

Review Article

Indian J Med Res 120, October 2004, pp 277-289

Epidemiology of HIV-TB in Asia

Jai P. Narain & Ying-Ru Lo

Department of Communicable Diseases, WHO Regional Office for South-East Asia, New Delhi, India

Received September 23, 2003

Tuberculosis (TB) has, for centuries, continued to remain a public health problem of enormous importance, particularly in the developing world, taking a heavy toll of those at their prime of life. The emergence of human immunodeficiency virus (HIV infection) and its close association with TB poses an even greater challenge to the health systems in general and TB programmes in particular, in African and Asian countries. HIV is considered to be the most potent risk factor for progression to active TB among those infected both with TB and HIV; as a result, TB is the most common life threatening opportunistic infection associated with HIV, and biggest cause of death among patients with acquired immunodeficiency syndrome (AIDS). In areas hard-hit by HIV, TB is increasing, leading to greater case load, thereby overstressing the already fragile health infrastructure. The deadly relationship between HIV and TB, each potentiating the effect of the other, requires a clearly defined strategy taking into consideration the natural history of the co-infection and its progression to clinical TB (and AIDS). It is clear that the only way to fight this is by bringing the two programmes to join forces and work creatively and innovatively. The strategy should include not only preventing HIV through community-based behavioural interventions and limiting progression to clinical TB through the use of isoniazid preventive therapy, but also early diagnosis and treatment of HIV-associated TB and AIDS using DOTS strategy and combination antiretroviral therapy respectively. The strategy probably would not succeed unless both the programmes are first strengthened before attempting to forge collaboration based on mutual strengths and comparative advantages. In addition, mobilizing national and international response, building partnerships and mobilizing resources will help a great deal in mounting an appropriate and effective response to HIV/TB in the Asian context.

Key words Antiretroviral therapy - co-epidemics - HIV - HIV-TB interventions - national programmes - tuberculosis

Developing countries, including India, have for centuries borne the heavy burden of tuberculosis (TB). Of the eight million people developing TB every year, nearly two-thirds live in Asia and the Pacific region¹. TB control efforts such as the (BCG) vaccine given to more than a quarter of a million people in South India have shown no efficacy². It is no surprise that even today TB is the leading infectious cause of mortality among adults. The problem is now being further complicated by the

alarming spread of human immunodeficiency virus (HIV) and the emergence of drug resistance. HIV not only makes the diagnosis of TB more difficult; it also contributes to an increase in TB incidence^{3,4}. The rate of breakdown to clinical TB is many times higher in individuals infected both with HIV and tuberculosis than in those without HIV. As a result, increase in TB attributed to HIV can be expected wherever the HIV epidemic is severe. The burgeoning TB burden and additional load

contributed by HIV will therefore overstretch the already fragile health infrastructure in the Region.

The problem of TB/HIV is an issue of critical importance, which needs to be seriously addressed by all countries. Although the overall impact in the Region is not yet substantially visible, a great challenge lies ahead for both TB and AIDS control programmes. Innovative approaches are required, to reach the vulnerable and socially marginalized populations most at risk for both infections. Experience shows that proper management of TB and care of patients with HIV/AIDS can improve their survival and also enhance the quality of their lives⁵ (Rai Mra, personal communication). Provision of care at the community level however requires measures which counter discrimination and enhance acceptance by the community of people living with HIV/AIDS.

The close link between TB and HIV also requires enhanced collaboration and harmonization of efforts in order to prevent HIV and to manage TB within the framework of the comprehensive care continuum, from institution to community and home. HIV and TB programmes must work in collaboration to maximize their outputs from the limited resources available. Enhanced political commitment, integrating relevant activities in various programmes and strengthening partnerships with governmental and nongovernmental sectors will help to meet the challenge posed by the dual epidemic. An attempt is made in this review to provide an overview of the problem as it relates to Asia and the Pacific region. It also provides a framework for minimizing the impact of HIV-TB through enhanced collaboration between the national TB and AIDS control programmes.

Epidemiology of HIV-TB

At the end of 2002, the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimated that over 42 million people were infected with HIV, and that 20 million people around the world had already lost their lives to AIDS⁶. Currently, 16 000 people get infected every day. During 2002 alone, 5 million new HIV infections

and 3 million deaths are estimated to have occurred. Six million children are currently living with HIV/AIDS. In Asia and the Pacific, the highest numbers of infected persons are in India (4.58 million), followed by Thailand (800,000), Myanmar (440,000), and Vietnam (88,000)⁷.

At the same time, at least one-third of the world's population (1.9 billion people) is estimated to be infected with TB¹. Every year, eight million people become sick with TB, 80 per cent of whom are in 22 high burden countries. Seven of these countries, namely India, Indonesia, Bangladesh, Vietnam, Cambodia, Thailand and Myanmar are in Asia and the Pacific. TB is the leading infectious cause of death among adults (15-59 yr) in developing countries. TB kills more than two million people each year, which constitutes about 26 per cent of the avoidable adult deaths in the developing world. Overall, every six out of ten TB cases worldwide live in Asia and the Pacific region¹.

The close association between TB and HIV, each potentiating the impact of the other, has been well described and is presently more pronounced particularly in Africa^{3,4,8,9}. In Asia and the Pacific, the impact is not yet visible but evidence is emerging clearly from epidemiological studies as well as from surveillance data (both published and not yet published), that the region could witness an enormous increase in TB cases in the future. Both TB and HIV/AIDS are conditions found mostly in poor socio-economic and underprivileged groups, marginalized from the mainstream population and having limited access to information and health services. The region which harbours a large population of the world's poor already has the highest number of people living with HIV after Africa. The problem of HIV-TB therefore presents both as a challenge as well as an opportunity for Asia and the Pacific.

It is estimated that about 1 billion people in the Region are infected with tuberculosis, of whom presently about 2.5 million are infected also with HIV (Fig.1). While 10 per cent of those infected with TB will progress to active disease over their life times, those who are co-infected with both TB and HIV on the other hand, will progress to active TB more

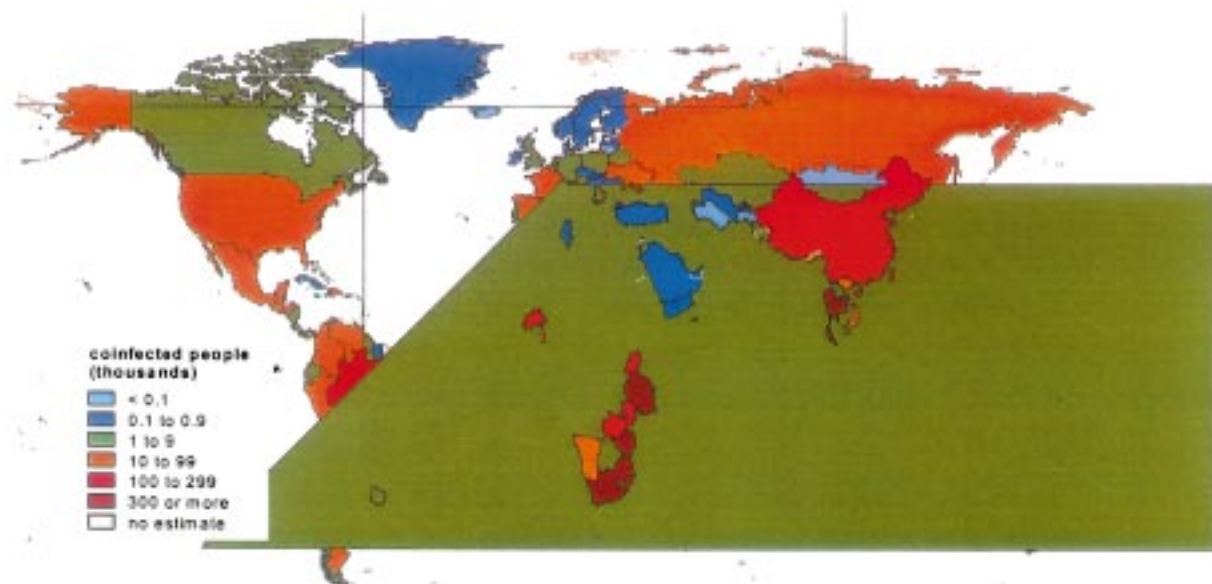


Fig.1. Distribution of TB/HIV in the world. Source: CDS department, WHO HQ, Geneva, 2002.

rapidly, at the rate of 10 per cent annually and about 60 per cent in their life time, increasing the numbers of people sick with TB. This increase in TB attributable to HIV although much less in absolute numbers compared to those resulting among TB infected individuals but free from HIV, will further lead to an increase in TB transmission in the community, posing considerable clinical and programmatic challenges to both the AIDS and TB control programmes.

HIV prevalence surveys in Africa as well as in Asia and the Pacific show that HIV prevalence among TB patients is many times higher than that seen in the general population. In New Delhi, a study of 555 medicine patients with TB demonstrated an HIV seropositivity of (9.4%), vs an overall seropositivity in this same hospital of 0.4 per cent from 1994-1999¹⁰. Prevalence rates among TB patients of 30 per cent in Mumbai¹¹, and 40 per cent in Northern Thailand¹² have been noted. In Africa, the countries with the highest HIV prevalence rates are also those with a high rate of tuberculosis¹³.

The linear relationship between HIV prevalence and TB notification rates demonstrate that rapid spread of HIV would lead to an increasing burden of TB¹³⁻¹⁵ (Fig.2). In many countries including Zimbabwe, Malawi, Tanzania, Kenya and Rwanda,

TB notifications have either doubled or quadrupled over the last few years¹⁵. In these countries, TB is becoming unmanageable and the achievement of the global TB targets of 85 per cent cure rate and 70 per cent case detection is becoming difficult.

The HIV epidemic is already having a profound and prolonged impact on TB in Asia and the Pacific. In the Chiang Rai province in Northern Thailand a case control study between 1990-1998 has shown that the proportion of TB cases attributable to HIV rose to 72 per cent in male patients and 66 per cent in female patients¹⁶. This continuing increase in TB cases attributable to HIV has occurred even when there is marked reduction in HIV prevalence in the area. HIV infection is now considered as the most potent risk factor for tuberculosis; it not only increases the risk of reactivating latent *Mycobacterium tuberculosis* (MTB) infections but also leads to the rapid progression to clinical TB soon after natural infection.

The increased risk of active TB among HIV infected persons compared with those without HIV-infection has been shown in both cohort as well as case control studies with the magnitude of the relative risk varying from 5 to 20 per cent¹⁷. While part of this variation is explained by differences in study design, the strength of association between HIV and

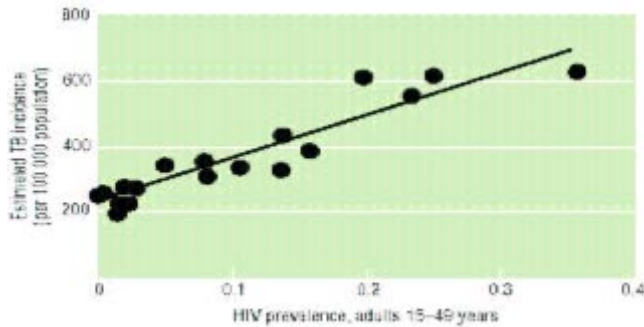


Fig.2. Relationship between estimated incidence of TB (all forms) and HIV prevalence in adults for 18 African countries in 1999 (HIV data supplied by UNAIDS).

TB is likely to increase with rising number of HIV infected persons being immunocompromised. In much of Africa therefore, spread of HIV is primarily responsible for driving the parallel epidemic of TB, often at a rate of 6 per cent per year¹⁸. HIV infected TB patients are considered less infectious because they have fewer cavitations and are less likely to be smear positive. Nevertheless, increase in TB is expected to enhance TB transmission in the community. In many countries, it has been noted that while TB incidence continues to increase due to reactivation by HIV, the annual risk of TB infection in children shows no increase; there is even a decline in areas where DOTS is being expanded⁵. This has important implications for TB control programmes.

Across Asia and the Pacific, 40-70 per cent of AIDS patients have tuberculosis which also is the biggest killer of AIDS patients. Tuberculosis has emerged as the most common life-threatening opportunistic infection associated with HIV accounting for at least one third of AIDS deaths worldwide and 40 per cent of AIDS deaths in Asia, although it is a preventable and curable condition. Moreover, an advanced HIV epidemic contributes to the emergence of drug-resistant strains as seen in Thailand and elsewhere which often do not respond to treatment¹⁹⁻²¹.

Impact of HIV on TB control

Tuberculosis is already a huge problem overstressing the fragile health infrastructure in most of Asia and the Pacific. With the increasing TB case

load attributable to HIV there will be greater demand to diagnose and treat TB cases, which otherwise would not have occurred. In Chiang Rai, Thailand, the TB notifications increased from 40/100,000 population to 144/100,000 between 1990-2002, a three-fold increase in TB mostly attributable to HIV.

HIV-associated TB poses difficult clinical challenges. Patients are relatively more likely to be sputum negative posing difficulty in diagnosis since sputum smear examination is the mainstay of diagnosing the disease. Moreover, the pathogenesis of both tuberculosis infection and the disease relates directly to cell-mediated immunity (CMI), especially CD4+T- lymphocytes. Not surprisingly, HIV infection which induces CD4+T- lymphocyte depletion, also leads to defective immunological response to *M. tuberculosis*. The pathogenesis of TB can be altered by HIV either through reactivation of latent tuberculosis infection to active disease (more common) or by causing rapid progression from recent infection with *M. tuberculosis* to tuberculosis disease. As HIV infection progresses, CD4+ T-lymphocytes decline in number and function. The immune system is therefore, less able to prevent the growth and local spread of *M. tuberculosis*. As a result, disseminated and extra-pulmonary disease is more commonly seen. Nevertheless, pulmonary TB is still the most common form of TB even in HIV infected patient; pulmonary involvement can occur in 70-90 per cent of all patients with TB⁴.

The presentation of pulmonary TB depends on the degree of immuno-suppression. In advanced HIV infection, the presence of many opportunistic infections affecting the lungs may cause difficulties in the diagnosis of TB. The occurrence of hilar and/or mediastinal adenopathy seen in a chest X-ray can also suggest the diagnosis of TB in an HIV infected patient. The most common forms of extra-pulmonary involvement include lymphadenopathies, pleural effusion, pericardial disease, miliary disease and meningitis. Cervical, supraclavicular, and auxiliary lymphnodes are the most common sites of peripheral lymphadenitis. Examination of the percutaneous needle aspiration of the lymph nodes can be useful in establishing the diagnosis.

In most cases, particularly at early stages of HIV infection, the presentation of tuberculosis among such patients with HIV is indistinguishable from other patients. However, some may show a bizarre pattern with a higher proportion of cases tending to have a negative sputum smear. In spite of that, sputum smear examination remains an essential component in the diagnosis of tuberculosis in countries where HIV infection is common, because of its ability to identify infectious cases.

The diagnosis of TB in HIV-positive patients is difficult for three main reasons: (i) The sensitivity of the direct sputum smear examination is reduced in HIV-positive patients. Compared to HIV-negative patients with pulmonary TB, a lesser proportion of HIV-positive patients with pulmonary TB will have positive sputum smears; (ii) X-ray abnormalities, which are not specific for TB in HIV-negative patients, are even more non-specific in the HIV-infected, with only minor abnormalities seen on chest X-ray or with abnormalities which do not look like classical TB, and (iii) patients infected with HIV have frequent illnesses with pulmonary involvement caused by agents other than *M. tuberculosis*.

The response to anti-TB therapy is similar among for HIV-positive and HIV-negative TB patients. HIV-related immunosuppression does not interfere with the effectiveness of therapy for TB. Since the management of TB and the response to standard short course regimen is similar in patients with or without HIV, there is no rationale for HIV tests in clinical settings from the patient management point of view.

Adverse reactions are generally more common in HIV-positive than in HIV-negative TB patients. Most reactions occur in the first two months of treatment. Skin rash and hepatitis are more common and most often attributed to rifampicin. The usual drug responsible for fatal skin reactions such as exfoliative dermatitis, Steven-Johnson syndrome, and toxic epidermal necrolysis is thiacetazone. Therefore, thiacetazone should never be given to HIV-positive TB patients. From a programmatic point of view, thiacetazone should not be prescribed in areas where HIV prevalence is shown to be high.

Rifampicin is a potent inducer of the hepatic cytochrome P450 enzyme system and can reduce the activity of several medications commonly used in HIV-infected patients. These include ketoconazole, fluconazole, methadone, and several anti-retroviral compounds such as the non-nucleoside reverse transcriptase inhibitors and protease inhibitors. Although the combination of anti-TB medications and zidovudine is well tolerated, pharmacokinetic data suggest that rifampicin may increase hepatic clearance of zidovudine and decrease zidovudine plasma levels²². There also are reports of decreased rifampicin absorption attributed to simultaneous administration of ketoconazole²². On the other hand, some protease inhibitors decrease the metabolism of rifampicin and increase the rifampicin blood level, thereby, resulting in increased frequency of sideeffects²². In such a situation, the appropriate dosage of the above-mentioned drugs should be closely monitored and adjusted as needed, in order to minimize the sideeffects from rifampicin and to maximize the effectiveness of other medications being given simultaneously. If possible, treatment for TB should be completed before starting protease inhibitors.

Impact of TB on the HIV programme

HIV and *M.tuberculosis* are both intracellular pathogens and act on the cell-mediated immunity. Patients with HIV infection are uniquely susceptible to TB, and TB on the other hand accelerates the course of infection. Besides contributing to progression from HIV infection to AIDS, contribution of TB to AIDS deaths is substantial; up to 40 per cent of AIDS deaths are due to TB¹⁸. The mortality rate for HIV infected persons with TB is approximately four times greater than the rate for TB patient not infected with HIV. The high mortality rate amongst patients with TB appears to be mainly due to progressive HIV infection and caused by other infections such as septicaemia, salmonella *etc.* The degree of immunosuppression is the most important predictor of survival of HIV infected patients with TB and low CD4 counts are associated with increased mortality. These data indicate that the relationship is one of deadly symbiosis; each potentiating the effect of the other.

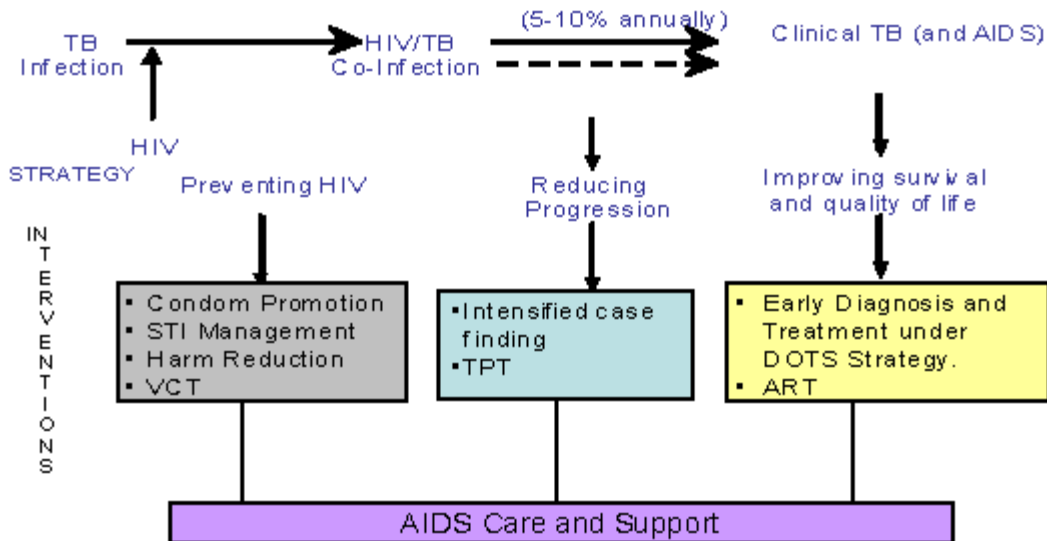


Fig.3. Combating TB/HIV: The conceptual framework and intervention points.

The above figure presents the strategic framework with points where the effects of TB and HIV can be either prevented or reduced through specific interventions.

ART, antiretroviral therapy; TPT, TB preventive therapy; STI, sexually transmitted infections; VCT, voluntary counselling and testing; DOTS, directly observed treatment short course.

The evidence that TB may accelerate HIV-induced immunological deterioration is as follows: (i) Active TB is associated with transient CD4+T-lymphocyte depletion; (ii) TB causes immune stimulation and increased production of cytokines, such as the tumour necrosis factor (TNF) which increases HIV replication *in vitro*; and (iii) HIV infected persons with TB appear to have a higher risk of opportunistic infections and death than do HIV-infected patients with similar CD4+ T-lymphocyte counts but without TB.

The shorter survival among patients with HIV partly attributable to death from TB has been observed both in developing and developed countries. The fact that TB accelerates the progression of HIV is observed by a six-to-seven fold increase in the HIV viral load as compared to the load in those without TB and by the decline in CD4 counts among people with HIV.

Due to major reduction in prices of antiretrovirals (ARV), these drugs are now available in many countries. Due to the high prevalence of tuberculosis among HIV-infected individuals living in Asia and the Pacific, many patients who are candidates for antiretroviral therapy (ART) will have active TB²³.

In addition, patients already receiving ART may develop clinical TB. Effective treatment and control of TB is a central priority when developing treatment strategies for co-infected patients. The management of HIV and TB co-infection is complicated because some antiretroviral agents produce unacceptable drug interactions with anti-tubercular agents and/or can increase toxicity of TB treatment. Tuberculosis treatment following the DOTS strategy should be initiated promptly in the diagnosed cases of TB.

Conceptual framework for combating HIV-TB

The control of TB/HIV and mitigating its impact requires an understanding of the natural history and pathogenesis. In most cases, tuberculosis infection comes first and HIV is contracted subsequently when the person achieves adolescence or adulthood (Fig.3). Once co-infected, the progression to active TB occurs quite rapidly, which could be prevented through the use of TB prevention therapy (TPT). Those who progress to active TB could be managed with DOTS and through provision of care and support, including the use of antiretroviral therapy. Therefore, at each point in the scheme, interventions can be planned and implemented to try and interrupt TB and HIV

infection from progressing to active TB and/or AIDS. Management of HIV-associated TB through DOTS can prevent community transmission of tuberculosis.

Interventions

Preventing HIV infection: Prevention of HIV infection, the most potent risk factor, is essential to prevent the devastating impact on tuberculosis. The strategy calls for support and care for those who have been infected with HIV, whether they are still healthy or have developed illnesses associated with their infection, including AIDS. The support and care of HIV-infected persons is not only humane, it is vital for the success of prevention. The majority, up to 85-90 per cent of all infections result through sexual transmission of HIV and an additional 5 per cent by injecting drug use; changing sexual and injecting behaviour is thus the prime focus of action for interrupting transmission. Action for prevention of HIV transmission must include: (i) information and education aimed at all men and women, particularly those at high risk of infection, including sex workers and injecting drug users; (ii) health and social services especially for the purpose of providing condoms, clean needles and syringes to reduce harm, and the early diagnosis and treatment of sexually transmitted infections using syndromic approach; and (iii) creating an enabling environment, in the absence of stigma and discrimination directed against people living with HIV/AIDS or those at risk. This should be linked with strategies aimed for the social and economic empowerment of women, and reducing the vulnerability of young people by providing accurate information about HIV transmission to pre-adolescent and adolescent girls and boys, and enabling them to learn and practice the related prevention skills.

Reducing progression to active TB: Preventing the occurrence of clinical TB among co-infected persons requires the people with HIV to be diagnosed in the first place. The primary intervention required thus is expanding and making available widely the Voluntary Counselling and Testing (VCT) services to those with HIV infection. Some studies have used the new diagnosis of TB counsel and test for HIV, a research technique that could be used in high seroprevalence

areas²⁴. Those found infected both with TB and HIV can use TB preventive therapy with isoniazid (INH) to prevent progression to TB. The co-infected persons must be screened for active TB through intensified case finding. Screening patients for clinical or active TB is important since they may require short-course chemotherapy over a period of 6 months instead of preventive therapy, as recommended by national TB programmes. VCT therefore provides an entry point not only identifying HIV infected persons but also of co-infected individuals who could benefit from TB preventive therapy as well as for diagnosing patients with active TB who would require TB treatment.

TB preventive therapy (TPT) with isoniazid may play a role in limiting a possible increase in the number of cases of symptomatic tuberculosis that is expected from the pool of HIV/TB co-infected individuals. This approach is supported by the knowledge that TB in HIV infected people is predominantly caused by the endogenous reactivation of dormant foci, that it can happen with a higher frequency among co-infected individuals than in the general population, and that the disease can therefore be prevented by chemotherapy. The efficacy of INH in preventing TB in HIV-positive people has been proven. However, it must be administered to the patient for a long period, for at least six months, a factor that may challenge patient compliance. A two-month course of rifampicin and pyrazinamide daily can be used instead of INH alone.

However, in many countries in Asia and the Pacific, facilities for voluntary HIV counselling and testing are yet to become widely available and tuberculin testing to identify TB infection is operationally difficult to implement in the field situation. There is also a problem of energy, since many with advanced HIV infection may not be able to mount immune response. Moreover, persons who live far away from TB service sites are unlikely to complete the course of preventive therapy. WHO therefore recommends TB preventive chemotherapy on an individual basis, as part of an HIV/AIDS care package wherever suitable, for those infected with both TB and HIV²⁵.

Preventing death and improving quality of life: Experiences in the Asia and Pacific region show that early diagnosis and treatment of HIV-associated TB is critical for improving survival and enhancing quality of life of patients. Intensive case finding of such patients should be followed by referral to the DOTS Centre for further investigation and treatment for active TB and for prophylaxis for other opportunistic infections.

Short-course chemotherapy under the DOTS strategy is as effective among HIV positive TB patients as in HIV negative patients in curing patients of TB and thereby rendering them non-infectious. Thus, besides lowering individual suffering, implementing DOTS through effective TB control programmes can reduce the transmission of TB infection, even in the context of increased HIV prevalence.

Strengthening the capacity of health services to be able to diagnose patients with TB, both pulmonary and extra-pulmonary, contributes to greater case finding and for putting them on the DOTS strategy^{25,26}. The quality of diagnostic infrastructure and of a responsive health service will improve the situation. The DOTS strategy depends primarily on passive case finding. However, in view of the close association between TB and HIV, actively looking for TB cases may be a helpful approach, particularly in high HIV prevalence areas. The clinical presentation, radiological and laboratory findings depend greatly on the stage of HIV infection and on the degree of suppression of host defences. For example, in the advanced stages of HIV, the mycobacterial load in the patients are high pulmonary lesions are mostly infiltrative, sputum smears are often negative and frequently the lesions are extra-pulmonary. HIV-associated tuberculosis is therefore not more infectious than tuberculosis in general.

In most cases, the clinical presentation of tuberculosis in patients with HIV is indistinguishable from those patients who do not have HIV infection. However, some HIV-positive TB patients particularly at an advanced stage of HIV may present with an atypical pattern, with a higher proportion of cases tending to have a negative sputum smear. In one

study in Pune, India, seropositive TB patients with cavitation were noted to have a higher CD4 cell count (and likely to be smear positive) vs those without cavitation, representing a more robust immune response²⁷. Nonetheless, sputum smear examination remains an essential component in TB diagnosis, even in countries where HIV infection is common, because of its ability to identify infectious cases.

Common problems with treating HIV infected TB patients include non-adherence with therapy, increased adverse reactions to anti-TB drugs and concomitant occurrence of other opportunistic diseases. The clinical and bacteriological response of HIV positive TB patients to treatment should be closely monitored. Therapy may be prolonged only for patients with slow or sub-optimal responses. The clinical, radiological and microbiological responses to short-course chemotherapy in HIV-positive and HIV-negative TB patients are similar in the two groups, barring HIV positive patients who may die due to other causes. The bactericidal activity of anti-TB drugs on the tubercle bacilli is similar in HIV-positive and HIV-negative patients; hence, the same drug regimens are employed in the two populations.

Antiretroviral therapy: New HIV medicines specifically antiretrovirals when given in highly active combinations significantly decrease viral replication in the organism and restore immune function. This leads even under programme conditions to decreased morbidity and mortality including incidence of HIV-associated opportunistic infections such as tuberculosis²⁸⁻³⁰.

The two major issues in the clinical management of patients with HIV and TB are when to start ART and which regimen to use. The optimum time at which to commence ART in a patient with HIV/TB co-infection is unknown. Initiation of ART for TB patients at very high risk for HIV disease progression and mortality is recommended. For patients with a CD4 count <200 cells/mm³ ART is recommended as soon as the TB therapy is tolerated, usually between 2 wk and 2 months (Table). For patients who develop TB with CD4 counts in the 200-350 cells/mm³ range, ART should be started after the first two months of TB therapy, because the toxicity of TB treatment is greatest in the first 2 months of treatment.

Table. Antiretroviral therapy for individuals with TB co-infection

Situation	Recommendations
CD4 count <200 cells/mm ³	Start TB therapy. Start one of these regimens as soon as TB therapy is tolerated (between 2 wk and 2 months): <i>Recommended regimen:</i> ZDV/3TC/EFV <i>Alternatives:</i> ZDV/3TC/SQV/r ZDV/3TC/ABC D4T/3TC/ABC or SQ/r (for ZDV intolerance)
CD4 200-350 cells/mm ³	Start TB therapy. Start one of these regimens after 2 months of TB therapy: <i>Recommended regimen:</i> ZDV/3TC/EFV <i>Alternatives:</i> ZDV/3TC/SQV/r ZDV/3TC/ABC
CD4 >350/mm ³	Treat TB. Monitor CD4 counts if available. Defer ART

In patients with CD4 count > 350 cells/mm³ ART should be deferred and the patient monitored closely.

The recommended first line treatment options include ZDV/3TC or d4T/3TC plus efavirenz. The dose of EFV should be increased to 800 mg/day when used in combination with rifampicin. There are currently no definite guidelines on the most appropriate dose of efavirenz to be used in combination with rifampicin.

Data on the use of NVP plus rifampicin are limited and conflicting. NVP levels are reduced by 37 per cent in the presence of rifampicin, and pharmacokinetic studies are examining if a dose adjustment in NVP is needed. Currently, the combination can be used without dose adjustment if there are no alternatives²².

SQV/r (1000/100 bid or 1600/200 once daily), in combination with the NRTI backbone is an alternative to EFV although resistance is a clear risk with suboptimal adherence due to the high pill burden of this combination. Except for SQV/r, use of other PIs (NFV, IDV/r, LPV/r) is contraindicated because rifampicin induces hepatic enzymes that reduce exposure to the protease inhibitors to sub-therapeutic levels. ABC (300 mg bid) plus two NRTIs is the last alternative.

If patients already receiving ART develop TB, they should be adjusted to the regimen compatible with TB treatment. Following completion of anti-tubercular therapy, the ART regimen can be continued or changed depending upon the clinical and immunologic status of the patient. With better understanding of genomics and proteomics new targets for TB treatment are being identified with the prospect of higher specificity and decreased drug interactions, which may alter some of the TB specific ART regimens³¹.

Mobilizing national and international support: The worsening co-epidemics of TB and HIV in Asia and the Pacific require urgent and effective attention. The two epidemics need a joint effort employing different but complementary strategies. The best approach to curb the HIV epidemic is so far based on an integrated prevention and care interventions. Prevention interventions should target all the possible ways of transmission, but especially the ones most frequently involved in the ongoing transmission in a given country. Unlike HIV, TB can be cured, even in people with HIV infection. DOTS strategy has been demonstrated to achieve TB cure rates of over 85 per cent¹. This is the most successful approach to stop further spread of the disease. A strategic framework is necessary to integrate the different interventions needed to combat the dual TB/HIV

epidemic and to avoid wasting the already scarce available resources.

Analysis of HIV/TB surveillance and research data is crucial for generating evidence and for promoting collaborative action between the HIV and TB control programmes. This would also be helpful for developing the strategic framework to address the HIV/TB co-epidemic in a given country. Multiple sources of data can be evaluated to generate the evidence of the association between HIV and TB and to quantify the extent of the problem. In a few countries these data are already available, since HIV surveillance activities include TB patients as part of the sentinel population. Other sources of data include TB notifications; HIV prevalence surveys among TB patients and the general population; cohort and case control studies evaluating risk of TB by HIV status; clinical and autopsy data indicating the proportion of AIDS patients having TB; and finally obtaining the population attributable fraction which indicates the proportion of all TB cases that would be attributable to HIV. Epidemiological data are extremely useful to obtain the baseline, monitor trends which can be helpful evidence to be used for advocacy, programme planning and for mobilizing resources (human and financial). The basis for good advocacy lies especially in skillful communication and articulation of available data and facts.

Partnerships at country level between the Government, non-governmental organizations (NGOs), private health sector, corporate bodies, foundations, universities and committed individuals are needed and fortunately are being forged to stop TB and HIV. A new initiative in the form of the Global Fund to Fight AIDS, TB and Malaria (GFATM) is a major contributor to this work and is bringing unprecedented opportunities to mobilize substantial additional financial resources to fight AIDS, TB and malaria. Through support from GFATM and other partners, hundreds of millions of more dollars are available now than in previous years for DOTS expansion, for innovative response to HIV-associated TB and drug-resistance TB, and for research and development for new diagnostics, drugs and

vaccines. Many experiences in countries, particularly in Myanmar and Thailand, show that joint collaboration between national TB and HIV/AIDS programmes is feasible. Among the activities, development of a national policy and strategic framework, a joint TB and AIDS programme team, and coordination at central level have been identified as the most crucial.

Implementing HIV/TB Interventions: A step-by-step approach

In order to combat HIV/TB, a clear strategic framework is needed based on epidemiological and public health rationale. The strategy should promote a co-ordinated and integrated approach and build on the existing activities to prevent and control both HIV and TB. This mandates clearly defining the interventions and activities that must be planned for and implemented including the roles that can be played by various stakeholders. A co-ordination mechanism, both at policy as well as at implementation levels is needed as a matter of urgency.

At regional level, WHO is promoting the concept of joint planning and coordination of both TB and AIDS programmes, for generating evidence for advocacy, mobilizing partnership and resources, for educating communities and for managing HIV-related TB. The principles that guide the regional strategy include establishing a functional collaboration between the two programmes, not integration, so that both programmes will benefit from the collaboration. The idea is to first assess the capacities of both programmes and strengthen them where needed, then establish collaboration by identifying responsibilities of each programme and including areas where both programmes would work together.

The HIV and TB programmes have traditionally functioned separately along different perspectives. HIV programmes have focussed on prevention and care under a broad multisectoral approach with emphasis on the involvement of the community and the civil society. TB programmes on the other hand, have more of a medical or clinical approach, where

TB prevention and control is carried out primarily through a case management approach. Communication and involvement of the civil society are only now beginning to get attention as an important part of the programme. More recently, however, the two programmes are adopting approaches that are becoming more complementary to each other with enormous scope for learning from each other's experience. For example, the use of antiretroviral therapy as a part of HIV care is becoming a major priority for AIDS programmes due to the drastic reduction in the prices of drugs and there are those who advocate the use of the DOTS approach for ART to ensure treatment adherence and follow up. On the other hand, TB programmes in order to enhance case detection rates, have now identified community mobilization through information and communication campaigns, and building partnerships with NGOs and the private sector as priority areas for attention.

Considerable progress is presently being made in a number of countries namely Thailand, Myanmar and to some extent in India in forging collaboration between the two programmes. The idea is simple – to try and strengthen each programme and then build collaboration by identifying areas where HIV programmes could contribute (VCT, ART, surveillance), where TB programmes could work (DOTS, intensified case finding), and areas where the two programmes could work together (joint planning, joint training, joint supervision and monitoring *etc.*).

In carrying out HIV-TB collaborative activities at country level, the following are some of the guiding principles that should drive the effort: (i) establish functional collaboration between National AIDS and TB programmes and not programmatic integration; (ii) build on existing programmes, strengthening both AIDS and TB programmes in order that they could complement each other in a better fashion; (iii) identify and agree on responsibilities to be carried out by respective programmes and those that could be performed jointly; and (iv) recognize that the collaboration is a win-win-win situation, where the two programmes as well as the community could benefit.

A step-by-step approach is therefore necessary to implement the collaborative programme. In many countries, WHO in the South-East Asia region is presently advocating for piloting of TB/HIV interventions at district level and based on the experience gained to expand these in other geographic areas in a phased manner. The process could start with a situation analysis at district level to review the HIV-TB epidemiological situation and risk factors; services available including what needs to be strengthened or introduced *i.e.*, whether DOTS is being implemented or sexually transmitted diseases (STD) syndromic management is being practiced or whether VCT services are available. The idea would be to identify the intervention gaps and also get to know the stake-holders active in the area and their relative strengths. Based on the situation analysis, a joint HIV-TB committee could prepare a plan of action. The resources needed to implement the plan could be mobilized primarily from the existing programme or from local resources. The programme could be reviewed periodically and the experience gained shared. Based on the practical experience, the interventions could be extended to other districts. WHO is presently funding pilot projects in selected districts in India, Bangladesh, Nepal, Indonesia and Myanmar.

Conclusion

HIV-TB is an important emerging crisis in Asia and the Pacific, as evidenced from the extent of both epidemics in the countries of the region and the high number of co-infected persons living in Cambodia, India, Myanmar and Thailand. The main strategies to successfully combat this deadly association, at least conceptually are: (i) preventing HIV through behaviour change in the context of sexual practices and injecting drug use; (ii) preventing the progression of TB infection to clinical TB through TB preventive therapy, (iii) effective case management of patients with HIV-associated TB or those with AIDS thereby preventing further TB or HIV transmission; and (iv) partnership-building for surveillance, advocacy and programme management for the control of TB and HIV.

In order to mount a more meaningful response to the TB/HIV co-epidemic, many countries in the region have initiated efforts by establishing collaborative activities between TB and AIDS programmes. These experiences show that joint collaboration is possible, including sharing of resources. In addition, regional and national strategies are being developed to combat HIV-TB. However, the first and foremost priority should be to strengthen and build the capacities of both the national AIDS and TB programmes. Resource allocation for TB control however remains desperately inadequate, despite proof that measures like DOTS have been highly successful. In the absence of increased resources and commitment, the problem of HIV-TB will continue to cause human suffering and death, particularly in poor and vulnerable populations. It would be tragic if TB, particularly MDR TB, was allowed to spin out of control, when proven strategies and inexpensive efficacious drugs are available to contain the HIV-TB epidemic.

References

1. WHO Report 2003. Global Tuberculosis Control. Surveillance, Planning, Financing. <http://www.who.int/gtb/publications/globrep02/index.html>. WHO/CDS/TB/2002.245 (Accessed on January 24, 2004).
2. Anonymous. Fifteen year follow up of trial of BCG vaccines in south India for tuberculosis prevention. *Indian J Med Res* 1999; 110 : 56-69.
3. Narain JP, Raviglione MC, Kochi A. HIV associated tuberculosis in developing countries: epidemiology and strategies for prevention. *Tuberc Lung Dis* 1992; 73 : 311-21.
4. Raviglione MC, Narain JP, Kochi A. HIV-associated tuberculosis in developing countries: Clinical diagnosis and treatment. *World Health Organ* 1992; 70 : 515-26.
5. Narain JP. Tuberculosis and HIV infection. In: Narain JP, editor. *Tuberculosis: Epidemiology and control*. New Delhi: World Health Organization Regional Office for South-East Asia; 2002 p. 84-100.
6. AIDS epidemic update: December 2002, Geneva, Joint United Nations Programme on HIV/AIDS, (UNAIDS) and World Health Organization; 2002.
7. World Health Organization. HIV/AIDS in Asia and the Pacific Region, 2003.
8. A deadly partnership : Tuberculosis in the era of HIV. World Health Organization. Global Tuberculosis Programme. World Health Organization Consensus Statement, Geneva. WHO/TB/96.204, 2002.
9. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Global burden of tuberculosis - estimated incidence, prevalence and mortality by country. WHO Global Surveillance and Monitoring Project. *JAMA* 1999; 282 : 677-96.
10. Sharma SK, Aggarwal G, Seth P, Saha PK. Increasing HIV seropositivity among adult tuberculosis patients in Delhi. *Indian J Med Res* 2003; 117 : 239-42.
11. Mohanty KC and Basheer PMM. Changing trend of HIV infection and tuberculosis in a Bombay area since 1988. *Indian J Tuberc* 1995; 42 : 117-20.
12. Yanai H, Uthairavit W, Panich V, Sawanpanyalert P, Chaimanee B, Akarasewi P, et al. Rapid increase in HIV-related tuberculosis, Chiang Rai, Thailand, 1990-1994. *AIDS* 1996; 10 : 527-31.
13. Godfrey-Faussett P, Ayles H. Can we control tuberculosis in high HIV prevalence settings? *Tuberculosis (Edinb)* 2003; 83 : 68-76.
14. WHO. *Global Tuberculosis Control*. WHO Report 2001. Geneva: World Health Organization, 2001. <http://www.who.int/gtb/publications/globrep01/contents.htm>
15. Tripathy S, Narain JP. Tuberculosis and human immunodeficiency virus infection. In: Sharma SK, Mohan A, editors. *Tuberculosis*. New Delhi: Jaypee Brothers Medical Publishers; 2001 p. 404-12.
16. Tansuphasawadikul S, Amornkul PN, Tanchanpong C, Limpakarnjanarat K, Kaewkungwal J, Likanonsakul S, et al. Clinical presentation of hospitalized adult patients with HIV infection and AIDS in Bangkok, Thailand. *AIDS* 1999, 21 : 326-32.
17. Glynn JR. Resurgence of tuberculosis and the impact of HIV infection. *Br Med Bull* 1998; 54 : 579-93.
18. Corbett EL, Watt CJ, Walker N, Williams BG, Raviglione MC, Dye C, et al. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch Intern Med* 2003; 163 : 1009-21.
19. Punnotok J, Shaffer N, Naiwatanakul T, Pumprueg U, Subhannachart P, Ittiravivongs A, et al. Human immunodeficiency virus-related tuberculosis and primary drug resistance in Bangkok, Thailand. *Int J Tuberc Lung Dis* 2000; 4 :537-43.

20. Sacks LV, Pendle S, Orlovic D, Blumberg L, Constantinou CA comparison of outbreak and nonoutbreak-related multi-drug resistant tuberculosis among human immunodeficiency virus-infected patients in a South African hospital. *Clin Infect Dis* 1999; 29 : 96-101.
21. Sapawitkul S, Yoshima T, Rienthong D, Akarasewi P, Kunyanone N, Saisorn S, *et al.* Increasing burden of tuberculosis and high rate of drug resistance in an HIV epicenter in northern Thailand 1989-1997. *Int Conf AIDS* 1998; 12 : 288 (abstract no. 452/22131).
22. Scaling up antiretroviral therapy in resource-limited settings. Treatment guidelines for a public health approach 2003 Revision. Geneva: World Health Organization.
23. Narain JP, Pattanayak S. AIDS and tuberculosis in Asia: a public health priority for the region. *Int Conf AIDS* 1994; 10 :337 (abstract no. PC0284)
24. Ramachandran R, Datta M, Subramani R, Baskaran G, Paramasivan CN, Swaminathan S. Seroprevalence of human immunodeficiency virus (HIV) infection among tuberculosis patients in Tamil Nadu. *Indian J Med Res* 2003; 118 : 147.
25. Maher D, Floyd K, Raviglione M. A Strategic framework to decrease burden of TB/HIV WHO/CDS/TB/2002. 296. Geneva: World Health Organization, 2002.
26. World Health Organization. WHO Tuberculosis Programme: Framework for Effective Tuberculosis Control. Geneva, Switzerland: World Health Organization 1994. WHO/TB/94.179.
27. Tripathy S, Menon P, Joshi DR, Patil U, *et al.* Preliminary observations on lymphocyte subpopulations in HIV seropositive & HIV seronegative tuberculosis patients in Pune, India. *Indian J Med Res* 2000; 111 : 195-9.
28. Sontoro-Lopes G, de Pinho AM, Harrison LH, Schechter M. Reduced risk of tuberculosis among Brazilian patients with advanced human immunodeficiency virus infection treated with highly active antiretroviral therapy. *Clin Infect Dis* 2002; 34 : 543-6.
29. Burman WJ, Jones BE. Treatment of HIV-related tuberculosis in the era of effective antiretroviral therapy. *Am J Respir Crit Care Med* 2001; 164 : 7-12.
30. Wagner KR, Bishai WR. Issues in the treatment of *Mycobacterium tuberculosis* in patients with human immunodeficiency virus infection. *AIDS* 2001; 15 (Suppl 5) : S203-12.
31. Chopra P, Meena LS, Singh Y. New drug targets for *Mycobacterium tuberculosis*. *Indian J Med Res* 2003; 117 : 1-9.

Reprint requests: Dr Jai P. Narain, Coordinator, HIV/AIDS, TB & Other Communicable Diseases, WHO Regional Office for South-East Asia, New Delhi 110002, India
e-mail: narainj@whosea.org