* 2059–2064.
19. Hung CC, Chen MY, Hsiao CF, Hsieh SM, Sheng WH, Chang SC, 2003. Improved outcomes of HIV-1-infected adults with tuberculosis in the era of highly active antiretroviral therapy. *AIDS 17:* 2615–2622.
20. Hung CC, Hsiao CF, Chen MY, Hsieh SM, Chang SY, Sheng WH, Sun HY, Chang SC, 2006. Improved survival of persons with human immunodeficiency virus type 1 infection in the era of highly active antiretroviral therapy in Taiwan. *Jpn J Infect Dis 59:* 222–228.
21. Hogg RS, Yip B, Chan KJ, Wood E, Craib KJ, O'Shaughnessy MV, Montaner JS, 2001. Rates of disease progression by baseline CD4 cell count and viral load after initiating triple-drug therapy. *JAMA 286:* 2568–2577.
22. Palella FJ Jr, Deloria-Knoll M, Chmiel JS, Moorman AC, Wood KC, Greenberg AE, Holmberg SD, 2003. HIV outpatient study investigators. Survival benefit of initiating antiretroviral therapy in HIV-infected persons in different CD4+ cell strata. *Ann Intern Med 138:* 620–626.
23. Lew WJ, Lee EG, Bai JY, Kim HJ, Bai GH, Ahn DI, Lee JK, Kim SJ, 2006. An internet-based surveillance system for tuberculosis in Korea. *Int J Tuberc Lung Dis 10:* 1241–1247.
24. Rolfhamre P, Janson A, Arneborn M, Ekdahl K, 2006. SmiNet-2: description of an internet-based surveillance system for communicable diseases in Sweden. *Euro Surveill 11:* 103–107.