REVIEW ARTICLE

Tuberculosis and AIDS

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Summary. Since the mid-1980s, the rate of decline in reported cases of tuberculosis (TB) has reached a plateau or reversed because of a combination of poverty and increased homelessness, immigration and displacement, poorly managed and supplied TB control programmes and, particularly in the developing world, the emergence of human immunodeficiency virus (HIV) infection. TB in HIV-positive patients may present atypically, both clinically and radiologically, with a lower probability of sputum positivity, greater difficulty in diagnosis, and a more rapid clinical deterioration than TB in HIV-seronegative patients. The emergence of multiple-drug-resistant strains of *Mycobacterium tuberculosis*, particularly in patients infected by HIV, carries a high mortality and has been associated with outbreaks in Europe and the USA. Microscopy and culture form the basis of diagnosis, but there is a need for more rapid diagnostic techniques and novel methods of drug susceptibility testing. Prolonged supervised treatment programmes and the development of new chemotherapeutic agents and regimens are essential prerequisites for successful TB therapy in AIDS patients. This review examines the clinical, microbiological and epidemiological issues associated with TB in HIV-infected individuals.

Introduction

Tuberculosis (TB) remains numerically the most significant single infectious cause of morbidity and mortality, infecting 8 million and killing 3 million people annually,^{1,2} and causing approximately one-quarter of all avoidable adult deaths from infection.³ The steady decline in cases of clinical TB seen in the developed, and parts of the developing world, ceased or reversed in the mid-1980s. In the USA, there was an increase of 18.4% in reported cases of TB between 1985 and 1991,⁴ corresponding to an excess of 28 000 cases over the number expected between 1985 and 1990 (increasing to over 60 000 cases by 1993) had the decline continued.⁵ Untreated, the mortality rate of clinical disease is 40–60%,⁶ a tragedy in view of the proven efficacy of chemotherapeutic regimens.^{7–8}

There are several possible explanations, or combinations of explanations, for the increase in cases of active TB worldwide. These vary in importance depending on the particular geographic location, but include: (a) co-infection with the human immunodeficiency virus (HIV), the single most important risk factor for progression from dormancy to clinical

disease; (b) failure to give priority to national TB control programmes, or poorly organised programmes with poor case finding, treatment rates and compliance; (c) reduction or withdrawal of donor agency support to international TB control programmes in the developing world; (d) increasing numbers of homeless people sheltering in crowded conditions, as well as overcrowding in institutions such as prisons; (e) intravenous drug abuse; (f) health immunocompromised by extremes of age, alcoholism, diabetes mellitus, renal failure, and infection with other acute immunosuppressive illnesses such as measles and malaria; (g) drug therapy, especially steroids used for the treatment of asthma, rheumatological and connective tissue disorders and transplant rejection; and (h) increasing immigration. This review considers recent advances in our understanding of clinical, microbiological and epidemiological issues associated with TB in HIV-infected individuals, including diagnosis, treatment and the potential risks of TB in immunosuppressed health care workers (HCWs).

Tuberculosis and HIV co-infection

The Global Programme on AIDS estimated that 16 million adults and 1 million children were infected

with HIV by mid-1994, with nearly 90 % of infections occurring in the developing world.^{1,9,10} The interaction between TB and HIV infection was investigated initially because of the high incidence of TB and HIV co-infection in sub-Saharan Africa and other parts of the developing world, which together account for 95 % of new TB cases and 98 % of TB deaths.^{1,5,9} In sub-Saharan Africa, the annual risk of becoming infected with *Mycobacterium tuberculosis* (MTB) is *c.* 2 %, with 1.3 million new cases annually—an incidence of 229/100 000—and an estimated total of 171 million infected individuals.^{2,5,11–13} Up to 50 % of the sub-Saharan population between 20 and 40 years old have been infected with MTB.^{12,14} Furthermore, it is estimated that 5.6 million people were infected with TB and HIV by mid-1994, with 3.8 million living in sub-Saharan Africa.¹ In HIV-seropositive individuals, annual incidences of active TB of 4.4 % and 3.6 % have been reported in Zambia and Zaire.¹⁵ In Zambia, up to 40 % of AIDS patients have TB,¹⁶ and in a recent study almost 70 % of new TB patients were HIV-positive.¹⁷ The prevalence of HIV infection in adults with TB in Abidjan, for example, increased from 25 % to 45 % over just 2 years.¹⁸ Overall, over one-half of AIDS patients in Africa, and approximately one-quarter of patients in Brazil, Mexico and Haiti, have clinical TB.¹

Co-infection with HIV and TB in children is now a significant health problem. In a recent study in Zambian children, the seroprevalence of HIV-1 in 237 hospitalised children between the ages of 1 month and 14 years with a clinical diagnosis of TB—but not a bacteriologically proven one—was 37 % compared to 10.7 % in a control group of 242 children without TB.¹⁹ Rates of TB among children in the developed world are much lower, except in some urban deprived areas—e.g., the incidence of tuberculosis in New York City rose 300 % between 1987 and 1991, particularly in those aged 0–4 years. Although HIV positivity remains the most important risk factor for clinical TB, a recent study of children in the Bronx, New York, reiterated the role of household overcrowding and poverty in transmission independently of HIV infection.²⁰

There is less overlap between TB and HIV in the developed world at the present time. In the USA, only *c.* 5 % of AIDS patients are also on the TB register,²¹ although recent changes in the Centers for Disease Control (CDC) case definition—which now includes pulmonary TB as an AIDS-defining illness—is likely to increase this percentage. However, a seroprevalence survey during 1991 in TB clinics in 20 USA cities indicated that 10.4 % (range 0–61 %) of TB patients were HIV-positive, with the highest percentage association in New York City.²¹ Matching the AIDS and TB registers in San Francisco indicated that 12 % of native-born Americans with TB also had AIDS.²²

In Western Europe, reported cases of TB fell by 5.4 % per annum from 1974 to 1991, with an annual death rate of 1–2/100 000 population at the end of the 1980s, principally in those aged > 65 years.²³ It is

difficult to assess accurately the current European situation as different criteria are used by states in formulating TB registers. Thus Switzerland changed its case definition in 1987, while Spain, until recently, recorded only cases of pulmonary TB, and Italy produced no official epidemiological data between 1978 and 1988.²³ Nevertheless, although TB notifications have continued to decline in Belgium, France, Germany, Finland and Spain since the mid-1980s, they have levelled off in the UK and Sweden, and have increased in Austria, Denmark, Ireland, Italy, The Netherlands, Norway and Switzerland.²³ Several European studies have examined the overlap between TB and HIV infection. In Paris and the surrounding region, 12–18 % of TB patients were HIV-positive, compared with 1 % in other parts of France.^{23,24} One Italian study demonstrated that 11.4 % of AIDS patients had TB,^{23,25} and two Spanish studies reported TB incidences of 37 % and 36 % in HIV-positive patients in Barcelona and San Sebastian, respectively.²³ In the UK, TB notifications fell from 12 496 to 5732 between 1974 and 1987, a decline of up to 10 % per annum,^{26,27} but rose to 6028 cases per annum in 1991. In the UK, only 4–5 % of TB cases occur in HIV-positive patients.²³ Similar or lower incidences have been reported in Norway, Sweden and The Netherlands.²³

Mortality is high in the developing world for those patients with dual infection. In one ward of a West African hospital, 40 % of deaths in HIV-positive adults were caused by TB, compared with 4 % in HIV-negative adults.^{18,28} In 1990, 4.6 % of all TB deaths were associated with HIV co-infection,¹⁰ and it is estimated that this will increase to *c.* 14 % by the year 2000.^{1,10} However, concurrent opportunist infections such as pneumococcal pneumonia and gram-negative septicaemia are responsible for much of the increased mortality.²⁹

Clinical TB disease in AIDS patients

In general, TB occurs at an early stage in HIV infection when the CD4 lymphocyte count can be in the normal range or only slightly below it, in contrast to infection with *M. avium-intracellulare* which is associated with very low CD4 counts, typically < 75 mm³. The diagnosis of TB depends on clinical symptoms and signs, tuberculin testing, radiology, and the microscopic examination and culture of sputum, bronchoscopic samples, cerebrospinal fluid, urine or tissue. Sputum-positive pulmonary disease is the most common presentation in HIV-seronegative patients, but in HIV-infected individuals, focal and disseminated extrapulmonary disease is more common.¹⁸ In immunosuppressed patients, clinical disease may present with atypical clinical and radiological features, including fewer lung cavities and a lower probability of sputum positivity. Anergy may negate the diagnostic value of tuberculin testing. However, MTB is

more likely to be isolated from blood cultures, which may aid diagnosis.³⁰

A recent study in Zambia compared the clinical features of 182 dually-infected patients and 67 HIV-seronegative patients with TB. Among HIV-negative patients, 72% had pulmonary disease alone, 16% extrapulmonary disease, and 12% both, whereas among HIV-positive patients, the equivalent figures were 40%, 34% and 26% respectively.³¹ Only 35% of HIV-positive cases were sputum-positive, compared with 55% of HIV-seronegative cases. In those patients presenting with pulmonary disease alone, 57% of HIV-positive cases were sputum-positive, compared with 76% of HIV-negative patients. The tuberculin test was positive in only 27% of HIV-positive cases, compared with 55% of HIV-negative cases. Rates of diagnosis from culture were similar.³¹

Patients infected with both MTB and HIV are more likely to progress rapidly to clinical TB,³² with an annual risk of 8% compared to a lifetime risk of 10% for HIV-seronegative subjects;²¹ this is probably caused by an immunological potentiation of HIV and MTB in co-infection (see below).

Reactivation or re-infection

TB results primarily from reactivation of endogenous infection, usually many years after primary infection. In a study of 520 i.v. drug abusers in New York City, 23% of HIV-positive subjects and 20% of HIV-negative subjects had an initial positive tuberculin response (PPD+ve), i.e., previous exposure to MTB. The seroconversion rates to tuberculin positivity over the 22-month follow-up period were similar in both sub-groups at 11% and 13%, i.e., the risk of infection with MTB was the same. Clinical tuberculosis developed in eight (4%) of the HIV-positive patients, but in none of the seronegative group; seven of these eight patients were initially PPD+ve, indicating that the risk of developing clinical disease was increased and was a result of reactivation of latent tuberculosis in the HIV-positive group.³³ In the developing world, TB precedes HIV infection, and re-infection occurs against a high background of endemic disease. Whether this is caused by reactivation or recent infection is difficult to demonstrate because of the endemic nature of the infection and the prolonged temporal relationship between infection and clinical disease. Application of molecular techniques such as DNA fingerprinting and PCR should aid our understanding of the epidemiology of TB in these areas.³⁴⁻⁴⁴ In a Hong Kong study, fingerprints of isolates from five (12%) of 42 patients who relapsed following treatment differed from pre-treatment isolates, suggesting that re-infection had occurred.³⁷ Two recent reports of DNA fingerprinting of isolates in New York City and in San Francisco showed that recent infection may account for 30-40% of clinical cases.^{35,36} A single individual in San Francisco may

have been responsible for up to 6% of the clinical cases identified in the study.³⁶ Similar techniques have been used successfully in conjunction with classical epidemiological investigations to demonstrate nosocomial transmission of multi-drug-resistant (MDR) strains of MTB—i.e., isolates which are resistant to at least two first-line chemotherapeutic agents—in outbreaks in the developed world.⁴⁵⁻⁵¹ Recent analysis of DNA fingerprinting patterns of MDR-MTB strains from 17 patients in New York City with repeatedly positive cultures has demonstrated that treatment failure caused by drug resistance can occur through superinfection with a MDR-MTB strain.⁴⁸

Therapy and resistance

HIV patients infected with TB respond well, both bacteriologically and clinically, to conventional drug regimens, although serious side-effects in patients on standard regimens are more common.^{17, 22, 29, 52-55} In HIV-positive patients infected with susceptible isolates, treatment should be with four drugs for 2 months, followed by isoniazid and rifampicin for a further 7 months. If drug susceptibility results are not available, then all four drugs should be continued for 9 months.⁵⁶ If there is a previous history of treatment for TB, or if MDR-MTB is likely, then treatment should be with five or six drugs for 18-24 months.⁵⁶ In spite of effective chemotherapy for TB, the mortality rate of Africans infected with HIV and TB is high, mainly because of the higher incidence of acute non-tuberculous infections such as pneumococcal or salmonella septicaemia seen in HIV-positive patients.⁵⁴ With adequate treatment and compliance, the response to treatment of pulmonary TB in HIV-positive and HIV-negative patients is similar, but HIV-positive patients are more likely to become culture-negative in the first month of treatment, mainly because of the lower mean pre-treatment viable counts of MTB in sputum specimens noted in HIV-positive patients.^{54, 57}

The rate of recurrence of TB is increased in HIV patients in the developing world where thiacetazone-based regimens are still employed. Thus, for example, in one prospective study in Kenya, the recurrence rate of TB in HIV-infected patients was 34-fold greater than in HIV-negative patients treated with thiacetazone-containing regimens.⁵⁸ In addition, serious cutaneous hypersensitivity reactions, including Stevens-Johnson syndrome, are particularly common with thiacetazone-based regimens in HIV patients.⁵⁸ In one recent study in Zambia, 22 (9%) of 237 children developed cutaneous hypersensitivity reactions whilst on a regimen that included thiacetazone; 12 of the 22 children who developed Stevens-Johnson syndrome were HIV-positive.¹⁹

Strains of MDR-MTB have emerged in several countries, with an overall mortality rate of 40-60% in HIV-seronegative patients which is equivalent to that

of untreated tuberculosis. In immunosuppressed HIV-positive patients, the mortality rate is $> 80\%$.^{45, 46, 49, 50, 51, 56, 57} In the USA, in the first quarter of 1991, 13% of new cases reported to the CDC were resistant to at least one anti-TB drug, and 3.2% were resistant to both isoniazid and rifampicin.²¹ Poor compliance and follow-up are the most significant factors in the development of secondary resistance. Mahmoudi and Iseman⁵⁹ reviewed the records of 35 patients with acquired MDR-MTB to ascertain whether clinical management decisions were associated with the acquisition of drug resistance. Errors were found in the management of 28 cases, of which the most common included the addition of a single drug to a failing regimen, failure to identify primary drug resistance, inappropriate isoniazid preventive therapy, and an inadequate primary drug regimen.

The increasing frequency of strains resistant to isoniazid and rifampicin has resulted in treatment failures; in one study in Denver, Colorado, treatment failed in 35% of 171 patients with MDR-MTB despite the use of individually tailored regimens with multiple agents.⁶⁰ The treatment of TB caused by MDR-MTB strains results in prolonged hospitalisation, the use of more toxic second-line therapies, and increased costs estimated at \$180 000 per patient in one American study.⁵⁹ There is no evidence that drug resistance is more common in TB in either HIV-positive or HIV-negative patients.^{61, 62}

Investigation of 16628 isolates submitted to the Public Health Laboratory Service Mycobacterial Reference Unit (MRU) and Regional Tuberculosis Centres (RTCs) in England and Wales between 1982 and 1992 demonstrated that 1833 (11%) were resistant to one or more first-line anti-TB drugs. Isoniazid resistance was found in 6.1% of these strains, with isoniazid and rifampicin resistance in 0.6% of isolates.⁶³ The actual number of MDR-MTB strains referred to the MRU and the RTC at Dulwich Public Health Laboratory, London, over the past decade has remained at about 80–90 per annum, with *c.* 80% resistant to isoniazid or streptomycin. Most strains were from migrants, principally from the Indian sub-continent.²⁶ Unlike recent outbreaks in the USA, there was no association with HIV infection, and there have been no outbreaks involving MDR-MTB strains.⁶⁴

Secondary resistance associated with poor compliance is more common in the groups that are likely to develop clinical disease. In one study in New York, 64% of patients were homeless, and 89% of these failed to complete therapy or were lost to follow-up, or both. In the following year, 27% of these patients were re-admitted with clinical tuberculosis.⁵

Infection with MDR-MTB increases morbidity and mortality significantly, especially in HIV-infected patients. Eight outbreaks caused by MDR-MTB were investigated by the CDC between 1990 and 1992, involving over 300 patients of whom 80% were HIV-positive.^{45, 46, 50, 51, 57, 60} MDR-MTB strains infecting

HIV-positive patients produced a significant drop in the median survival period, from 14.8 months for susceptible isolates of MTB to 2.1 months in one series.⁵¹ Transmission of MDR-MTB to HCWs, family members and prison warders has produced fatalities.^{46, 65–67} In most cases the deaths occurred in HIV-positive individuals, raising the issue of safety for HIV-positive HCWs who care for AIDS patients with TB. However, TB in patients infected with HIV-1 is no more infectious than TB in the immuno-competent.⁶⁸

In the USA, concern over the risks posed to HCWs by MDR-MTB strains led to the promulgation of sweeping guidelines by the CDC in 1990 and 1993.^{69, 70} The guidelines included simple individual measures, such as patients covering their mouths when coughing, but included more controversially a series of environmental measures, such as negative pressure isolation rooms with six changes of air each hour and ultraviolet germicidal lamps. Many of the guidelines have been criticised on the grounds of cost, negligible contribution to overall safety, or both. Recommendations for the use of high efficiency particulate (HEPA) respirators for personnel attending infectious patients have come under particular criticism as expensive and unproven. For example, one study estimated that the use of these respirators would cost \$7 million per case of TB prevented and \$100 million per life saved, and a second concluded that it would cost between \$1.3 and \$18.5 million to prevent one case at the hospital studied.^{71, 72} Comparable guidelines have been promulgated in the UK, and also by the International Union Against Tuberculosis and Lung Disease and the World Health Organization.^{73, 74} In general, these guidelines argue for the sensible application of less draconian infection control measures, including room isolation and adequate ventilation to the outside environment, BCG vaccination, pre-employment screening and vigorous contact tracing.⁷³ Preventative therapy for TB has also been recommended for HIV-positive patients who yield a positive tuberculin test in the absence of active tuberculosis, with a daily isoniazid dose of 5 mg/kg, up to a maximum of 300 mg, for 6–12 months.⁷⁵ Isoniazid may be given twice weekly at a dose of 15 mg/kg, although there are no clinical studies demonstrating the efficacy of intermittent preventative therapy.⁷⁵ All cases of tuberculosis in HCWs in the USA have been reviewed extensively.⁷⁶

Significant advances have been made in our understanding of the mechanisms of drug resistance and drug therapy^{44, 77–84} which, coupled with the development of rapid methods for determining drug resistance, will be of particular benefit to HIV patients infected with MTB.

Immunology of TB and HIV co-infection

The immunology and pathogenesis of TB is under intensive study,^{82, 85–87} but is outside the scope of this

review. However, the rapid progression of TB in HIV-positive patients does provide some insights into the underlying immunological mechanisms influencing the progression of clinical disease, particularly the importance of the reduction in CD4+ T-lymphocyte number and function (which also occurs to a lesser degree in TB without concurrent HIV infection). CD4+ cells have an important role in inducing cytotoxicity, leading to lysis of infected monocytes^{20, 85-90} and to the panoply of cytokines released, such as TNF- α , IFN- γ , IL1, IL6 and IL10. Two subsets of T-helper CD4+ lymphocytes, TH1 and TH2, co-ordinate the overall response and inhibit the presence of the other subset. TH1 cells secrete γ -IFN and other cytokines responsible for macrophage activation in response to mycobacterial antigens, whilst TH2 cells produce IL4, 5 and 10 which stimulate B cells and antibody production. As HIV disease progresses, the number of TH1 cells declines, correlating with a reduction in macrophage activity against mycobacterial antigens, the loss of Langhans giant cells, epithelioid macrophages and granuloma formation, and a shift from a paucibacillary to a multibacillary state.^{20, 85-92} Caseating necrosis is replaced by a suppurative and coagulative necrosis.^{18, 86}

Conversely, HIV replication may be enhanced by the multiplication of MTB in monocytes or macrophages through the up-regulation of transcription, or the increased release of TNF- α and β -2 microglobulin.⁹³⁻⁹⁶ The levels of HIV-1 p24 antigen in culture supernates of monocytes taken from patients with active pulmonary TB who were infected subsequently with HIV-1 were significantly higher than for culture supernates of monocytes from non-tuberculous individuals.⁹³ Enhanced susceptibility to HIV infection or reproduction may be a direct result of monocyte activation by exposure to MTB. Interestingly, studies have now demonstrated that

isoniazid prophylaxis given to HIV-positive individuals also infected with MTB, but not exhibiting active disease, may delay the progression of HIV disease.^{97, 98} Isoniazid prophylaxis given to asymptomatic HIV-positive adults in a placebo-controlled trial for 12 months, with a 3-6 year follow-up, reduced the risk of developing TB by 83% in PPD-positive individuals and by 71% in the group overall.⁹⁷

Conclusion

HIV infection is a contributing factor to the deteriorating TB situation in the developing world and amongst at-risk groups in some European and American cities, creating a new challenge to those charged with TB control. In the developing world, the control, treatment and prophylaxis of TB may offer the greatest chance of prolonging the lives of those with AIDS, in the same way that treatment and chemoprophylaxis of *Pneumocystis carinii*, toxoplasmosis and other opportunist infections have prolonged the lifespan of those with AIDS in the developed world. Thus a recent computer model⁹⁹ predicted that in communities where 20% of the population was infected with HIV and 25% of those with TB were receiving treatment, TB-related deaths would be 100% higher than in communities where no-one was infected with HIV. In a country with a population the size of Uganda's, this would lead to an extra 530 000 deaths over a decade. If 50% of patients with active TB received treatment, one death would be averted for every 2.5 people receiving treatment.⁹⁹ The transmission cycle would also be interrupted.

A high index of suspicion of TB in all patients, combined with accurate and early diagnosis by conventional and molecular techniques, and prompt and aggressive chemotherapy with multiple agents will help to avert or ameliorate an impending international disaster.

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