

Childhood tuberculosis and infection with the human immunodeficiency virus

ABSTRACT—TB in HIV-infected individuals is a major cause of morbidity and mortality in developing countries and poses enormous problems to the health services. Despite the availability of curative therapy, the incidence of TB in children and adults is increasing at an alarming rate and poses a grave threat to TB control programmes in developing countries. Prospective studies to define basic clinical, microbiological and epidemiological features of the resurgence of childhood TB in the light of the HIV epidemic are required.

Assessing the size of the problem

The close relationship between the human immunodeficiency virus (HIV) infection and tuberculosis (TB) is now widely appreciated [1–3] and both have been declared global emergencies by the World Health Organisation (WHO).

In January 1992, the WHO estimated that between nine and 11 million adults and one million children, mostly in developing countries, had been infected with HIV and approximately four million of them were infected with both HIV and TB, most of those (3.12 million) in sub-Saharan Africa [1]. Data from sub-Saharan Africa show that a serious TB epidemic linked to HIV infection is also currently in progress in children [4–7]. From a global perspective, data on the importance of tuberculosis in HIV-infected children are scanty.

Unlike AIDS in the USA and Europe, over 80% of HIV infections in Africa are attributable to heterosexual transmission, while mother to child transmission and 'other risk factors' account for the remaining 20% [1]. With women in Africa acquiring HIV as often as men, the number of children affected by HIV disease has increased dramatically. HIV-seropositivity rates in pregnant women are between 20–30% in some Central African countries and significant numbers transmit the infection to their children [8]. Newborns are particularly vulnerable to TB if the mother has active disease. In a cohort of infants born to HIV-infected mothers in Lusaka, followed up for three years, 12% of children developed TB [7]. In infants who were HIV-seropositive, TB manifested clinically in

more than 25% of cases within the first two years of life. A study from Kinshasa, Zaire, showed that TB occurred in 28% of 60 HIV-seropositive infants in the first year of life [5]. In a three-year follow up study of 16 HIV-seropositive children aged between five and 12 years in Kigali, Rwanda, TB was diagnosed in four [9], while a study from the Central African Republic in 1988 reported that four out of 37 children with TB were HIV-seropositive [4]. In Zambian children the risk of TB was nearly six times greater in HIV-seropositive children than in HIV-seronegative ones. HIV seroprevalence rates in children with TB presenting to the University Teaching Hospital in Lusaka, Zambia have risen at an alarming rate from 24% in 1989 to 68.9% in 1992 [10–13]. All paediatric age groups are affected by dual infection with TB and HIV.

Diagnosis of paediatric tuberculosis

The diagnosis of TB in children remains difficult even in the best centres [14], particularly in infants and small children in whom the disease is often non-specific and sputum induction or gastric lavage is difficult. Several diagnostic criteria have been devised by paediatricians, and combinations of symptoms and signs with diagnostic scoring appear to be useful [14–18]. The lack of a definitive diagnostic tool for paediatric tuberculosis is a limiting factor for ascertaining the actual size of the TB problem in children. Current techniques for the diagnosis of TB are resource intensive, slow and not sufficiently sensitive or specific [16]. More rapid, reliable, sensitive and specific diagnostic tests and better clinical criteria for the diagnosis of TB remain a high research priority.

Clinical presentation of TB in HIV-infected children

TB in HIV-seropositive adults presents a clinical picture which differs from that in HIV-seronegative patients [17–25]. They often do not produce any sputum, and when they do, mycobacteria are often absent from sputum smears on microscopy; sputum cultures are mostly negative; the chest x-ray appearances are atypical and extrapulmonary manifestations are more common. In a ten year retrospective study of 345 HIV-seropositive children in Miami, Florida [25], nine were found to have TB which presented predominantly with extrapulmonary features. In Zambian children the predominant clinical presentation of TB in both HIV-seropositive and HIV-seronegative cases was as pulmonary TB (including miliary TB) and as lymphadenopathy (Table 1). Pericardial effusion,

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Table 1. Clinical features of 237 children with tuberculosis in Lusaka, Zambia*

Clinical presentation	Number	HIV + ve		HIV -ve
		Number	(% of total)	
Pneumonia	204	78	(32.9)	126
Miliary (disseminated)	9	3	(1.3)	6
Pleural effusion	5	0	(0)	5
Lymphadenitis	11	3	(1.3)	8
Pericardial effusion	4	2	(0.8)	2
Abdominal	2	0	(0)	2
Bone	1	1	(0.4)	0
Meningitis	1	1	(0.4)	0
Total	237	88	(37)	149

*Adapted from Chintu *et al* [10].

meningitis, ascites and bone involvement were less common [10].

In adults, TB is the most common cause of pleural effusions and is strongly associated with HIV-1 infection [26]. In contrast to this, pleural effusions are not an important feature of TB in HIV-infected Zambian children [10,11].

Patient compliance and follow-up

Patients' non-compliance with anti-TB treatment and non-attendance at follow-up clinics are responsible in part for the breakdown of TB control programmes and the emergence of drug resistance. Prolonged compliance is difficult to achieve even in the more organised health systems in the USA and Europe [15,27]. In a study of Zambian children with TB, Luo *et al* [11] recorded that over 50% of children were lost to follow-up within three months of starting treatment. Compliance is further hindered by the effects of HIV on the health of children's parents and also by the growing problem of the disintegration of the extended family support system caused by the HIV pandemic. An active search for clinic non-attenders to minimise loss to follow-up should be carried out and operational research is needed to identify the reasons for non-attendance and find solutions for them.

Anti-TB treatment

There is no agreement yet on the optimal treatment for TB in children infected with HIV. Data on the efficacy of treatment regimens for such children are only just emerging. Current opinion is that HIV-seropositive children with drug-susceptible pulmonary TB should receive the same regimen as HIV-infected adults with TB: two months of isoniazid, rifampicin and pyrazinamide, followed by isoniazid and

rifampicin for a further four months [28]. In areas of high endemicity, treatment should be continued for not less than nine months, and for at least six months after culture conversion as evidenced by three negative sputum cultures, or after a clinical response has been noted.

In general, children tend to tolerate anti-TB therapy better than adults. Although most clinical trials of TB chemotherapy have so far been carried out in adults, information on short course chemotherapy in children is accumulating. In the treatment of pulmonary TB and TB lymphadenitis the use of triple drug regimens for six months (isoniazid, rifampicin, plus pyrazinamide or streptomycin for the first two months and rifampicin and isoniazid for the remaining four months) is thought to be just as effective as a nine to 12 months regimen [15,27-29]. While initial response to therapy in both HIV-seropositive and HIV-seronegative children appears encouraging, long-term follow-up studies in developing countries show that HIV-seropositive children with TB have a higher mortality rate [10,12]. Possible reasons are an inadequate immune response, drug resistance, or other concomitant HIV-associated complications such as diarrhoea, malnutrition and failure to thrive. Corticosteroids (prednisolone or dexamethasone) appear useful adjuncts to anti-TB chemotherapy [15,29,30], particularly when the host inflammatory reaction contributes significantly to tissue damage as in TB meningitis, miliary TB, large pleural effusions and massive pericardial effusions. No data are available on the value of continuing lifelong therapy with isoniazid after nine months of anti-TB therapy. There are no controlled clinical trials to assess whether chemoprophylaxis with anti-TB drugs can prevent drug susceptible TB infection in HIV-seropositive children without TB.

Adverse reactions to anti-TB treatment

In Africa, cutaneous hypersensitivity reactions attributed to thioacetazone during anti-tuberculous therapy of adults infected with the human immunodeficiency virus type-1 have been well documented [31]. Nearly 10% of children in Zambia with a clinical diagnosis of tuberculosis developed hypersensitivity skin reactions within two to four weeks of the course of therapy [7]; they were more frequent amongst HIV-seropositive (19.3%) than HIV-seronegative (2.0%) children; nearly one half of the children with these skin reactions developed the Stevens-Johnson syndrome (SJS); all of them were HIV-seropositive. The mortality amongst the children who developed the SJS was 91% (11 out of 12 died within three days of onset of the reaction). After thioacetazone was discontinued, no further reactions occurred in the children who recovered from the cutaneous hypersensitivity reactions over a period of six months of continuing anti-tuberculous therapy. The result of this study were in part responsible for the WHO recommendations that

thioacetazone should not be used in the treatment of tuberculosis in children infected with HIV [32]. The pathophysiological mechanisms responsible for the development of the SJS are not clear; there is no adequate explanation as to why only certain HIV-positive individuals should react so adversely to thioacetazone. An analysis of the clinical or immunological characteristics of patients who have experienced adverse reactions to thioacetazone that differentiate them from other HIV-infected patients may help resource-poor countries to identify at risk groups and avoid thioacetazone-containing treatment regimens for this group of HIV-infected individuals.

Strategies for prevention

The main strategies currently being practised to control TB in children are to improve the cure rate of adult and paediatric TB, and widescale BCG vaccination of children. The principles of these strategies still hold true even in the face of the HIV pandemic. Case finding and diagnosing adult and paediatric cases of TB quickly and rendering them non-infectious by adequate treatment could remove a substantial portion of sources of infection. The recent increased burden of HIV-associated TB in children requires interventions to limit its occurrence in HIV-positive individuals. No studies of preventive anti-TB drug regimens have been reported in children. Problems in patient compliance and the high cost of administering effective chemoprophylaxis makes this a low priority for developing countries.

Role of BCG

Routine immunisation with BCG at birth is used in most developing countries without knowledge of the children's HIV status [33-35]. Although there have been reports of adverse reactions to BCG, such as lymphadenopathy or adenitis, among HIV-infected individuals, most cases resolve without major complications. Prospective follow-up of infants who were immunised with BCG after birth showed no significant difference in the frequency of BCG-related lymphadenitis between HIV-infected and uninfected children [36]. It is generally accepted that it is safe to use BCG vaccine in asymptomatic HIV-infected children. Current WHO recommendations for countries where TB is common are that BCG should be administered to infants as early as possible, even when the mother is known to be infected with HIV [33,37,38]. However, BCG should be withheld from known symptomatic HIV-infected children.

Acknowledgements

Alimuddin Zumla gratefully acknowledges support from the Camden and Islington Community Health Services NHS Trust, London.

References

- 1 World Health Organisation Global Programme on AIDS. Current and future dimensions of HIV/AIDS pandemic. A capsule summary. Document WHO/GPA/RES/SF/92.1 1992a.
- 2 Raviglione MC, Narain JP, Kochi A. HIV-associated tuberculosis in developing countries: clinical features, diagnosis and treatment. *Bull WHO* 1992;**70**:515-26.
- 3 IUATLD. Tuberculosis in children. Guidelines for diagnosis, prevention and treatment. A statement of the scientific committee of the IUATLD. *Bull Int Union Tuberc Lung Dis* 1991;**66**:61-7.
- 4 Cathebras P, Vohito JA, Yete ML, Lagarde R, et al. Tuberculosis et infection par le virus de l'immunodéficience humaine en République Centrafricaine. *Med Trop* 1988;**48**:401-7.
- 5 Muganga N, Nkuadiolandu A, Mashako LM. Clinical manifestations of AIDS in children in Kinshasha. *Paediatrie* 1991;**46**:825-9.
- 6 Bhat GJ, Diwan VK, Chintu C, Kabika M, Masona J. HIV, BCG and TB in children: a case control study in Lusaka, Zambia. *J Trop Paed* 1992;**vi**:10.
- 7 Chintu C, Luo C, Bhat G, Raviglione M, et al. Cutaneous hypersensitivity reactions to thioacetazone in the treatment of tuberculosis in Zambian children infected with HIV-1. *Arch Dis Child* 1993b;**68**:665-8.
- 8 Hira SK, Mwale C, Kamanga J, Tembo G, et al. Perinatal transmission of HIV in Zambia. *Br Med J* 1989;**299**:1250-2.
- 9 LePage P, Van de Perre C, Van Vliet G, Nsangumunemyi F, et al. Clinical and endocrinologic manifestations in perinatally acquired human immunodeficiency virus type-1 infected children aged five years or older. *Am J Dis Child* 1991;**145**:1248-51.
- 10 Chintu C, Bhatt G, Luo C, Raviglione M, et al. Seroprevalence of HIV-1 in Zambian children with tuberculosis. *Paed Infec Dis J* 1993;**12**:499-504.
- 11 Luo C, Chintu C, Bhatt G, Raviglione M, et al. HIV-infection in Zambian children with tuberculosis: changing seroprevalence and evaluation of a thioacetazone-free regimen. *Tubercle Lung Dis* 1994;**75**:110-115.
- 12 Luo C, Chintu C, Bhatt G, Diwan V, et al. Impact of HIV on common paediatric illnesses in Zambia. *J Trop Pediatr* (in press).
- 13 Malek AN, Mukelabai K, Luo NP. Pulmonary tuberculosis and HIV disease in infants and children. Vth International Conference on AIDS; 1989 Jun 4-9; Montreal (Abstr MBP372:284).
- 14 Glassroth J. Diagnosis of tuberculosis. In: Reichman LB, Hershfield ES (eds). *Tuberculosis*. New York: Marcell-Dekker, 1993;149-65.
- 15 Starke JR. Tuberculosis in children. In: Reichman LB, Hershfield ES (eds). *Tuberculosis*. New York: Marcell-Dekker, 1993;329-67.
- 16 Stegen G, Jones K, Kaplan P. Criteria for guidance in the diagnosis of tuberculosis. *Pediatrics* 1969;**43**:260-3.
- 17 Cundall DB. The diagnosis of pulmonary tuberculosis in malnourished Kenyan children. *Ann Trop Paediatr* 1986;**6**:249-55.
- 18 Gilks CF, Brindley RJ, Otieno LS, Simani P, et al. Extrapulmonary and disseminated tuberculosis in HIV-1 seropositive patients presenting to the acute medical services in Nairobi. *AIDS* 1990;**4**:981-5.
- 19 Chaisson RE, Spector GF, Theuer CP, Rutherford GW, et al. Tuberculosis in patients with the acquired immunodeficiency syndrome. Clinical features, response to therapy, and survival. *Am Rev Resp Dis* 1987;**136**:570-4.
- 20 Chaisson RE, Slutkin G. Tuberculosis and human immunodeficiency virus infection. *J Infec Dis* 1989;**159**:1082-5.
- 21 Coleblunders RL, Ryder RW, Nzilambi N, Dikulu K, et al. HIV infection in patients with tuberculosis in Kinshasha, Zaire. *Am Rev Resp Dis* 1989;**139**:1082-5.
- 22 Elliott AM, Luo NP, Tembo G, Halwiindi B, et al. Impact of HIV on tuberculosis in Zambia: a cross sectional study. *Br Med J* 1990;**301**:412-5.
- 23 Barnes PF, Bloch AB, Davidson PT, Snider DE Jr. Tuberculosis in patients with human immunodeficiency virus infection. *N Engl J Med* 1991;**324**:1644-9.
- 24 Sudre P, ten Dam HG, Kochi A. Tuberculosis: a global overview of the situation today. *Bull WHO* 1992;**70**:149-59.
- 25 Khouri YF, Mastrucci MT, Hutto C, Mitchell CD, Scott GB.

- Mycobacterium tuberculosis* in children with human immunodeficiency virus and routine childhood immunisations. *Lancet* 1987;**2**:669-72.
- 26 Batungwanayo J, Taelman H, Allen S, Bogaerts J, *et al.* Pleural effusion, tuberculosis and HIV-1 infection in Kigali, Rwanda. *AIDS* 1993;**7**:73-9.
- 27 Starke JR. Tuberculosis in children with acquired immunodeficiency syndrome. *Pediatr Infect Dis J* 1992;**11**:683-4.
- 28 Biddulph J. Short course chemotherapy for childhood TB. *Pediatr Infect Dis J* 1990;**9**:794-801.
- 29 Kumar KL, Dhand R, Singhi PD, Rao KLN. A randomized trial of intermittent short course chemotherapy for childhood tuberculosis. *Pediatr Infect Dis J* 1990;**9**:802-6.
- 30 Wong GWK, Oppenheimer SJ. Childhood tuberculosis. In: Davies PDO (ed). *Childhood tuberculosis*. London: Chapman and Hall, 1994;211-223.
- 31 Nunn P, Kibuga D, Gathua S, Brindle R, *et al.* Cutaneous hypersensitivity reactions due to thiacetazone in HIV-1 seropositive patients treated for tuberculosis. *Lancet* 1991;**337**:627-30.
- 32 World Health Organisation. Severe hypersensitivity reactions to thiacetazone among HIV-seropositive patients with tuberculosis treated with thiacetazone. *Weekly Epidemiol Rec* 1992;**67**:1-3.
- 33 Quinn TC. Interactions of the human immunodeficiency virus and tuberculosis and the implication for BCG vaccination. *Rev Infect Dis* 1989;**11**:S379-84.
- 34 Weltman AC, Rose DN. The safety of Bacille Calmette-Guerin vaccination in HIV infection and AIDS. *AIDS* 1993;**7**:149-57.
- 35 Bregere P. BCG vaccination and AIDS. *Bull Int Union Tuberc Lung Dis* 1988;**63**:40-1.
- 36 Lallemand-Le CS, Lallament M, Cheynier D, Nzingoula S, *et al.* BCG immunization in infants born to HIV-1 seropositive mothers. *AIDS* 1991;**5**:195-9.
- 37 Tarantola D, Mann JM. Acquired immunodeficiency syndrome (AIDS) expanded programmes on immunisation. Special programme on AIDS. Geneva: World Health Organisation, 1987.
- 38 Von Reyn CF, Clements CJ, Manu JM. Human immunodeficiency virus and routine childhood immunisations. *Lancet* 1987;**2**:669-72.

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Homelessness and ill health

Report of a working party of the Royal College of Physicians

The number of homeless people in the UK is rising. Ill health is both a contributory cause and often a consequence of homelessness. This new and important report examines why this should be so.

The report recognises three main groups of homeless people: families (Group 1); rough sleepers and hostel dwellers (Group 2); and those who, against their will, live in shared or inadequate accommodation (Group 3). The first two groups are described in relation to availability of housing, health status (including mental health) and access to health services. There is little data available on the third group.

Homeless families and people in inadequate accommodation are more likely to experience mental, physical and obstetric problems, and single homeless people are prone to a wide spectrum of physical illness and are more likely to have serious mental illness than the general population. All are likely to have difficulty in gaining access to appropriate health care.

Government, local authorities, Housing Corporation and the NHS are asked to co-ordinate and develop a housing and community care policy to prevent people with disabilities and ill health from becoming homeless. The report also recommends that health services for homeless people should be integrated with those for the rest of the population and also that special interim arrangements should be put in place for primary care, accident and emergency services, community care and discharge planning to improve existing services.

The report provides demographic data on the availability of housing, the number and type of homeless people and their disorders and characteristics.

All those responsible for planning health services, social services and housing policies, organisations and individuals working with homeless people, policy makers and researchers will find this report a valuable source of information.

Price: £8.50 (overseas £10.50). ISBN 1 86016 009 3. Paperback book. 143 pages. Obtainable from the Royal College of Physicians and from bookshops.

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