CHAPTER 14

CO-INFECTION WITH HIV AND TUBERCULOSIS

Abstract

As compared to their HIV negative counterparts, HIV positive individuals infected by *Tubercle bacillus*, have about 10 times higher risk of progression from latent to clinically active tuberculosis. In India, the strategy of HIV testing of all newly diagnosed tuberculosis patients is neither feasible nor cost-effective, due to the large number of new cases of tuberculosis that are detected each year. The standard treatment regimens used in the Revised National Tuberculosis Control Programme (RNTCP), are equally effective in HIV positive patients. Directly Observed Treatment, Short Course (DOTS) strategy has been shown to improve survival of patients with co-infection. Concurrent treatment with protease inhibitors can either reduce activity or prolong half-life of rifampicin. Chemoprophylaxis against tuberculosis is currently not recommended in India.

14.1 – MAGNITUDE

14.1.1 – Tuberculosis

Currently, tuberculosis is the single biggest infectious disease that kills about 2–3 million persons worldwide each year. Annually, about 8 million new cases are diagnosed. The global incidence of tuberculosis is increasing at the rate of 0.4 per cent per year. Globally, the economic cost of tuberculosis is estimated at US$12 billion. Despite the availability of effective drugs, tuberculosis remains a global health challenge. In 1993, the WHO declared tuberculosis a global emergency (Health Action Information Network – HAIN, 2003). The re-emergence of tuberculosis in the developed countries in the 1990s is attributed to the HIV epidemic and environmental and social changes. The advent of HIV epidemic and multi-drug resistant (MDR) strains of tuberculosis has made the re-emergence of tuberculosis even more dangerous (HAIN, 2003). In 2001, the WHO drafted a "Global Plan to Stop TB". The plan seeks to expand the DOTS approach and to

improve the existing tools for diagnosis, treatment, and prevention. In its first phase, the plan envisages a detection rate of 70 per cent and a cure rate of 85 per cent by the year 2005 (HAIN, 2003).

Of the world's tuberculosis patients, 40 per cent live in South and South-East Asia. Of the world's annual 700,000 tuberculosis-related deaths, 95 per cent occur in Bangladesh, India, Indonesia, Myanmar, and Thailand. Though India leads in the total number of world's cases, Philippines has a higher rate of cases per 100,000 population (HAIN, 2003). Tuberculosis remains the leading cause of infectious death in India, killing close to 500,000 persons each year. There is an additional burden of two million new cases every year. Since most victims are aged between 18 and 45 years (the most economically productive age group), the disease causes losses in family income and national productivity. Studies show that on an average, a patient loses 3–4 months of work with lost earning amounting to 20–30 per cent of a family's annual income (HAIN, 2003). The economic burden of tuberculosis in India has been estimated to be Rs. 148.5 billion (about US$3 billion) per year (Pathni & Chauhan, 2003). The overall prevalence of HIV infection among tuberculosis patients was 9.0 per cent in 2005 (NACO, 2006).

14.1.2 – HIV-Tuberculosis Co-infection

Sub-Saharan Africa: Tuberculosis is the most common opportunistic infection in Sub-Saharan Africa. The HIV seroprevalence in tuberculosis patients is up to 75 per cent. It is the most frequent cause of death among HIV-infected persons in sub-Saharan Africa (Harries *et al.*, 2004). Tuberculosis-related deaths are expected to double by the year 2010 as the immune system (of currently HIV-infected persons) becomes more vulnerable to active disease (HAIN, 2003). In much of Africa, the spread of HIV is primarily responsible for driving the parallel epidemic of tuberculosis, often at the rate of 6 per cent per year (Corbett *et al.*, 2003).

Thailand: A case control study in Northern Thailand between 1990 and 1998 has found that 72 per cent of males and 66 per cent of females had tuberculosis that was directly attributable to HIV infection (Tansuphasawadikul *et al.*, 1999). Both cohort and case control studies have shown that the relative risk of acquiring active tuberculosis among HIV-infected persons varied from 5 to 20 per cent (Glynn, 1998). Seropositivity rate of 40 per cent has been reported among tuberculosis patients in Northern Thailand (Yanai *et al.*, 1996).

India: Since India has a high prevalence of tuberculosis, the problem of HIV-tuberculosis co-infection is overwhelming. An estimated 40 per cent of adults in India are already infected with *Mycobacterium tuberculosis* (Pathni & Chauhan, 2003). According to HIV sentinel surveillance report for 2005, released by NACO in April 2006, the overall prevalence of HIV infection among tuberculosis patients was 9.0 per cent. The HIV prevalence among tuberculosis patients in four sentinel sites was – Davangere district, Karnataka: 9.5 per cent; Guntur

district, Andhra Pradesh: 16 per cent; Nashik district, Maharashtra: 4.3 per cent; and Tiruvannamalai district, Tamil Nadu: 6.3 per cent (NACO, 2006). A study conducted in New Delhi hospital during 1994–1999 reported that out of 555 patients with tuberculosis, 9.4 per cent were HIV-positive while the overall seropositivity rate at the same hospital was 0.4 per cent (Sharma *et al*., 2003). Seropositivity rate of 30 per cent has been reported among tuberculosis patients in Mumbai (Mohanty & Basheer, 1995).

14.2 – SOURCES OF TUBERCULOUS INFECTION

The predominant source of infection is an individual with pulmonary tuberculosis whose sputum smear is positive. Coughing, talking, sneezing, spitting, and singing by such an individual produce droplet nuclei that contain *Tubercle bacilli*. Droplet nuclei are infectious particles of respiratory secretions usually less than 5 μ in diameter. Owing to their small size, they can directly lodge in the terminal alveoli of the lungs by avoiding the mucociliary defences of the bronchi. A single cough can produce up to 3,000 droplet nuclei that remain suspended in air for prolonged periods. Transmission by droplet nuclei generally occurs indoors and in the dark because direct sunlight can kill *Tubercle bacilli* within 5 minutes (Harries *et al*., 2004). Milk-borne tuberculosis is spread by consumption of milk from cattle infected by *M. bovis*. Infection of the tonsils presents as cervical lymphadenitis ("scrofula"). The intestinal tract may also be infected (Harries *et al*., 2004). Since milk is boiled before consumption in India, milk-borne tuberculosis is not a public health problem.

14.3 – HOST FACTORS

Some host factors associated with increased risk of HIV infection also predispose to tuberculosis. These include poverty, migration, and gender and they share a symbiotic relationship (HAIN, 2003).

Poverty: Poverty forces people to live in overcrowded conditions that increase the risk of transmission of the disease. Poverty is also accompanied by under-nutrition, lack of access to health care and poor living conditions such as poor ventilation, lack of safe drinking water, and inadequate sanitation. Workers exposed to silica-containing dust are also vulnerable. These factors compromise the body's ability to fight infections. Therefore, poor people are more vulnerable to tuberculosis, as compared to their relatively affluent counterparts. Thus, tuberculosis control programmes can succeed only if the socio-economic condition of the target population is improved. Due to losses in earnings, many families are forced to sell their land or livestock, or take their children out of school. These school dropouts help out with domestic chores or work outside their homes as child labourers. In India, 300,000 children from tuberculosis-afflicted households are forced to leave school every year (HAIN, 2003).

Migration: Migrants are pushed to poverty if they are unable to find work. Actual or perceived discrimination and social maladjustment prevents these migrants from seeking health care. Illegal international migrants do not seek health care services for fear of detection and deportation. Single migrants also constitute a high-risk group for HIV infection.

Gender: Female tuberculosis patients face more social stigma and discrimination as compared to their male counterparts. For fear of social ostracism, many families in male dominated societies do not seek tuberculosis treatment for their womenfolk. In India alone, more than 100,000 tuberculosis-afflicted wives are abandoned by their husbands, each year (HAIN, 2003). HIV-infected women also face a similar situation.

14.4 – NATURAL HISTORY OF TUBERCULOSIS

14.4.1 – Risk of Infection

The risk of infection of a new host is determined by: (a) concentration of infected droplet nuclei in the inhaled air, (b) duration of exposure to inhaled droplet nuclei, and (c) susceptibility of the new host to infection (HAIN, 2003). The risk of infection is high with prolonged, close, indoor exposure to a person with sputum positive pulmonary tuberculosis. The risk of transmission of infection from a person with sputum negative pulmonary tuberculosis is low. The risk is even lower from a person with extrapulmonary tuberculosis (Harries *et al.*, 2004).

14.4.2 – Risk of Progression of Infection to Disease

Infection with *M. tuberculosis* can occur at any age. Once infected, the person may stay infected probably for life. In India, an estimated 40 per cent of the adult population is already infected with *M. tuberculosis*. (Pathni & Chauhan, 2003). About 90 per cent of persons who are infected with *M. tuberculosis* (but without HIV infection) do not develop tuberculosis disease. In such asymptomatic but infected individuals, the only evidence of infection may be a positive tuberculin skin test. Infected persons can develop tuberculosis disease at any time. Infants, children, the elderly, and persons with immune suppression (due to malignancy, malnutrition, measles or pertussis infection, corticosteroid therapy, HIV infection) are more vulnerable to develop tuberculosis. Infants and children have an immature immune system and usually develop the disease within 2 years of exposure and infection. The disease is more likely to spread from the lungs to the other parts of the body in this age group. Those who do not develop the disease in this age group may do so later in life. Physical or emotional stresses may also trigger progression of infection to disease (Harries *et al.*, 2004).

14.4.3 – Untreated Tuberculosis

HIV infection, *per se*, is not fatal. HIV destroys the immune system and makes the infected person vulnerable to multiple infections. If left untreated, by the end of 5 years, 50 per cent of patients with pulmonary tuberculosis will be dead; 25 per cent will be self-cured by strong immune defence; and the remaining 25 per cent will remain ill with chronic infectious tuberculosis (Harries *et al.*, 2004).

14.5 – PATHOGENESIS AND IMMUNOPATHOLOGY

14.5.1 – Primary Infection

Primary infection occurs in persons who have not had any previous exposure to *Tubercle bacilli*. Droplet nuclei, which are usually less than 5 μm in diameter, can directly lodge in the terminal alveoli of the lungs by avoiding the mucociliary defences of the bronchi. Infection begins with multiplication of *Tubercle bacilli* in the lungs and the resulting lesion is called *Ghon focus*. The lymphatics drain the bacilli to hilar lymph nodes. The Ghon focus, together with the enlarged hilar lymphadenopathy, forms the *primary complex* (Harries *et al.*, 2004).

From the primary complex, bacilli may spread via the blood stream, throughout the body. Rapid progression to intra-thoracic disease is more common in children under 5 years of age. The immune response (delayed-type hypersensitivity (DTH) and cellular immunity) develops about 4–6 weeks after primary infection. The ensuing events are determined by the quantum of infecting dose and the strength of the immune response.

14.5.2 – Immunopathology of Primary Infection

M. tuberculosis multiplies and within about 3 weeks, the population of the bacilli reaches 10^3–10^4 (the number required to trigger an immune response). Once this number is reached, the mycobacterial multiplication suddenly stops.

If the tubercular antigens are represented by *class-I MHC molecules*, cell mediated immunity (CMI) is developed by activating the CD4 cells. However, if class-II MHC molecules represent the tubercular antigens, CD8 cells – cytotoxic cells concerned with DTH – are activated. CD8 cells also have the ability to recognise infected macrophages and destroy them by direct cytotoxic action. Various immunological chemicals activate the resting macrophages to engulf, ingest, and digest the mycobacteria. This process is further enhanced by vitamin D3, which is tuberculostatic.

The activated macrophages release chemicals from the cell wall of the digested mycobacteria, which results in converting monocytes into epithelioid cells and Langhan's giant cells, forming a granuloma (called the *Tubercle*). The centre of the granuloma has low pO_2 and low pH, which is unfavourable for the growth of *M. tuberculosis*. Thus, during this stage, immunologic control can

be achieved, by "walling off" the infection. The granuloma may get *fibrosed* (in adult tuberculosis), or *calcified* (in childhood tuberculosis). As long as the infection is "walled off", the person remains infected, but clinically asymptomatic. About 90 per cent otherwise healthy persons, infected with the *Tubercle bacillus* do not develop clinical tuberculosis.

14.5.3 – Outcome of Primary Infection

In about 90 per cent of cases, the immune response stops the multiplication of bacilli, but a few dormant bacilli may persist. A positive tuberculin (Mantoux) test would be the only evidence of infection. In some individuals, the immune response is not vigorous enough to prevent the multiplication of bacilli and various manifestations of the disease may occur after a latent period of months or years. Some may develop hypersensitivity reactions such as phylctenular conjunctivitis, erythema nodosum, and dactylitis. Intra-thoracic disease (lung infiltrates, pneumonia, consolidation, collapse, or pleural effusion) may occur. Lymphadenopathy (particularly in cervical region), meningitis, or miliary tuberculosis constitute disseminated type of tuberculosis (Harries *et al*., 2004).

14.5.4 – Post-Primary Tuberculosis

Post-primary tuberculosis occurs either by: (a) *reactivation* – dormant bacilli acquired from a primary infection begin to multiply due to trigger factors like weakening of immune system by HIV infection, or (b) *reinfection* – occurrence of repeat infection in an individual who has previously had a primary infection (Harries *et al*., 2004).

14.5.5 – Immunopathology of Post-Primary Tuberculosis

In the later stages of primary infection, gamma and delta lymphocytes become responsive to antigens of *M. tuberculosis*. There seems to be a balance between CMI and DTH. If the immunologic control by CMI and DTH is not balanced, then the tissue-damaging action of DTH may predominate. This leads to liquefaction necrosis of the tubercular granuloma and subsequent activation of the disease. In pulmonary tuberculosis, this leads to development of cavities. Thus, DTH is more harmful, and not helpful, to the host. The immune response results in a pathological lesion that is localised, often with extensive tissue destruction and cavitation.

14.5.6 – Outcome of Post-Primary Tuberculosis

Though post-primary tuberculosis usually affects the lung, it can affect any part of the body. *Pulmonary* tuberculosis may manifest as cavities, upper lobes infiltrates, progressive pneumonitis, endobronchial tuberculosis, fibrosis, and

pleural effusion. The common clinical features of *extrapulmonary* tuberculosis are lymphadenopathy (usually cervical), meningitis, cerebral tuberculoma, pericardial effusion, constrictive pericarditis, ileo-caecal and peritoneal tuberculosis, and involvement of the skeletal system (spine, bone, and joints). Involvement of skin (lupus vulgaris, tuberculids), miliary tuberculosis, involvement of kidney and adrenals, tuberculous epididymitis and orchitis, tubo-ovarian or endometrial tuberculosis and empyema are rare manifestations of extrapulmonary disease. The hallmarks of post-primary tuberculosis are – extensive destruction of lung tissue with cavitation, involvement of upper lobe, positive sputum smear, usually with absence of intra-thoracic lymphadenopathy. Patients with these lesions can spread infection in the community (Harries *et al.*, 2004).

14.6 – DIAGNOSTIC TECHNIQUES

Clinical manifestations such as cough, fever, and chest pain are also seen in other diseases and are thus not typical for diagnosis of tuberculosis. Sputum microscopy is not very accurate and is also subject to observer errors. Interpretations of chest radiographs are also subjective. Though *M. tuberculosis* was identified in 1882, and its entire genome was completed only in 2002, there is no modern diagnostic kit for tuberculosis till date. On the other hand, within a few months of outbreak of Severe Acute Respiratory Syndrome (SARS), the entire genome of the pathogen was identified and a diagnostic kit was developed. PCR that amplifies specific DNA sequences of the *Tubercle bacillus* is available, but very expensive (Bezbaruah, 2004).

In the developed countries, all newly diagnosed tuberculosis patients are tested for HIV serostatus. However, in India, this strategy is neither feasible nor cost-effective, due to the large number of new cases of tuberculosis that are detected each year. Pulmonary tuberculosis can be diagnosed in HIV positive individuals by sputum examination. Diagnosis of extrapulmonary and disseminated forms of tuberculosis is possible by histopathology and various sophisticated imaging techniques. Based on the genome sequence of *M. tuberculosis* (which was completed in 2002), sensitive DNA-based diagnostic tests are being developed. The Foundation for Innovative New Diagnostics (FIND), a WHO-funded organisation, is working on cheap innovative diagnostic tests. A colour-based assay (wherein cultures of *M. tuberculosis* will light up bright green) is being developed. The All India Institute of Medical Sciences (AIIMS), New Delhi, has developed a specific PCR technique and a solution for spotting mycobacteria more clearly (Bezbaruah, 2004).

14.7 – DIRECTLY OBSERVED TREATMENT, SHORT COURSE

The WHO and the International Union Against Tuberculosis and Lung Diseases (IUATLD) recommend "DOTS" as the most effective and affordable strategy to control tuberculosis. The DOTS strategy involves: (a) diagnosis of

cases by sputum microscopy from among patients with symptoms suggestive of tuberculosis, (b) free-of-cost intermittent therapy with a standardised drug regimen, (c) direct observation of drug consumption by a trained health worker to ensure adherence, (d) reliable and regular drug supply, (e) adequate health infrastructure and trained health personnel, (f) political commitment, and (g) monitoring and evaluation of the programme (HAIN, 2003).

Treatment supporter is a health worker or a community volunteer who provides encouragement and support for the person taking antitubercular treatment. DOTS strategy was first introduced in 1991. Since then, incidence rates have decreased in high-burden countries. High cure rates have been reported in selected areas, but these areas may be isolated islands of excellence. An adequate public health infrastructure is a pre-requisite for starting DOTS. Critics point out that the DOTS programme will only be as efficient as the public health services of the country where it is being implemented. In countries where the basic health services are inadequate, the long-term sustainability of DOTS is endangered. The current treatment regimens involve the use of four or five antitubercular drugs, to be taken for at least 6 months. Studies reveal that most patients stop treatment after the initial 2–3 months since the symptoms are relieved. Poor compliance to treatment increases the risk of multi-drug resistance. If the treatment is stopped after 2 months, the estimated risk of relapse is 70 per cent, while after 4 months it is 40 per cent (HAIN, 2003).

14.7.1 – Fixed-Dose Combinations

These contain two or more drugs within the same tablet. Currently, fixed-dose combinations are more expensive than the total cost of single drugs. The situation is likely to change with increase in production of fixed-dose combinations. The WHO and IUATLD recommend the use of fixed-dose combinations for the following reasons:
1. Increase in patient adherence: the probability of patients forgetting to take a particular medication is reduced since they have fewer pills to swallow.
2. Improves adherence of health care personnel to standardised regimens.
3. Drug management becomes easier (fewer items with a single expiry date).
4. Managing drug supplies becomes easier since fewer drugs and lower volumes need to be procured and delivered to rural and remote areas.
5. Reduces possibility of drug resistance by reducing the likelihood of prescription errors or use of wrong drug combinations (HAIN, 2003).

14.7.2 – DOTS in India

The government of India introduced DOTS strategy under the RNTCP in 1997. By the end of 2001, the population covered by DOTS increased to 45 per cent and the number of DOTS-notified smear positive cases nearly doubled. But at the national level, the total numbers of smear positive cases (both DOTS and

non-DOTS taken together) changed little. In order to reach the targeted case detection rate of 70 per cent, DOTS must be extended geographically and at the same time, the proportion of cases detected under DOTS programme must be increased. The cure rate for patients registered in the year 2000 was 84 per cent (HAIN, 2003). The World Bank has provided a loan of US$142.5 million to the government of India. Danish International Development Agency (DANIDA), Global Fund for AIDS, Tuberculosis and Malaria (GFATM), and Global Development Fund financially support the DOTS expansion programme (HAIN, 2003).

Despite sound financing, the key problem in the DOTS programme continues to be access to drugs, information, and treatment. Many patients and even medical practitioners are still not aware of the DOTS programme (HAIN, 2003). Given the low Indian health budget, the long-term sustainability of the programme is uncertain (Bezbaruah, 2004).

14.8 – HIV-TUBERCULOSIS CO-INFECTION

14.8.1 – Effect of HIV Epidemic on Tuberculosis

HIV infection expedites the spread of tuberculosis by re-activating latent tubercular infection, accelerating progression of recently acquired tubercular infection, and by predisposing to exogenous re-infection by *M. tuberculosis* (Pathni & Chauhan, 2003). Among those infected by *M. tuberculosis*, it is estimated that the *lifetime risk* of progression from latent to clinically active tuberculosis is 50 per cent (i.e. about 10 times higher) in HIV positive individuals, as compared to the *lifetime risk* of 5–10 per cent faced by their HIV negative counterparts (Harries *et al*., 2004). HIV infection along with active tuberculosis leads to depletion of CD4 lymphocytes, increased multiplication of HIV, and elevated plasma levels of HIV-RNA. In HIV positive individuals, progressive depletion of CD4 cells results in predominance of CD8 cells and DTH, which helps the re-activation of primary tubercular infection and dissemination of the disease. In pulmonary tuberculosis, HIV also impairs the innate resistance of alveolar macrophages. Thus, HIV and *M. tuberculosis* form a *deadly alliance* (WHO, 2002). Besides complicating the diagnosis of tuberculosis, HIV contributes to increase in incidence of tuberculosis (Narain *et al*., 1992; Raviglione *et al*., 1992). The deadly alliance between HIV and tuberculosis, each potentiating the impact of the other, has been documented and is currently obvious in Africa (Narain *et al*., 1992; Raviglione *et al*., 1992; WHO, 2002; Dye *et al*., 1999).

Since the rate of progression from infection with *M. tuberculosis* to clinical tuberculosis is accelerated in persons who are HIV-infected, an increase in incidence of tuberculosis can be expected in areas with high incidence of HIV seropositivity. In Africa, countries with high HIV prevalence rates also have a high prevalence of tuberculosis (Godfrey-Faussett & Ayles, 2003). The linear relationship between prevalence of HIV seropositivity and tuberculosis indicate

that rapid spread of HIV infection would increase the case load of tuberculosis (Godfrey-Faussett & Ayles, 2003; WHO, 2001; Tripathy & Narain, 2001).

Pathogenesis: Pathogenesis of both HIV and tuberculosis relates directly to CMI. HIV infection, which depletes CD4 lymphocytes, also causes defective immunological response to *M. tuberculosis*. HIV infection can alter the pathogenesis of tuberculosis by reactivation of latent tuberculous infection to active disease, which is more common, or by causing rapid progression from recent infection to clinical tuberculosis.

Diagnostic Challenges: As compared to HIV-negative patients, a lesser proportion of HIV-positive patients with pulmonary tuberculosis will have sputum positive smears. This will *reduce* the *sensitivity* of sputum smear examination (mainstay for diagnosis of tuberculosis). Chest radiographic findings that are not specific for tuberculosis in HIV-negative patients are even more non-specific in the HIV-infected. Patients with HIV-tuberculosis co-infection have frequent illnesses with pulmonary involvement caused by organisms other than *M. tuberculosis* (Narain & Lo, 2004).

Chest Radiographic Findings: No chest radiographic finding is *typical* of pulmonary tuberculosis, especially with concomitant HIV infection. The chest radiographic abnormalities in patients with concomitant HIV infection are indicative of the degree of immune suppression. If the immune suppression is *mild*, the appearance is often "classical" (i.e. presence of cavitations and upper lobe infiltrations). Thus in patients with early HIV infection, the chest radiographic findings are indistinguishable from that in seronegative patients. In *severe* immune suppression, the appearance is often "atypical": (a) less often cavitating and smear positive, (b) lesions are bilateral, diffuse, and reticular or reticulonodular, (c) miliary pattern is more common, (d) lower lobe infiltration, and (e) mediastinal lymphadenopathy. If mediastinal lymphadenopathy is seen, it is necessary to rule out bronchial carcinoma, lymphoma, and sarcoidosis (very rare in India).

Response to Antitubercular Treatment: The response to antitubercular treatment is similar among HIV-positive and HIV-negative patients. HIV-induced immune suppression does not seem to interfere with the effectiveness of antitubercular treatment (Alwood et al., 1994). Since the treatment and response to treatment are similar for HIV-positive and HIV-negative patients, there is no justification for carrying out HIV tests in clinical settings (Narain & Lo, 2004).

Adverse Reactions: Adverse drug reactions are more common in HIV-positive patients, as compared to their HIV-negative counterparts. Most reactions occur in the first 2 months of treatment. Skin rash and hepatitis is attributed to rifampicin. Rifampicin can reduce the activity of several drugs used in HIV-infected patients. Thiacetazone is usually associated with exfoliative dermatitis, Stevens–Johnson syndrome, and toxic epidermal necrolysis. Therefore, thiacetazone should *never* be given to HIV-positive tuberculosis patients and should not be prescribed in areas where HIV prevalence is high (Narain & Lo, 2004).

14.8.2 – Effect of Tuberculosis on the HIV/AIDS epidemic

Up to 40 per cent of deaths in HIV-infected patients are due to tuberculosis (Corbett *et al.*, 2003). Tuberculosis accounts for one-third of deaths among HIV-infected individuals worldwide (HAIN, 2003; WHO, 2004). The degree of immune suppression is the most important predictor of survival of HIV-infected patients with tuberculosis and low CD4 counts are associated with high mortality (Narain & Lo, 2004). Tuberculosis occurs earlier in the course of progression of HIV infection, when CD4 counts are around 400 cells per μL. Extrapulmonary (especially lymphadenititis) and disseminated forms of tuberculosis are more common (HAIN, 2003). More than 2–3 million HIV-infected persons in India are also afflicted with tuberculosis (HAIN, 2003).

Accelerated Progression of HIV: Tuberculosis intensifies the HIV/AIDS epidemic by accelerating progression of HIV infection and by shortening the survival of HIV positive patients. There is a six- to sevenfold increase in viral load in patients with co-infection, as compared to HIV-positive patients without tuberculosis.

Accelerated HIV-Induced Immune Suppression: Active tuberculosis is associated with transient depletion of CD4 lymphocytes. Tuberculosis increases production of cytokines like tumour necrosis factor (TNF) which increases replication of HIV in vitro. HIV-infected persons with tuberculosis appear to have higher risk of opportunistic infections and death, as compared to their counterparts with similar CD4 counts, but without tuberculosis.

14.8.3 – Clinical Manifestations of Co-infection

Though disseminated and extrapulmonary tuberculosis is relatively more common in patients with co-infection, pulmonary tuberculosis is still the most common manifestation. The manifestations depend on the degree of immune suppression (Harries *et al.*, 2004). The most frequently seen forms of extrapulmonary tuberculosis in HIV-infected persons are pleural effusion, widespread tuberculous lymphadenopathy, miliary tuberculosis, pericardial involvement, meningitis, and disseminated tuberculosis with mycobacteriemia (Harries *et al.*, 2004).

The clinical manifestations in HIV-positive children are similar to that in their HIV-negative counterparts in early stages of HIV infection. In late stages, disseminated forms of tuberculosis may occur. In the *early stage*s of HIV infection in adults, the clinical manifestations of pulmonary tuberculosis often resembles that of *post-primary* pulmonary tuberculosis, the sputum smears are frequently positive, and chest radiographs often show cavitary lesions or localised parenchymal involvement in the upper lobes (HAIN, 2003). In the *late stage*s of HIV infection in adults, disseminated forms of tuberculosis are seen, the sputum smears are frequently negative for acid-fast bacilli, and chest radiographs are not "typical" and often show diffuse infiltrates, with no cavities.

14.8.4 – DOTS for Co-Infection

The principles of control of tuberculosis are the same even for patients with co-infection. The standard treatment regimens used in the RNTCP, are equally effective in HIV positive patients (Espinal *et al*., 2000). The DOTS strategy has improved survival of patients with co-infection (HAIN, 2003; NACO). The DOTS strategy depends primarily on *passive case finding*. In view of the symbiotic association between HIV and tuberculosis, active case finding for tuberculosis may be a helpful approach in areas with high HIV prevalence (Narain & Lo, 2004).

   In areas with high prevalence of co-infection, the rise in number of tuberculosis patients may increase the workload of public health facilities, with the following possible outcomes: (a) excess laboratory workload leading to over- or under-diagnosis of pulmonary tuberculosis, (b) inadequate supervision of antitubercular chemotherapy, (c) low cure rates and high rate of recurrence, (d) high morbidity and mortality during treatment, (e) poor adherence of patients due to adverse drug reactions, and (f) increased transmission of multidrug-resistant tuberculosis among HIV-infected patients (Harries *et al*., 2004).

14.9 – MULTIDRUG-RESISTANT TUBERCULOSIS (MDR-TB)

Multidrug-resistant tuberculosis (MDR-TB) is defined as "disease caused by *M. tuberculosis*, which is resistant to at least two first-line antitubercular drugs – isoniazid (INH) and rifampicin" (NACO). Some bacilli are inherently resistant to some drugs. If a single drug is used to treat a patient, only those bacilli that are sensitive to that drug are killed, allowing resistant bacilli to multiply. Multiple drugs are used in the intensive phase of tuberculosis treatment so that the number of viable *M. tuberculosis* is greatly reduced (HAIN, 2003). There are two specific types of drug resistance.

Primary Resistance: occurs when someone who harbours drug-resistant forms of *M. tuberculosis* infects another individual. Sometimes, a patient may withhold information on previous treatment with antitubercular drugs. Such cases may be wrongly labelled as that of primary drug resistance (HAIN, 2003).

Secondary (or Acquired) Resistance: is due to the emergence of drug resistant strains as the dominant population. Secondary drug resistance is attributable to –
1. Use of correct combinations for inadequate duration – This can occur due to interruptions in drug supply. Another reason is poor adherence of patients to the prescribed drug regimen due to ignorance, poverty, or relief of symptoms after partial treatment. DOTS programme requires biweekly visits to a designated health facility. During each visit, the patient loses the day's wages and has to bear the additional cost of to and fro travel. Ignorance of patients is because some health personnel do not care to provide information about the disease and its treatment.

2. Use of wrong combinations – Non-adherence of doctors to current recommendations on treatment of tuberculosis is either due to ignorance or recalcitrance (HAIN, 2003).

The best way to prevent MDR-TB is to ensure that patients with drug-sensitive disease are given the correct drug regimens and that they continue treatment for the prescribed duration, till they are declared cured. When drug resistance occurs, the treatment has to be individualised. A combination of reserve second-line drugs (amikacin, capreomycin, ciprofloxacin, cycloserine, ethionamide, kanamycin, levafloxacin, ofloxacin, and prothionamide) is prescribed. Second-line drugs are expensive (therefore, not available in many developing countries) and cause serious side effects. They need to be taken for up to 2 years to prevent relapse. DOTS-PLUS is a pilot project for treating MDR-TB with second-line drugs (HAIN, 2003).

14.10 – ANTIRETROVIRAL THERAPY IN CO-INFECTION

14.10.1 – Drug Interactions

Drug interactions can result in ineffectiveness of ARV therapy or antitubercular drugs or increase risk of drug toxicity. Protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), used in ARV therapy, should be administered cautiously to patients with co-infection because rifampicin stimulates the activity of the hepatic microsomal enzyme cytochrome P450. This leads to decreased blood levels of PIs and NNRTIs. These drugs can also stimulate or inhibit the same enzyme system and cause altered blood levels of rifampicin. Isoniazid can interact with abacavir and cause peripheral neuropathy. NsRTIs (didanosine, zalcitabine, and stavudine) may also cause peripheral neuropathy (Harries *et al.*, 2004).

In patients with co-infection (particularly those with sputum positive pulmonary tuberculosis), the priority is to treat tuberculosis in order to stop transmission of the disease. With careful evaluation and management, patients with co-infection can be administered ARV therapy and antitubercular drugs at the same time. In a patient with risk of dying (low CD4 count and disseminated tuberculosis) it may be necessary to start ARV therapy and antitubercular drugs simultaneously. In HIV-infected patients with smear-positive tuberculosis, who are not at risk of dying, ARV therapy may be deferred until the completion of intensive phase of antitubercular treatment. This decreases the risk of immune reconstitution syndrome and prevents risk of interaction between antitubercular and ARV drugs (Harries *et al.*, 2004).

14.10.2 – Immune Reconstitution Syndrome

Patients with HIV-tuberculosis co-infection may develop temporary worsening of clinical or radiographic manifestations of tuberculosis, after initiation of antitubercular treatment. This paradoxical reaction is believed to be due to

immune reconstitution that occurs as a result of simultaneous administration of antitubercular and ARV drugs. Features include high fever, lymphadenopathy, expanding lesions of central nervous system, and worsening of findings on chest radiography. Such patients should be thoroughly investigated and tuberculosis treatment failure should be ruled out. Patients with severe paradoxical reactions may be given prednisolone in the dose of 1–2 mg per kg body weight for 1–2 weeks followed by gradually tapering doses. However, the efficacy of prednisolone is not clinically proven (Harries *et al.*, 2004).

14.11 – PREVENTION

Chemoprophylaxis: In various studies abroad, different drug regimens of varying duration have been tried for reducing the risk of developing active tuberculosis. The possible target groups include HIV seropositive individuals, household contacts of tuberculosis patients, and health care providers exposed to tuberculosis patients (WHO, 2004). It is difficult to recommend this strategy in the Indian situation. It is necessary to study the drug regimens, dosage, and duration of chemoprophylaxis, and their efficacy in reducing the risk of developing active tuberculosis. The *NACO Technical Resource Group on Chemoprophylaxis* has deferred antitubercular chemoprophylaxis till the availability of more scientific data in the Indian setting (NACO).

Immunoprophylaxis: BCG (*Bacille Calmette-Guérin*) vaccine was developed over a 13-year period from 1908 to 1921. The mother (original) vaccine was released in 1921. Currently, this is the only vaccine available for preventing tuberculosis. BCG is still used for routine immunisation of infants because it is thought to protect against life-threatening forms of childhood tuberculosis. It is not effective against adult forms of tuberculosis. More than 5 billion doses have been administered but tuberculosis continues to be rampant in most regions of the world. It is not effective against adult forms of tuberculosis. The disease cannot be controlled by BCG vaccine and a new vaccine needs to be developed (Bezbaruah, 2004). Prolonged use of BCG vaccine is one of the selective forces implicated in the spread of Beijing serotype of *M. tuberculosis* in East Asia (Van Soolingen *et al.*, 1995). If this hypothesis is proved, the use of live vaccines against tuberculosis may need reconsideration (Deivanayagam, 2003).

14.12 – RESEARCH

14.12.1 – New Antitubercular Drugs

A total of eight new drugs are undergoing trials worldwide. In India, the Tuberculosis Research Centre, Chennai is conducting clinical trials on ofloxacin, which can shorten the duration of treatment to 4 months. A combination of

gatifloxacin and moxifloxacin is also under trial. The GFATM has developed a new drug called PA-824, which appears to be effective against multidrug-resistant tuberculosis (MDR-TB). This drug acts like a "Trojan Horse" and "fools" the mycobacterium to come out of its dormant state. The drug then destroys the mycobacterial cell wall (Bezbaruah, 2004).

The Council of Scientific and Industrial Research (CSIR) coordinates New Millennium Indian Technology Leadership Initiative (NMITL). NMITL is a public-private sector partnership, which includes Lupin Laboratories, Central Drug Research Institute (Lucknow), Indian Institute of Chemical Technology (Hyderabad), National Chemical Laboratory (Pune), and University of Hyderabad. Currently, 33 research projects are underway, for developing drug delivery systems and bio-enhancers for tuberculosis treatment. In September 2004, NMITL announced the discovery of a new antitubercular drug named *sudoterb*. Pre-clinical studies show that the drug is relatively less toxic and is compatible with the currently used antitubercular drugs. A multi-drug regimen that includes sudoterb may bring down the treatment period from 6–12 months to just 2 months. Patent protection has been secured in India and the United States. The team has applied to the Drug Controller of India for permission to start clinical tests. Three phases of clinical trials may be conducted over a 4-year period after which, the drug can be marketed (Kashyap, 2004).

14.12.2 – New Vaccines

The WHO-funded GFATM has allocated US$2 billion, while Bill and Melinda Gates Foundation has pledged US$89 million for research on tuberculosis vaccine. In 2003, the pharmaceutical company AstraZeneca established a Tuberculosis Research Centre in Bangalore (WHO, 2004). In 2003, Central Drug Research Institute (Lucknow) reported the development of a new vaccine against tuberculosis, based on a related non-pathogenic mycobacterium. This vaccine is undergoing clinical trials (Bezbaruah, 2004).

A genetically modified BCG vaccine (containing new tuberculosis-specific genes) has been developed at Delhi University. Pre-clinical studies of this vaccine at Tuberculosis Research Centre (Chennai) have shown promising results. DNA vaccines (based on two genes found in *M. tuberculosis*) are under development at the Indian Institute of Science, Bangalore. The US Biotechnology Company Aeras has also developed two vaccines (Bezbaruah, 2004).

Invitrogen, also an American Biotechnology Company, has used DNA that codes for a *M. leprae* antigen to prepare a vaccine against tuberculosis. This new DNA vaccine produces an immunogenic peptide, which stimulates the T-cells of the host's immune system to produce gamma-interferon. This vaccine was found to be effective in killing the *Tubercle bacilli* in mice that were heavily infected with *M. tuberculosis*. Scientists believe that if this vaccine is used along with antitubercular drugs, it could produce faster cure in tuberculosis-afflicted patients (Nature, 1999).

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