

The spectrum of pulmonary disease in HIV-infected children

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Respiratory complications in HIV-infected children are common and responsible for substantial morbidity and mortality.¹ With advances in diagnostic, therapeutic and preventive strategies for HIV, the spectrum of childhood respiratory disease has changed. In developed countries, programs to prevent perinatal HIV-1 transmission, early diagnosis of HIV-1 infection in infants and use of *Pneumocystis* prophylaxis, and highly active antiretroviral therapy (HAART) have led to a substantial decline in paediatric HIV incidence and associated respiratory infections.^{2,3} In contrast, the major burden of paediatric HIV now exists in developing countries.⁴ In these areas, acute and chronic HIV-associated respiratory disease remain a major cause of childhood morbidity and mortality.^{1,5} This is compounded by limited access to appropriate health care and anti-retroviral therapy. In the absence of HAART, up to 90% of HIV-1 infected children will develop a severe respiratory illness sometime in the course of their HIV disease.¹ Pneumonia is the commonest cause of hospitalization in African HIV-1 infected children with pneumonia-specific mortality rates 3-6 times higher than those of HIV-1 negative patients.^{1,6,7}

The burden of HIV-associated respiratory disease in developing countries often occurs in the context of existing high rates of childhood pneumonia, poverty, co-existing malnutrition, suboptimal immunization coverage and under resourced or inaccessible health care facilities. HIV-infected children have a higher risk of respiratory infections and disease and of more severe illness compared to immunocompetent children. However, increasing evidence also suggests that HIV-exposed but uninfected children are also at greater risk of respiratory infections and illness compared to those who born to an uninfected mother.⁷

Globally, there are approximately 33 million HIV-1 infected people of whom 2.5 million are children under the age of 15 years.⁴ The majority of HIV-infected children live in sub-Saharan Africa.⁴ The HIV pandemic has altered the epidemiology of respiratory illness, the spectrum and antimicrobial susceptibility of pathogens, the efficacy of diagnostic investigations and the efficacy of therapeutic and preventative strategies. The epidemic has also created an increased demand for health care resources, with financial

and ethical implications, particularly for use of limited resources such as intensive care support.

The spectrum of HIV-associated respiratory illness includes acute and chronic respiratory disease.

Acute respiratory infections

The rate of acute respiratory infections and opportunistic infections has decreased dramatically with the use of HAART.^{2,3} Pre-HAART, bacterial pneumonia, *Pneumocystis pneumonia* (PCP), disseminated *Mycobacterium avium* complex (MAC) and tracheobronchial candidiasis were the most frequent respiratory infections, occurring at an event rate of more than 1 per 100 child-years.^{2,3} Although the frequency of bacterial infections has declined substantially, pneumonia or secondary respiratory failure remains the predominant cause of death in children on HAART accounting for 27% of deaths.² In children not taking HAART or those resistant to antiretroviral therapy, acute respiratory infections are common, often severe and the most frequent cause of hospitalization or death.¹ Bacteria, mycobacteria, viruses, *pneumocystis* or fungi may cause respiratory infections. Mixed infections occur commonly and polymicrobial infections lead to higher mortality.⁷ HIV exposed but negative children are also at higher risk of respiratory infections including PCP compared to HIV unexposed infants.⁷

Bacterial pneumonia is an important cause of hospitalization and death in HIV-infected children in developing countries.⁷⁻¹⁰ *S. pneumoniae* is the most important bacterial pathogen.^{1,8-10} Other common pathogens include *Staphylococcus aureus* or gram negative pathogens such as *K pneumoniae*, *P aeruginosa*, *H influenzae*, non-typhoid salmonella and *E coli*. Methicillin-resistant *S aureus* (MRSA) has increasingly emerged.⁷ *M tuberculosis* may manifest as acute pneumonia.^{1,7,10} HIV-infected children have an increased risk of bacteraemia and recurrent infections compared to immunocompetent children.^{1,7,9}

Respiratory viruses are identified less frequently in HIV-1 infected children hospitalized for pneumonia compared to HIV negative children but the absolute burden of

hospitalization for viral associated pneumonia is 2-8 fold greater in HIV infected children.¹¹ Respiratory syncytial virus (RSV), cytomegalovirus, adenovirus, influenza, parainfluenza, measles viruses and human metapneumovirus (hMPV) may cause pneumonia. Concurrent bacterial infection has been reported in 30-50% of children hospitalized with viral pneumonia.⁷

In developing countries, *Pneumocystis jirovecii* pneumonia (PCP) remains a frequent presentation of HIV infection in infants and a major cause of severe pneumonia and death.^{7,8,12-14} In addition, HIV-exposed but infected children have also been described to have a higher risk of PCP compared to children born to HIV-uninfected mothers.⁷ In developed countries, the incidence of PCP has declined substantially with widespread use of HAART and pneumocystis prophylaxis.^{2,3}

The outcome of HIV-infected children with pneumonia is worse than that for immunocompetent children with more severe disease and higher case fatality rates.^{1,6,7} In addition, HIV-exposed but uninfected children have higher rates of treatment failure and mortality compared to children born to uninfected mothers.⁷

Chronic lung disease

Chronic lung disease is common in HIV-infected children with increasing age.^{15,16} A longitudinal birth cohort study reported a cumulative incidence of chronic radiographic lung changes in HIV-infected children of 33% by 4 years of age.¹⁵ The commonest chronic radiological changes were increased bronchovascular markings, reticular densities or bronchiectasis.^{15,16} Chronic changes were associated with lower CD4 cell counts and higher viral loads; radiological resolution of these may reflect declining immunity.¹⁵ The spectrum of HIV-associated chronic lung disease includes lymphocytic interstitial pneumonia (LIP), chronic infections, immune reconstitution inflammatory syndrome (IRIS), bronchiectasis, malignancies, bronchiolitis obliterans and interstitial pneumonitis. In HIV and TB high prevalence areas, TB is a common cause of chronic lung disease.^{5,17}

LIP is common in HIV-infected children. The etiology is unknown but serological data suggests that co-infection with Epstein-Barr virus and HIV may initiate a lymphoproliferative response.¹⁸ Clinically children develop chronic respiratory symptoms principally cough and mild tachypnea.^{5,17} Lymphoproliferation also manifests as generalised lymphadenopathy, bilateral parotid enlargement and enlargement of the liver or spleen. Clubbing of the fingers and toes frequently occurs. Hypoxemia, if present is usually mild. Children may survive for years with a course characterised by recurrent episodes of acute lower respiratory tract infections. Cor pulmonale or bronchiectasis may develop.¹⁹

Chronic lung disease may result from recurrent or persistent pneumonia. HIV-infected children have an increased risk of developing pulmonary TB and of complicated or disseminated mycobacterial disease compared to uninfected children.^{5,7,8,17} Localised or disseminated *M bovis* infection including pneumonia has been reported in HIV-infected children occurring weeks to years after receiving BCG immunization.^{20,21} Non tuberculous mycobacteria (NTM) particularly *M avium-intracellulare* complex (MAC) may cause disseminated disease in severely immunosuppressed HIV-infected children; isolated pulmonary disease is rare.²² Chronic candida infection is common in HIV-infected children and may produce oropharyngeal, laryngeal or esophageal candidiasis and promote the development of gastro-esophageal reflux disease.²³ The incidence of tracheobronchial or esophageal candidiasis has declined substantially with HAART.^{2,3} Pulmonary disease may also occur in the context of severe disseminated fungal disease.

An immune reconstitution syndrome (IRIS), occurring weeks to months after initiation of HAART therapy, associated with mycobacterial infection or other opportunistic infections like CMV has been reported.²⁴⁻²⁶ IRIS may result either from unrecognised mycobacterial infection or from a florid immune response directed against a mycobacterial antigen in those already on therapy for mycobacterial infection.²⁴ IRIS is increasingly being recognised in HIV-infected children from high TB prevalence areas but may also occur due to other mycobacterial species including *M bovis* or MAC infection.^{27,28} Clinically, IRIS is characterised by a seemingly paradoxical worsening in

signs with increasing lymphadenopathy, new clinical and radiological respiratory signs and fever, fig 5.²⁴⁻²⁸ The tuberculin skin test may become positive and chest radiographs may show development of lymphadenopathy or new infiltrates.²⁴⁻²⁶ IRIS must be distinguished from other infections, multidrug resistant TB or non-response to TB therapy. To minimise the risk of IRIS, HIV-infected children with confirmed or probable TB should be treated with anti-tuberculous drugs for 1-2 months before commencing HAART.

Bronchiectasis may result from chronic infection including *M tuberculosis*, following recurrent bacterial infections, after a severe viral lower respiratory tract infection or as a consequence of LIP.^{19,29} Clinical features include sputum production, halitosis, digital clubbing and abnormalities on chest auscultation. Development of bronchiectasis may be associated with the severity of immunosuppression; amongst 23 HIV-infected children with bronchiectasis all had CD4 T-cell counts less than 100 cells per cubic millimeter.²⁹

Children with HIV have an increased risk of malignancy. Non-Hodgkins lymphoma (NHL) occurs most commonly, followed by Kaposi's sarcoma (KS), leiomyosarcoma and Hodgkins lymphoma.^{30,31} In African HIV-infected children, Kaposi's sarcoma (KS) is a common AIDS-defining malignancy probably due to the prevalence of human herpes virus-8 infection (HHV-8).³¹ Pulmonary manifestations of Kaposi's sarcoma include upper airway obstruction or chronic progressive dyspnea, cough, and fever; hemoptysis may occur with endobronchial lesions.³¹

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