Review article

HIV /AIDS and Tuberculosis - co-infection

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According to WHO / UNAIDS estimates to date, approximately 36 million people are living with HIV infection globally (1). People living with HIV infection are vulnerable to a variety of opportunistic infections and other diseases, one of the most important of which is tuberculosis (TB). In 1997, approximately 1.86 million people were estimated to be infected with *M. tuberculosis* recording a global prevalence of 32% (2).

The upsurge in TB cases in the recent past has been attributed primarily to three factors: development of multi-drug-resistant TB strains mainly because of incorrect or incomplete treatment, populations moving from high to low TB prevalence areas and the emergence of the HIV pandemic. Several epidemiological and clinical studies have established the close link between HIV and TB (1,2).

When the AIDS pandemic began, WHO estimated that 1.7 billion or one-third of the global population was latently infected with tubercle bacilli (3). Yet, as the bacilli are kept under control in a quiescent state by the immune system, only about 5-10% of such infected persons with *M. tuberculosis* will develop active TB during their lifetime (3,4,5). HIV infection has reversed this situation and the lifetime risk of a HIV positive person developing TB has increased to as much as 50% (3,5).

HIV, in addition to reactivating latent TB infection, also causes individuals with recent TB infection to rapidly progress to active disease (4,5). Today, HIV has become the most significant risk factor for progression to active TB. Active TB in turn may accelerate the course of HIV infection (4,5). Similarly HIV infection is a risk factor for recurrent TB (hazard ratio 2.4). HIV-1 infection was strongly associated with disease caused by re-infection (adjusted hazard ratio 18.7) but not with relapse (hazard ratio 0.58). The proportion of cases attributable to re-infection varies from 12% to 75% (6). Therefore, TB will also increase concurrently as the HIV pandemic advances. This is corroborated by the increase in TB cases reported from areas that have been most affected by the HIV epidemic.

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In countries where both infections are common, HIV sero-prevalence is much higher among TB patients than in the general population. Both infections are fuelled by the same demographic and socio-economic factors.

The prevalence of dual infection is estimated by applying the prevalence of TB infection in the 15-49 year age group, to populations, which are thought to be infected with HIV in this age group (7). However, a crude prevalence estimate of TB/HIV co-infection can be obtained from the product of TB and HIV prevalence in the whole population (3).

In the developing world an estimated 50% of HIV infected individuals are co-infected with TB. The vast majority of them (78%) are living in Africa where the HIV prevalence is high (5). In these countries the largest increase in TB cases is occur in the 15-49 year age group which is the same age group affected by HIV /AIDS. In Africa an estimated 48% of the 15-49 year age group are infected with TB (7). The overlap in the age groups is epidemiologically important.

The prevalence of dual infection in developed countries show a different picture. Although more than 1.5 million individuals are infected with HIV in Europe and the five industrialized countries, the prevalence of TB among the 15-49 year old persons is relatively low in these countries. As a result the prevalence of dual infection is low. It is estimated that less than 6% of all dual infected people live in these countries (7).

The picture in Sri Lanka has been somewhat similar to the profile in developed countries. The prevalence of TB in the general population is considered low. Approximately 6500-7000 new cases of TB are detected annually in Sri Lanka (8). BCG immunization which covers almost 100% newborns does not leave room for a reservoir of dormant bacilli. Moreover, reported tuberculosis morbidity rates are highest in the older age groups, mainly 55-74 years in comparison to HIV infection. As at the end of 2000, a cumulative total of 358 HIV sero positives were reported in Sri Lanka with 92% of them being in the 15-49 year age group (8). Dual infection has been reported only in a few cases.

TB is the biggest killer of people who are HIV positive. Three million of 30 million TB deaths worldwide were estimated to be associated with HIV. Thus one-tenth of TB-associated deaths are attributable to HIV infection. Once active TB develops in HIV infected persons, mortality is reported to be high despite good clinical and

microbiologic responses to active TB therapy. In resource poor countries many HIV infected individuals die prematurely of TB (3,5).

Immunology

Passive immunity against *M. tuberculosis* is based on cell-mediated immunity, involving certain interactions between T cells and cells of the monocyte-macrophage lineage (5,9). CD4+ T lymphocytes are involved in many aspects of the immune response to *M. tuberculosis* including binding to processed antigen, secreting cytokines, killing mycobacteria infected cells and persisting as antigen specific memory cells. Some of the key cytokines involved are T cell derived interleukin-2 (IL-2) and interferon gamma (IFN γ) as well as monocyte derived IL-12 and tumour necrosis factor (TNF- α) and macrophage derived interleukin IL-8, tissue growth factor (TGF β) and tumour necrosis factor (TNF- β). The ease with which macrophages kill tuberculosis organisms is enhanced by cytokines. Evasion of these mechanisms and defects in the mechanism are essential for establishment of illness (5,9).

Quantitative and qualitative defects in T lymphocyte function that result from direct HIV infection of CD4 cells, severely limit the production of macrophage-activating cytokines capable of inducing an antimycobacterial state in cells of the monocyte lineage in HIV patients, leading to more extensive and life threatening disease than in immunocompetent individuals (5,9).

Protection from TB is associated with a predominant Th-1 response, while a Th-2 response is associated with disease progression. Th-1 type cytokines are reduced in individuals co-infected with TB and HIV with a shift towards Th-2 production leading to progression of disease (5).

Clinical Presentation

Tuberculosis in HIV infected persons, as in other populations is primarily a pulmonary infection. Extra-pulmonary sites are affected with advancing immune deficiency (10,11). The clinical manifestations are dependent upon the immune stage of the patient. In early immune suppression (CD4>200), the disease resembles that found in non-HIV infected individuals. As the immune response to *M. tuberculosis* declines with advancing HIV infection the clinical illness becomes more devastating and management becomes more complex (10,11).

In early HIV disease, pulmonary manifestations resemble adult post-primary disease. The respiratory symptoms of tuberculosis in HIV positive patients are similar to those encountered in other patients. The onset is usually gradual taking several weeks and is difficult to differentiate from other opportunistic infections such as *Pneumocystis carinii* pneumonia (PCP). If symptoms appear abruptly it is more suggestive of pyogenic pneumonia. Sputum microscopy and chest radiography should be performed on all patients with HIV infection who present with respiratory or constitutional symptoms (10,11). The classic form of tuberculosis, with cavitating, upper zone, pulmonary lesions is known to be determined by the interaction between the bacillus and the host's immune system (11). As such during early HIV infection with less immune deficiency a clinical picture similar to that seen in HIV negative patients with pulmonary TB is seen. The chest radiography shows upper lobe consolidation and cavitation (10,11). The tuberculin test is usually positive and there is a high rate of sputum/ broncho-alveolar fluid smear positivity.

In late disease, clinical features are more atypical and in pulmonary disease the pattern is often similar to primary infection, with chest radiography most often showing diffuse pulmonary infiltrates with hilar shadowing or pleural effusions (3). Cavitation is unusual and, in some, the chest radiograph may be normal. Intra-thoracic adenopathy may be found in up to 25% of patients with AIDS related TB. Since neither PCP nor persistent generalized lymphadenopathy is associated with mediastinal lymphadenopathy, its presence should raise suspicion of TB. The tuberculin test is usually negative and sputum and broncho-alveolar lavage fluid are often smear negative. With advancing immune deficiency the disease becomes more widespread and extra-pulmonary disease occurs in about 70% (3,11). The link between extra-pulmonary tuberculosis and HIV is now well established.

Infection with *Mycobacterium kansasii* a non-tuberculous mycobacterium that causes disease that is clinically indistinguishable from that caused by *Mycobacterium tuberculosis*, has been reported in a small number of patients with AIDS (10,11).

Multiple drug resistance (MDR)

MDR is usually defined as resistance to both INAH and rifampicin, with or without the presence of resistance to another antibiotic. Risk factors that may predict MDR are inadequate treatment programmes, delayed diagnosis of tuberculosis,

delayed recognition of drug resistance, close contact with another MDR patient, country of origin (Latin America, Asia, Africa), age, patients infected with HIV and intra-venous drug use. Nonetheless 32% to 60% of drug resistant cases have no apparent risk factors (13).

Drug resistance may be either primary or acquired (13). Primary resistance occurs in patients who have had no previous anti-mycobacterial treatment. Acquired resistance occurs in patients who have been treated in the past and it usually is a result of non-adherence to the recommended regimen or incorrect prescribing. Sometimes it results from exogenous re-infection of patients with profound HIV-induced immuno-suppression who are already receiving treatment for drug-sensitive disease. TB caused by MDR organisms should be suspected in patients who are not responding to initial therapy.

The prevalence of MDR-TB is increasing worldwide. In the USA it accounts for about 3% of all tuberculosis in HIV-positive patients. Outbreaks have been reported in HIV infected patients from Spain, Italy, and UK. In the South East Asian region cases have been reported from Vietnam and Thailand (13).

MDR has emerged as a significant clinical problem in HIV infected patients. HIV however, has not caused the MDR problem but has heightened its recognition. Although the association of HIV and MDR-TB is clear, HIV positive patients are not more prone to MDR-TB than to drug susceptible strains of *Mycobacterium tuberculosis*. Similarly in HIV infection, resistant strains are not more virulent than susceptible strains, but inadequate treatment leads to rapid progression of the disease (12,13).

Despite anti-tuberculosis therapy, the prognosis of MDR tuberculosis in HIV infected patients is poor. About 70% of patients with HIV and MDR-TB die within 4-16 weeks of diagnosis (3,12,13). While isolated resistance to isoniazid and rifampicin can be managed with first line of drugs, combined isoniazid and rifampicin resistance demands treatment with at least four agents including a quinolone and an injectable agent such as an aminoglycoside. The treatment has to be maintained for 18-24 months, is expensive and produces multiple side effects (11,12).

Diagnosis

TB is often the earliest HIV associated illness to manifest, hence the diagnosis of TB may be the first opportunity to diagnose HIV. A high index of suspicion and an aggressive diagnostic approach is

necessary to diagnose TB when jointly infected with HIV.

The most common method of diagnosis is the demonstration of acid-fast bacilli (AFB) in sputum and at least three sputum samples should be sent for mycobacterial smear and culture (11,12). Neglecting to correctly obtain enough sputum may be the most common diagnostic mistake. The sensitivity of sputum examination is between 40% to 67% (3,9). AFB may be seen less frequently in sputum samples from TB patients with advanced HIV infection. Nonetheless, sputum smears are frequently positive in HIV infected patients with even minimal radiographic changes (3). Stool specimens have also been reported to demonstrate AFB in HIV infected persons with smear-negative pulmonary TB (11). Definitive diagnosis of TB requires a culture of MTB from clinical specimens on BACTEC or Lowenstein-Jensen media. In view of the atypical presentations all suspected biopsy specimens should be sent for mycobacterial culture. When immuno-suppression becomes more severely impaired, the classical granulomatous features of TB may be absent in histological specimens (3,9,11).

PCR and other nucleic acid amplification techniques can directly detect small quantities of the organism DNA or RNA in a clinical sample of sputum or CSF. Detection of mycobacterial antigen by enzyme linked immuno-sorbent assay (ELISA) in sputum is difficult as most antigens are denatured during processing of sputum. The sensitivity of antigen immuno-assays varies from 39% to 79% and the specificity from 98% to 100% (3). Because the sensitivity of AFB in CSF is less than 30% in most series these assays have greatly facilitated rapid diagnosis of TB meningitis (3). Antibodies have been detected in serum and body fluids such as cerebrospinal fluid (CSF), pleural fluid, and bronchial washings. The sensitivity of antibody detection is reduced in smear negative tuberculosis, presumably because lower bacillary burdens yield decreased antibody production (3).

Identification of individual *M. tuberculosis* strains is now possible through "DNA finger printing" (3). Specific immune-based diagnostic approaches for TB are being studied, as identification of individuals latently infected with *M. tuberculosis* is an important part of tuberculosis control. The tuberculin skin test (TST) which is the method currently used, has poor specificity because of the antigenic cross-reactivity of purified protein derivative (PPD) with *M. bovis*, BCG vaccine and environmental mycobacteria (14,15). Accurate identification of those infected with *M. tuberculosis*

by TST for targeted therapy is therefore difficult. ESAT-6 specific T cells are considered as an accurate marker of *M. tuberculosis* infection. ESAT-6 is an antigen that is highly specific for *M. tuberculosis* complex, but is absent from *M. bovis* and BCG. A low molecular mass antigen ESAT-6 was cloned as a new diagnostic method and the ELISPOT assay seems to accurately identify individuals with *M. tuberculosis*. Strong positive relation between ESAT-6 ELISPOT assay results and *M. tuberculosis* exposure and the lack of relation with BCG vaccination status will be able to identify symptom less mycobacterial infections from BCG vaccination (14,15). This assay has the potential to be used to identify recently infected contacts as well as other individuals at high risk of MTB infection particularly in low prevalence countries. Identification of the latter group is important to target chemoprophylaxis; in addition, this would help unnecessary chemoprophylaxis in uninfected individuals (15).

Management

In 1993, WHO declared TB control as a global emergency and promoted implementing the strategy called Directly Observed Treatment Short Course (DOTS). The goal of DOTS is to detect 70% of all sputum smear positive TB cases and to cure 80% of them through passive detection and directly observed treatment. The DOTS strategy is made up of five operational components : diagnosis and follow-up through sputum microscopy; use of standardized short-course drug regimens, regular uninterrupted supply of drugs, accurate cohort recording and analysis and direct observation of treatment (13). All components other than the latter have been in use for many years. The direct observation of treatment component is intended to address patient non-compliance and has two important elements: observation of every scheduled dose of medication a patient takes during at least the initial 2-month intensive phase of treatment and giving positive encouragement to patients to ensure treatment completion.

Patients infected with HIV-1 initially respond well to treatment for active tuberculosis (11,16). The standard therapy is to use four anti tuberculous drugs for two months and two drugs for four months which is similar to the therapy given to HIV uninfected people. Similar cure rates have been observed between HIV positive and HIV negative patients completing treatment, and the response was not related to CD4 counts. But severity of immune deficiency was the major determinant of mortality in HIV associated tuberculosis (16).

With the introduction of highly active antiretroviral therapy (HAART) for HIV patients, a significant decrease in most of the opportunistic infections including TB has been observed. The clinician should be aware that HAART however might cause a transient worsening of clinical and radiological manifestations of TB within days to weeks after commencement of therapy, which probably is due to immune restoration against tuberculous antigen. Therefore, it is recommended to delay HAART until the first two months of treatment of TB have been completed. In addition drug interactions with overlapping toxicities between the two groups of drugs have been reported (11).

Prophylaxis

The use of anti tuberculous drugs as primary prophylaxis in HIV infected people is subject to debate. It is estimated that 10% of HIV infected patients with positive tuberculin tests from previous TB infections who do not receive chemotherapy develop TB each year (11,17).

A great deal of accumulated evidence from studies is available to show that isoniazid (INAH), usually given at a daily dose of 300 mg for 6-12 months significantly reduces the subsequent incidence of TB (17,18). Yet, whether INAH offers protection only whilst it is being taken is still not very clear. Further, in countries with a high prevalence of TB, although prophylactic therapy seems to offer protection against TB, it has not been shown to have an effect on HIV progression or mortality in the long run. It has also been shown that multidrug regimens with isoniazid and rifampicin taken for three months reduce the risk of tuberculosis (18).

Among subjects with anergy, both cross sectional and randomized control trials have shown that there was evidence of only a small benefit with INAH preventive therapy (19). The reason INAH did not confer the same degree of protection in the subjects with anergy is unclear. It is speculated that failure with primary prophylaxis may be because of drug malabsorption or other host factors associated with advanced disease. Decisions concerning the use of chemoprophylaxis in anergic patients should be considered individually. Those who have been exposed to active TB patients may warrant chemoprophylaxis (19). Before commencing on chemoprophylaxis any possibility of having active disease has to be excluded.

Although patients with HIV-1 infection respond well to treatment for active tuberculosis, whether such patients are at an increased risk of disease recurrence after cure is uncertain. A randomized

trial in Haiti observed that HIV-1 positive individuals were more likely to have recurrent tuberculosis after therapy than HIV-1 negative individuals (Relative risk 10.7% to 95%, CI 1.4 – 81.6, $p = 0.004$). Post treatment INAH prophylaxis decreased the rate of recurrent TB in HIV-1 positive patients but did not prolong survival (20).

Whether primary prophylaxis should be offered to HIV patients in Sri Lanka is a question that has to be balanced taking into consideration the low prevalence of TB and high rate of BCG vaccination, patient compliance and potential toxicity of drugs. A positive tuberculin test is the commonest method used to identify the patients who would benefit from prophylaxis. It becomes difficult to interpret tuberculin tests with regard to previous exposure to tuberculosis since BCG immunization has been extensively carried out in Sri Lanka. Furthermore, the higher the proportion of TB cases from reactivation, the greater is the potential for preventive therapy to have a public health impact. Conversely, if many cases result from recent infection, the effect of preventive therapy given for a limited time is likely to be short-lived. Therefore, there should be accurate data on the incidence of TB in HIV positive patients before deciding on the need for prophylactic therapy. In the alternative the best practice would be interruption of transmission by case finding and treatment.

Introduction of HAART has decreased death and opportunistic infections in affluent countries but the majority in the developing countries have no access to therapy. Even in the absence of such therapy there are other interventions that could be of some benefit for HIV positives. Voluntary counseling and testing will help to know the sero status. In the mean time HIV positives should not be deprived of HAART. HAART can reduce active M. tuberculosis infection at all CD4 T cell counts.

References

1. UNAIDS. AIDS Epidemic update: December 2000. Geneva: UNAIDS, 2000.
2. Dye C, Scheele S, Doilin P, Pathania V, Raviglione M C. Global burden of Tuberculosis. Estimated incidence, prevalence and mortality by country. *Journal of American Medical Association* 1999; 282: 677-685
3. Barnes F P, Barrows S A. Tuberculosis in the 1990s. *Annals Internal Medicine* 1993;119:400-410
4. Miller Robert. Tuberculosis. *Lancet* 1996;348:307-312
5. Gazzard B. Tuberculosis, HIV and the developing world. *Clinical Medicine* 2001;1: 62-68
6. Sonnenberg P, Murray J, Glynn J R, Shearer S, Kambashi B, Godfrey F P. HIV-1 and recurrence, relapse and reinfection of tuberculosis after cure: a cohort study in South African mineworkers. *Lancet* 2001;358:1687-1693
7. Sudre P, Dam Ten G, Kochi A. Tuberculosis: a global review of the situation today. *Bulletin of the World Health Organization* 1992 ;72(2):149-159
8. Ministry of Health, Annual health bulletin Sri Lanka 2000.
9. Tuberculosis Research Center. Report on Research Activities 1999-2000 - Chennai
10. Chaisson R E, Slutkin G. Tuberculosis and Human immuno-deficiency virus infection. *The Journal of Infectious Diseases* 1989;159:1:96-100
11. Shafer R W, Tuberculosis. In: Samuel Border, Thomas C Merigan, Dani Bolognesi eds: *Text book of AIDS*. William and Wilkins 1994; 259-282
12. Comstock G W, Reichman L B, Starke J R. Can we control TB this time? *Patient care* 1995; 97-117
13. Bastian I, Rigouts L, Van Deun A, Portaels F. Directly observed treatment, short course strategy and multi-drug-resistant tuberculosis: are any modifications required? *Bulletin of the World Health Organization* 2000; 78(2):238-251
14. Anderson P, Munk M E, Pollock J M, Doherty T M. Specific immune-based diagnosis of tuberculosis. *Lancet* 2000; 356:1099-1104
15. Lalvani A, Pathan A A, Durkan H, Wilkinson K A, Whelan A, Deeks J et al. Enhanced contact tracing and spatial tracking of Mycobacterium tuberculosis infection by enumeration of antigen-specific T cells. *Lancet* 2001; 357:2017-2021

16. Ackah A N, Coulibay D, Digben H, Diallo K, Vetter K M, Coulibaly I et al, Response to treatment, mortality and CD4 lymphocyte counts in HIV-infected persons with tuberculosis in Abidjan, Cote d'Ivoire. *Lancet* 1995; 345:607-610
17. Brook G M, Miller R F. Prevention and management of tuberculosis in HIV positive patients living in countries with a low prevalence of *Mycobacterium tuberculosis*. *Genitourinary Medicine* 1996; 2:89-92
18. Whallen C C, Johnson J L, Okwera A, Hom D L, Huebner R, Mugenyi P et al, A Trial of three regimens to prevent tuberculosis in Ugandan adults infected with the HIV. *The New England Journal of Medicine*. 1997; 337:801-808
19. Gordin F M, Matts J P, Miller C , Brown L S, Hafner R, John S L et al, A controlled trial of isoniazid in persons with anergy and human immunodeficiency virus infection who are at high risk for tuberculosis. *New England Journal of Medicine* 1997; 337:315-320
20. Fitzgerald D W, Desvarieux M, Severe P, Joseph P, Johnson W D, Pape W J. Effect of post-treatment isoniazid on prevention of recurrent tuberculosis in HIV-1-infected individuals: a randomized trial. *Lancet*; 2000; 350:1470-1474