

may be associated with a high prevalence of AIDS, which was ten times higher than in the general population.

The Impact of the HIV/AIDS Pandemic on Tuberculosis

Infection by HIV is now by far the most important of the factors predisposing to the development of overt tuberculosis in those infected by the tubercle bacillus. For this reason, Chretien (1990) referred to the combination of these pathogens as 'The Cursed Duet'.

The HIV pandemic is having three major effects on the behaviour of tuberculosis. It markedly increases the chance of an infected person developing overt disease, it leads to a considerable reduction in the time interval between infection and the manifestation of such disease and it modifies the clinical features of the disease, notably in the more profoundly immunosuppressed. A fourth, indirect and delayed effect is the increased transmission of the infection in the general population as a result of the greater numbers of source cases (Lienhardt and Rodrigues, 1997).

As described above, people infected by the tubercle bacillus have about a 10% chance of developing overt tuberculosis at some period later in their lives. If infected when young, this risk is spread over several decades. If, on the other hand, the infected person is also HIV positive, the chance of developing active tuberculosis is increased to 50% over what is often a considerably shortened life span. The *annual* risk of developing active tuberculosis in HIV-positive persons is between 8 and 10%, which is over 40 times greater than the risk in HIV-negative persons (Dolin *et al.*, 1994; Antonucci *et al.*, 1995). Put another way, a co-infected person has roughly the same chance of developing tuberculosis in a single year as a person infected only by *M. tuberculosis* has in their entire lifetime.

HIV-related tuberculosis may be the result of either primary infection of a previously uninfected person, endogenous reactivation of latent disease or an exogenous reinfection. The proportion of these three

possibilities depends on the prevalence of infectious tuberculosis patients in a given community. In high prevalence regions where most at-risk people have been infected by the tubercle bacillus before they become HIV positive, the incidence of reactivation disease in such communities is relatively high. In regions where tuberculosis is an uncommon disease, and the risk of infection is therefore lower, it is more likely that tuberculosis will be due to primary infection occurring after HIV seroconversion (Leitch *et al.*, 1995). The precise effect of HIV positivity on the risk of developing overt tuberculosis after primary infection is not known but observations on mini-epidemics among HIV-positive persons strongly indicate that the risk is very high (Communicable Disease Report, 1995).

The considerable shortening of the interval between infection and the development of overt tuberculosis has been demonstrated by a number of examples, confirmed by DNA fingerprinting or other bacteriological examinations, of clusters of HIV positive people developing extensive disease within a few months of exposure in a hospital to patients with open tuberculosis (Bouvet *et al.*, 1993; Kent *et al.*, 1994).

The impact of the HIV/AIDS pandemic on tuberculosis has been devastating. In 1994, it was estimated that 5.4 million people were infected with both HIV and *M. tuberculosis*: the global distribution of this dually infected population is shown in Table 5. By 1996 the number had risen to over six million (World Health Organization, 1996). Given that approximately 8% of dually infected people develop overt tuberculosis each year, it may be calculated that HIV was responsible for over half a million *additional* cases of tuberculosis in 1996. The number of additional cases in 1997 may have been much higher, possibly well over one million; as in December of that year it was estimated that the total number of HIV-positive people worldwide was 30.6 million and could rise to 40 million by the year 2000 (UNAIDS/WHO, 1997).

Owing to the global distribution of HIV infection, Africa is the continent most affected by HIV-related tuberculosis. In 1995, it was estimated that about 8% of cases of tuberculosis worldwide, and at least 20% of those in Africa, were HIV related. By the year 2000, 14% of all

Table 5. Estimated distribution of HIV-infected adults alive in mid 1994 and those also infected with *M. tuberculosis*. Data from the World Health Organization.

Region	Total HIV positive	Dually infected
Sub-Saharan Africa	8,000,000	3,760,000
North Africa/Middle East	100,000	23,000
Western Europe	450,000	49,000
Eastern Europe/Central Asia	50,000	9,000
Latin America/Caribbean	1,500,000	450,000
North America	800,000	80,000
East Asia/Pacific	50,000	20,000
South/South-East Asia	> 2,500,000	> 1,150,000
Australia	> 20,000	> 4,000
Total	c.13,500,000	c.5,600,000

cases of tuberculosis could be HIV related, accounting for 1.4 million cases worldwide and 600,000 cases in Africa alone (Dolin *et al.*, 1994).

In 1996, about 70% of all co-infected persons lived in sub-Saharan Africa and, as a result, many countries in that region are experiencing considerable increases in the prevalence of tuberculosis. The estimated one million cases in the region in 1990 is expected to double by the year 2000, and in ten studied countries there was a close relationship between the number of excess cases, based on pre-1985 trends, and the percentage of patients who were HIV positive (Cantwell and Binkin, 1997). In Tanzania, for example, patients with tuberculosis are between 5.4 and 7.1 times more likely to be HIV positive than the general population (Chum *et al.*, 1996). An association between tuberculosis and HIV positivity is also seen in children in Africa (Chintu and Zumla, 1997). In Lusaka, Zambia, 37% of children admitted to hospital with tuberculosis in 1990 were HIV positive, compared to 11% of those with other conditions. This increased to 56% in 1991 and 68.9% by 1992 (Luo *et al.*, 1994).

Although the burden of co-infection currently falls principally on Africa, the situation in Asia is very worrying as this is a region where

two-thirds of all the people infected by *M. tuberculosis* live and where HIV infection is spreading more rapidly than anywhere else in the world. In South India, the incidence of HIV seropositivity in patients with pulmonary tuberculosis rose from 0.77% in 1991 to 3.4% in 1993 (Solomon *et al.*, 1995).

The future epidemiological behaviour of HIV-related tuberculosis will depend on the annual infection rate, particularly in the age group principally at risk from HIV, and the prevalence of HIV infection. Future trends in Africa have been predicted for four different scenarios (Schulzer *et al.*, 1992), as summarised in Table 6. In the worst-case scenario, which is certainly within the bounds of possibility, tuberculosis would affect up to one in 50 of the general population and one in 25 of the population particularly at risk annually.

Table 6. Estimated incidence rates (per 100,000) of tuberculosis in sub-Saharan Africa in the year 2000. Data from Schulzer *et al.* (1992).

Scenario:*	Smear-positive cases				Total cases			
	1	2	3	4	1	2	3	4
15–49 years	142	272	681	1,769	300	573	1,540	4,218
Percentage increase since 1980	59.5	52	280	888	67.5	60	330	1,078
Adjusted for total population	77	150	325	792	162	312	727	1,875
Percentage increase since 1980	40	36	195	620	47	42	230	752

*Scenario 1: 1% risk of tuberculosis infection in 1980, 45% tuberculosis infection prevalence and a 1989 HIV prevalence of 2%.

Scenario 2: 2%, 60%, 2%

Scenario 3: 2%, 60%, 10%

Scenario 4: 2%, 60%, 20%

The nature, presentation and clinical course of tuberculosis in HIV-positive patients differs from that in non-immunosuppressed patients (Festenstien and Grange, 1991). Although the disease in HIV-positive patients with relatively high CD4+ T cell counts may not differ substantially from that occurring in HIV-negative patients, atypical forms are frequently encountered in the more profoundly immunosuppressed.

In particular, the pulmonary cavitation characteristic of post-primary tuberculosis is unusual in those with CD4+ counts of less than 50/mm³. Instead, radiology often reveals rather nondescript spreading opacities (Daley, 1995). Disseminated disease is common and may manifest as asymmetrical lymphadenopathy or multi-organ involvement. The sputum of patients with HIV-related tuberculosis who do not show cavity formation is often negative on microscopy although the relationship between sputum negativity and non-infectiousness in HIV-positive patients may not be as straightforward as in those who are HIV negative. For practical purposes, it appears that the infectivity of the two groups of patients is similar (Nunn *et al.*, 1994). Assumptions of infectivity, or the lack of it, based on microscopy could have very serious consequences for other patients and health care workers, particularly in regions where many HIV-positive patients have multidrug-resistant tuberculosis.

Although tuberculosis in HIV positive patients responds bacteriologically to standard short course chemotherapy, provided that the bacilli are susceptible to the drugs, there is a high mortality rate both during and after treatment. Such patients are four times more likely to die than HIV-negative patients within a year of diagnosis, with many deaths occurring early during the course of chemotherapy. Although the details are far from clear, tuberculosis appears to accelerate the progression of HIV infection to the full picture of AIDS. Indeed, tuberculosis in any form is now an AIDS-defining condition in HIV-positive persons (Centers for Disease Control, 1993). This acceleration has been attributed to various forms of immunological synergy and it has been shown that the viral load, determined by detection of RNA copies of the HIV genome, may increase 160-fold when overt tuberculosis develops (Goletti *et al.*, 1996). The consequent foreshortening of life, despite adequate anti-tuberculosis chemotherapy, is a serious cause for concern and emphasises the need for more intensive research into ways of preventing the development of overt tuberculosis in co-infected persons.