TUBERCULOSIS AND HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION

According to WHO estimates by the end of the year 1995, up to 10 million of African people will have been infected with HIV (Chin, 1992). In Africa, HIV infection is transmitted predominantly through heterosexual intercourse and the highest seroprevalence rates are observed among young urban adults (*Lancet*, 1989). On the other hand, one third of the African population had been infected with tuberculosis (*Porter*, 1992). More than 1 million cases of active tuberculosis occur annually in Africa which, with 220 cases of tuberculosis out of 100,000 population, has the highest incidence of tuberculosis over the world (Sudre *et al.*, 1992).

Worldwide prevalence of tuberculosis infection, 1990

Region	Prevalence %	Number infected (Millions)	Percentage of total
Africa	33.8	171	9.9
Americas	25.9	117	6.8
Eastern Mediterranean	19.4	52	3.0
South-East Asia	34.3	426	24.7
Western Pacific	43.8	195	11.3
China	33.7	379	22.0
Europe and others	31.6	382	22.2
All regions	32.8	1,722	100

As HIV infection is more frequent among young urban adults in whom the prevalence of tuberculosis approaches nearly 50% (Allen *et al.*, 1992), it is easy to understand that the majority of individuals (77%) infected at the same time with HIV and tuberculosis are living in Africa (Raviglione *et al.*, 1992).

1. Epidemiological data

Early evidence of interaction between HIV infection and tuberculosis in developping countries was suggested by high rates of tuberculosis among AIDS patients originating from Haiti and Africa (Pitchenik *et al.*, 1984; Sonnet *et al.*, 1987) In addition, reports from Africa have shown high levels of HIV seroprevalence in tuberculous patients, with a range from 17 to 88% (Harries, 1990; Batungwanayo *et al.*, 1991).

Recent cohort studies carried out in USA and Africa (Braun *et al.*, 1991; Allen *et al.*, 1992) have shown an increased risk of tuberculosis in individuals dually infected with HIV and tuberculosis. This risk has been found to be 24 to 26 times higher in HIV-infected persons than in HIV-negative individuals. In HIV and/or AIDS patients, tuberculosis (TB) may result from reactivation of latent infection or from exogenous reinfection with rapid progression to disease. The epidemiological data are consistent with the recent resurgence of TB in many HIV-epidemic African countries. A definite increase of TB notified cases has been registered in some countries such as Burundi, Tanzania and Uganda (Standaert *et al.*, 1989; Styblo, 1990; Goodgame, 1990).

2. Clinical pattern

The clinical presentation of HIV-associated tuberculosis is similar to the disease experienced by non-HIV-infected patients. Common symptoms are weight loss, fever, cough, chest pain and dyspnoea, also encountered in many other HIV-related pulmonary diseases such as *Pneumocystis carinii* pneumonia or isolated pulmonary cryptococcosis (Batungwanayo *et al.*, 1994). Other conditions frequently diagnosed in HIV-positive patients with tuberculosis are: oral candidiasis, active or past herpes zoster, non-typhi salmonella bacteraemia and Kaposi's sarcoma (Batungwanayo *et al.*, 1992). These manifestations are uncommon in HIV seronegative patients and are clinical markers highly predictive for concurrent HIV infection.

The radiographic pattern of HIV-associated pulmonary tuberculosis depends on the degree of immuno-suppression. At the early stage of the infection, the chest film usually reveals a post-primary pattern with upper lobe infiltrates and cavities. In more advanced HIV-disease, the radiographic pattern is similar to that of primary tuberculosis with diffuse and miliary infiltrates, intra-thoracic adenopathies, middle or lower lobe infiltrates, pleural effusion (Pitchenik and Rubinson, 1985; Kamamfu *et al.*, 1990; Batungwanayo *et al.*, 1992).

Another striking clinical manifestation of tuberculosis in patients with HIV infection is the high frequency of extra-pulmonary involvement. Data from USA have reported an extra-pulmonary involvement in 25-75% of the patients with AIDS/HIV infection (Chaisson and Slutkin, 1989). In Africa, during the pre-AIDS era, only a small proportion (10-12%) of

TB cases involved extra-pulmonary sites (Kenya, 1984; Tanzania, 1985). This distribution has dramatically changed with the advent of the HIV epidemic. For instance, in a series of 334 HIV-associated TB cases from Kigali, Rwanda 56% had at least one extra-pulmonary site of involvement (Batungwanayo *et al.*, 1991). In another series from Malawi, 57% of HIV seropositive patients had extra-pulmonary tuberculosis compared with 20% of HIV seronegative patients (Kelly *et al.*, 1990). The most frequent forms of extra-pulmonary tuberculosis are peripheral and/or intrathoracic lymphadenitis and miliary forms (Barmes *et al.*, 1991).

However, reports from Africa have showed that pleural and pericardial tuberculosis are extremely frequent in HIV-infected patients with tuberculosis (Taelman *et al.*, 1990; Batungwanayo *et al.*, 1991). Tuberculous meningitis is however less frequent in Kigali, Rwanda (Taelman *et al.*, 1992).

3. Diagnosis of HIV-associated tuberculosis

In many developping countries, diagnosis of pulmonary TB relies on microscopic detection of acid fast bacilli on sputum smear specimens. Some authors (Klein *et al.*, 1989; Long *et al.*, 1991) have reported a decrease in sensitivity of sputum examination in HIV-seropositive patients with pulmonary TB.

Negative sputum smear examination usually requires the use of flexible fiber-optic bronchoscopy which allows bronchial aspiration, broncho-alveolar lavage and transbronchial biopsies. Microbiological and histological examination of these respiratory samples may provide diagnosis of pulmonary TB and therefore differentiate it from other clinically similar conditions such as *Pneumocystis carinii* pneumonia, primary pulmonary cryptococcosis, non-specific interstitial pneumonitis (Stoven *et al.*, 1984; Batungwanayo *et al.*, 1991).

Unfortunally, fiber-optic bronchoscopy is unavailable in most African settings. Furthermore, the diagnosis of extra-pulmonary tuberculosis depends also on available diagnostic procedures allowing examination of tissue and fluid samples. When these facilities are unavailable, physicians have to rely on clinical and radiological findings to establish a diagnosis of tuberculosis.

4. Prognosis

Mortality is high among the HIV/AIDS patients with tuberculosis. In post-mortem studies, TB was diagnosed in 31% of Zairean AIDS cases and in 42% of Ivorian cases dying in a chest Department (Nelson *et al.*, 1990; Abouya *et al.*, 1992). Cohort studies have also recorded a higher mortality among HIV-infected patients.

In Nairobi, Kenya, Nunn *et al.* (1992) have recently reported a mortality rate four times higher in the HIV-seropositive group at the end of a 6 months treatment.

Perriëns *et al.* in Zaire (1991) have reported after one year of follow-up, a mortality rate of 31.5% and 4.4% among respectively HIV-seropositive and HIV-seronegative patients with pulmonary TB. During the first month, mortality is likely to be related to advanced tuberculosis and occurs at the same rate among HIV-seropositive and negative patients with tuberculosis. Thereafter, deaths are due to other AIDS/HIV-associated diseases which in Africa are mainly non-AIDS-defining bacterial infections such as pneumococcal and non-typhi *Salmonella* bacteraemia (Taelman *et al.*, 1990).

5. Treatment

Patients with HIV-associated tuberculosis appear to respond well to anti-tuberculous treatment (Small *et al.*, 1991). Conversion of sputum culture to negativity occurs nearly 3 months after the start of the treatment.

Some cohort studies have stressed a high rate of relapses among HIV-positive patients treated with long regimens containing thiacetazone. This recurrence rate was found 34 times greater in HIV-1 positive patients than in HIV-1 negative patients (Hawken *et al.*, 1993). Factors associated with relapses were cutaneous thiacetazone-induced hypersensitivity and a smaller number of lung zones affected. A study from Zaire by Perriens *et al.* (1991) has found a recurrence rate of 18.1 per 100 persons per year of observation (PYO) in HIV-positive patients (where dual HIV and TB infection is highly prevalent) compared with 6.1 per 100 persons per year among HIV-negative patients.

By contrast, short-course rifampicin-containing regimens evaluated in Zaire (Mukadi *et al.*, 1991) appear to be more effective. One hundred fifty-eight HIV-seropositive patients and 192 HIV-negative patients with pulmonary tuberculosis were offered 2 months of treatment with rifampicin, isoniazide, pyrazinamide and ethambutol, followed by isoniazide-rifampicin twice weekly for 4 months. Relapse rates were 9% and 6% 6 months after the end of the treatment in HIV-positive and HIV-negative patients respectively. Such short-course chemotherapy should be recommended in geographical areas where HIV and

Mycobacterium tuberculosis infection are highly endemic, especially in Central Africa.

6. Implications for tuberculosis control programmes

It is now well established that HIV infection is the most potent factor favouring reactivation of latent tuberculosis infections. Nearly 80% of dually infected patients with HIV and tuberculosis are now living in Africa. These persons will experience a 5 to 10% annual incidence of tuberculosis (Selwyn *et al.*, 1989; Allen *et al.*, 1992). This will enormously increase the burden of TB cases on the already overwhelmed national tuberculosis programme. So far, preventive chemotherapy is not as yet an integral part of TB national control programmes in developing countries. The increased burden of TB cases may require preventive chemotherapy to lower the incidence of active tuberculosis among HIV-infected individuals. The efficacy of isoniazide in preventing TB in dually infected persons has been recently assessed in Haiti and Zambia: this drug was found to successfully decrease the incidence of TB and to delay the onset of other HIV-associated diseases (Wadhaven *et al.*, 1990; Pape *et al.*, 1993).

However, before implementing anti-TB preventive chemotherapy in Africa, further studies evaluating the cost-efficacy of various preventive anti-tuberculosis regimens are necessary.

J. Batungwanayo, H. Taelman and J. Clerinx

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