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Co-infection with human immunodeficiency virus and tuberculosis in Asia

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Abstract

Asia has had historically high levels of tuberculosis (60% of the global total) and has experienced a marked rise in HIV seroprevalence (22% of the global total) in key subpopulations of these highly populous nations. Thus, co-infected patients are a challenge for practitioners and public health workers alike. The U.S.-Japan Cooperative Medical Science Program is spearheading interdisciplinary collaborations in Asia to address the many outstanding research priorities for HIV-tuberculosis co-infection. There is an urgency to this agenda for many reasons, including the frequency with which tuberculosis accounts for the death of HIV infected persons in Asia, and the continued rise of multiple drug-resistant *Mycobacterium tuberculosis*. We review briefly the public health situation in Asia, highlighting research questions from US-Japan-Asian partner joint meetings, and cite salient studies to indicate trends and challenges.

Keywords

tuberculosis; HIV; AIDS; Asia; epidemiology; immune reconstitution syndrome; co-infection

Introduction

The foremost cause of death due to human immunodeficiency virus (HIV) in developing countries is tuberculosis (TB), responsible for at least 13%, and perhaps $\geq 30\%$ of all deaths.^{1,2} In turn, HIV-induced immunosuppression is a substantial contributor to TB reactivation; one study in Cambodia suggested nearly one-quarter of HIV cases from January 2004-February 2005 had active tuberculosis.³ Furthermore, the problem is growing despite the antiretroviral therapy (ART) “roll-out” in developing countries for at least four reasons. First, there is a substantial lag in ART availability compared with the clinical need in Asia. Second, the ongoing high incidence of HIV continually generates a cadre of newly at-risk persons. Third, the increasing age of previously HIV-infected persons increases the risk of *Mycobacterium tuberculosis* reactivation due to advancing immunosuppression. Fourth, there remain serious program limitations that inhibit application of measures to control and prevent both HIV and TB, e.g., directly observed therapy-short course (DOTS).⁴⁻⁹ HIV transmission is expanding to the huge and populous Asian continent rapidly. A metaphor is apt: this is a time when oil (HIV) is poured into the fire (TB infected persons) in Asia.

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Of an estimated 8.9 million active TB cases worldwide in 2004, the World Health Organization (WHO) estimated that 13% were in HIV infected persons, perhaps double the proportion of a decade ago (Table).^{2,10,11} This reflects the Asian situation in which more and more TB cases are attributable to HIV co-infection and immunosuppression.¹²⁻¹³ In the context of this on-going challenge in research, as well as in both training and service, the 40th anniversary meeting organizers of the U.S.-Japan Cooperative Medical Science Program (USJCMSP) (Kyoto, Japan, December 2005) chose to highlight this link through a joint symposium in the form of the USJCMSP 10th International Conference on Emerging Infectious Diseases in the Pacific Rim, involving the US-Japan Panels on AIDS¹⁴ and on Tuberculosis-Leprosy. This article serves to highlight and update selected themes that were highlighted in the conference and that remain potent priorities in the area of co-infection research.

Research questions in HIV-TB

The synergy of HIV and TB takes several forms (Figure 1). HIV-induced immunosuppression increases the likelihood that quiescent *M. tuberculosis* will reactivate.¹⁵ The newly active TB patient is now infectious for TB whereas without the HIV co-infection, the patient might have remained uninfected. TB itself up-modulates the host immune system; an activated T cell that is activated in response to infection from *M. tuberculosis* (or a number of other infections such as helminthes or herpesviruses) produces more HIV than a quiescent cell such that HIV expression increases in the face of co-infections.¹⁶ Higher HIV viral loads increase the rate of disease progression and also increases HIV infectiousness.¹⁷⁻²¹ It may be that TB infection in the HIV-uninfected person results in activated T cells that are now more susceptible to HIV upon exposure. Hence, prevention and treatment of either infection can be expected to assist in the control of the other.²² HIV and TB are clearly synergistic, such that their joint clinical management must be considered an essential component of global primary care and public health, as has been argued for HIV and sexually transmitted infections.²³⁻²⁸

An anchor for any joint program of HIV and TB control and prevention is to promptly and accurately identify and discriminate patients who are individually and co-infected. Two points are key in interrupting further spread of HIV-TB: 1) efficient discovery of the patient who should introduce antiretroviral therapy and/or modified DOTS, with longer-than-usual course of antituberculosis drugs; and 2) proper management of the patient after beginning of the treatment such that drug interactions, side effects, the immune reconstitution syndrome and managed well, and that drug adherence is facilitated. HIV programs must screen and treat all discovered TB cases; TB programs must offer HIV counseling and testing with proper bridges to HIV care. WHO seeks to expand DOTS, whose success rate is high when properly implemented for just 6-9 months for each patient. However, none of this is easy in the face of infrastructure and manpower limitations; research is essential to guide us in program evaluations and to offer future improvements.

Many research questions are being addressed in the clinical interface of HIV and TB,^{29,30} some of which were highlighted at the 10th International Conference on Emerging Infectious Diseases in the Pacific Rim TB-HIV co-infection symposium. A few of these are listed here:

1. By what molecular and cellular mechanisms do tuberculosis infections upregulate HIV expression?¹⁶
2. What is the nature of the immunological changes induced by HIV infection that permit reactivation of *M. tuberculosis*?
3. In the immunosuppressed, co-infected patient with HIV and TB, what is the optimal approach to treatment in order to avoid the paradoxical worsening of TB through the immune reconstitution syndrome (IRIS)?³¹⁻³⁴

4. What is the extent to which certain antituberculosis and antiretroviral drugs interact such that doses must be modified or selected combinations avoided?³⁵⁻³⁹
5. What innovative TB diagnostics can be developed, such as the Microscopic Observation Drug Susceptibility Assay (MODS), to improve the ability of care providers to identify tuberculosis and its resistant strains rapidly and effectively, especially in settings with suboptimal skin testing, radiologic, microscopic, and/or microbiologic capacities?⁴⁰⁻⁴⁴
6. How can we develop vaccines for HIV and for TB?⁴⁵⁻⁵²
7. How can we develop new classes of drugs for HIV and for TB to address cost, toxicities, and drug-resistant organisms?⁵³⁻⁵⁶
8. How can we identify recently infected persons even before they mount easily identifiable immune (for HIV) and/or inflammatory (for TB) responses?⁵⁷⁻⁶⁰
9. How can we reduce high risk behavior to reduce transmission, such as high risk sex for HIV and alcohol abuse for TB?⁶¹⁻⁷²

Additional research questions are in the realm of program implementation:

1. How can TB and HIV programs be integrated to the benefit of the co-infected patient?^{73,74}
2. How can isoniazid prophylaxis be integrated into HIV therapy regimens?⁷⁵⁻⁷⁹
3. How can obstacles to HIV testing and counseling in TB clinics be overcome?⁷⁴
4. What is an approach globally to implement TB resistance surveillance for HIV infected patients who are at highest risk of the emergence of multiple-drug resistant (MDR) and extensive drug resistant (XDR) TB strains? What basic laboratory services can be established and sustained for TB testing in resource-limited, rural settings?⁴¹
5. How can drug supplies and delivery be guaranteed for both HIV and TB to avoid drug resistance?⁸⁰⁻⁸³
6. How can successful behavioral and community-organization approaches be applied to maximize drug adherence for both HIV and TB therapy?⁸⁴⁻⁸⁸
7. How can contact tracing be developed and sustained in all venues of need.⁸⁹⁻⁹⁴
8. What are programs that can integrate institutional TB and HIV control programs (e.g., jails and prisons, orphanages, homeless shelters, long-term mental health facilities, health care facilities) with community programs? Program features should include bridges to community care for persons discharged from institutions, reducing risk to family members who visit loved ones in institutions, and protection of institutional employees.⁹⁵⁻¹⁰²
9. How do we train health practitioners adequately in both HIV and TB care and prevention, building on many decades of experience in the TB and leprosy fields, both of which depend on long-term sustenance of antimicrobial therapy?¹⁰³

Global investigators are addressing these and other questions. HIV is far better funded in the research arena than is TB. In the United States, fully \$2.89 billion (11%) of the total fiscal year 2007 president's budget (i.e., proposed) for the National Institutes of Health in the US is devoted to HIV/AIDS research and development, for example.¹⁰⁴ Since TB research is an opportunistic infection, acknowledging the linkages between the two infectious diseases and permitting substantial increases in TB research funding will be beneficial.

HIV and Tuberculosis Co-Infection in Asia

Asia is characterized by highly variable HIV transmission patterns. In China, injection drug use (IDU) and commercial sex work (CSW) are driving the HIV epidemic.⁷² In India, IDU is most relevant in the northeast, but heterosexual transmission drives the larger epidemic in south India.¹⁰⁵ Thailand, Vietnam, Burma (Myanmar), Tajikistan, and Pakistan, among others in Asia, have serious IDU problems.¹⁰⁶⁻¹¹¹ Men who have sex with men contribute to risk in Hong Kong, Taiwan, China, Thailand, India, and elsewhere in Asia.¹¹²⁻¹³⁰ Given high background rates of TB, no subgroup with HIV infection can be considered at low TB risk.

TB in Asia tracks with poverty, crowding, poor public health and medical infrastructures, and prisons; it can be controlled with familiar approaches such as DOTS, even in the context of HIV co-infection.¹³¹⁻¹³⁵ HIV-TB co-infection is common in all regions where HIV is most prevalent, and can be extremely high among certain subgroups, such as IDUs and prisoners. Only the higher income nations of Asia are controlling TB adequately.

A principal concern for Asia is its vast population and crowding that works towards efficient TB transmission where public health infrastructures are inadequate for screening, case finding, and successful therapy (Figure 2).¹³⁶ Exacerbated by HIV, TB will continue to be a major cause of mortality and illness in Asia. And since HIV continues to rise in Asia, including China and India that house 2.3 billion (>35%) of the world's 6.5 billion persons, the potential for HIV-TB co-expansion can well be viewed as a looming disaster for Asia. The economics of HIV and TB indicate that their joint control is cost-effective, including tackling the costly challenge of MDR-TB.¹³⁷⁻¹⁴² U.S.-funded efforts to expand the DOTS program in Mexico, Haiti, and the Dominican Republic, among other nations, reduce tuberculosis-related morbidity and mortality among migrants to the United States, producing a net cost savings for the United States.¹⁴³ This may be wise for higher income nations in Asia to consider; their own overseas donor support can help reduce the overall burden of TB in Asia, protecting even the richer nations. This is timely as a new threat faces Asia, the potential emergence of so-called XDR-TB, or extensively drug-resistant TB, as has occurred in South Africa.¹⁴⁴ The theme of HIV-TB co-infection will remain a priority for the U.S.-Japan Cooperative Medical Science Program and it seeks to engage a broader Asian constituency for its mission to nurture collaborative scientific work between the United States, Japan, and Asian partners.

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Figure 1.
The epidemiological synergy of human immunodeficiency virus (HIV) and tuberculosis.

8.55 of 39.50 million (22%) HIV-infected persons worldwide live in Asia as of 2006 (UNAIDS estimate)

Figure 2.

The prevalence of human immunodeficiency virus (HIV) and tuberculosis co-infection in Asia. Estimates from UNAIDS and from reference 136.

Table

Estimated incidence, prevalence and TB mortality, 2004, WHO²

WHO region	Incidence ^a		Smear-positive ^b		Prevalence ^a		TB Mortality	
	# in 1000s (% of global total)	Per 100,000 pop	# in 1000s	Per 100,000 pop	# in 1000s	per 100,000 pop	# in 1000s	Per 100,000 Pop
Africa	2,573 (29)	356	1,098	152	3,741	518	587	81
Americas	363 (4)	41	161	18	466	53	52	5.9
East Mediterranean	645 (7)	122	289	55	1 090	206	142	27
Europe	445 (5)	50	199	23	575	65	69	7.8
SouthEast Asia	2,967 (33)	182	1,327	81	4,965	304	535	33
Western Pacific	1,925 (22)	111	865	50	3,765	216	307	18
Global	8,918 (100)	140	3,939	62	14,602	229	1,693	27

^aIncidence - new cases arising in given period; prevalence - the number of cases which exist in the population at a given point in time.

^bSmear-positive cases are those confirmed by smear microscopy, and are the most infectious cases. "pop"=population. Regions with Asian nations in **bold**.