HIV disease and respiratory infection in children

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Over one million children world-wide are living with HIV infection and respiratory disease is the commonest cause of morbidity and mortality in these children. The initial presentation of respiratory infection is usually in infancy or early childhood. There is enormous potential to prevent childhood HIV infection that is being realised in industrialised countries but not yet elsewhere. Increasingly, therefore, the burden of HIV disease is in children living in or from non-industrialised countries. This review describes and contrasts the pattern of respiratory infection from both regions. This pattern has changed with the implementation of PCP prophylaxis and the availability of potent antiretroviral therapy for children in resource-rich countries, such as the UK. More data are required from resource-poor regions such as tropical Africa, but it is clear that the major differences reflect greater background risk for respiratory infection and very limited management options rather than specific aetiology.

Respiratory infection is the major cause of morbidity and mortality in children infected with human immunodeficiency virus (HIV)1,2. Most childhood HIV infection is vertically acquired and the first clinical presentation of HIV-related pneumonia is usually in infancy or early childhood. Knowledge of disease presentation and management options are much less advanced in resource-poor regions such as sub-Saharan Africa1 than in resource-rich countries2 even though sub-Saharan Africa bears the major burden of global childhood HIV infection3. There is, of course, considerable overlap and variation within regions. Availability of health services and standards of care vary widely according to means within communities of Asia, Latin America and Africa, where expensive antiretroviral therapy (ART) is generally available only to those that can afford it. Alternatively, in resource-rich countries, the presentation of respiratory infection with Pneumocystis carinii pneumonia (PCP) may be the first indicator of HIV infection if the maternal status was not recognised in pregnancy. This has been reported to occur in immigrant communities from HIV endemic regions4. This review aims to describe and contrast the pattern.
of respiratory disease in HIV-infected children living at either end of the socio-economic spectrum.

Prevention of childhood HIV infection

By the end of 2000, UNAIDS estimated that 1.4 million children were living with HIV, of whom approximately 600,000 were infected during 2000 alone, and 4.3 million had already died. Over 90% of infected children each year are from Africa which is home to over two-thirds of HIV-infected persons. Although contributing less than 1% of children infected with HIV world-wide, there are currently around 15,000 children living with the disease in the US and Western Europe. In all parts of the world, most HIV in children is acquired from mother-to-child transmission (vertical transmission), although in some areas, such as Romania, large numbers of children were infected through contaminated blood/blood products in the late 1980s.

The rate of mother-to-child transmission prior to the advent of interventions in Europe and the US was around 15–20%, compared with around 30% in Africa. Most of this difference is accounted for by breast-feeding which accounts for about one-third of transmission in Africa. Since 1995, mother-to-child transmission rates have decreased dramatically, due to wide-spread implementation of interventions including refraining from breast-feeding, the use of antiretroviral therapy for the mother and newborn and elective Caesarean section delivery. Since 1995, mother-to-child transmission rates have decreased dramatically, due to wide-spread implementation of interventions including refraining from breast-feeding, the use of antiretroviral therapy for the mother and newborn and elective Caesarean section delivery. Mother-to-child transmission rates below 1% are currently reported among women on potent ART therapy with undetectable HIV viral load at delivery. Guidelines recommending the universal provision of antenatal HIV testing have been developed and implemented successfully in most Western countries. Thus, new paediatric HIV infections in industrialised countries are increasingly in children from countries with a high prevalence of HIV infection. In the UK, over 75% of seropositive new-borns are delivered to mothers born in sub-Saharan Africa, and approximately one-third of HIV-infected children were themselves born overseas.

As in industrialised countries, almost all childhood HIV infection in non-industrialised countries is acquired perinatally through mother-to-child transmission. In stark contrast, however, vertical transmission rates are around 30%. Antenatal care is often inadequate, maternal HIV status is usually not known, very few women have access to interventions and breast-feeding is almost universal. In the last 2 years, breakthrough clinical trials have demonstrated the efficacy of low cost ART regimens to reduce mother-to-child transmission, including the perinatal use of single dose nevirapine to the mother and neonate, costing only about $4. Data from this Ugandan trial suggested that 35–40% reduction in mother-to-child
transmission could be maintained at 12 months even among breast-feeding women. Thus, in the last year, a number of implementation programmes have been established in African countries to undertake antenatal HIV testing and to offer ART to women to reduce mother-to-child transmission. Major implementation barriers including poor infrastructure exist in most countries and the issue of breast-feeding is unresolved. Breast-feeding results in about one-third of mother-to-child transmission in Africa, but alternatives to breast-feeding remain expensive, dangerous in the absence of clean water, and culturally unacceptable.

**Diagnosis of HIV infection in infancy**

In well-resourced countries, the majority of HIV infected children can be diagnosed within the first month of life by use of DNA PCR techniques. HIV antibody is of no value in the first 12–18 months of life as it is not possible to distinguish the child’s antibody from maternal antibody acquired transplacentally. As PCR testing is technically difficult and expensive, the possibility of early diagnosis for HIV infected children in Africa is rarely available, and the sensitivity and specificity of clinical symptoms and signs to predict HIV infection is very limited in infancy in the African setting.

**HIV-related morbidity and mortality**

In Europe and the US before the availability of antiretroviral therapy for children, around 20–25% progressed to AIDS or died in infancy, most commonly from *P. carinii* pneumonia (PCP). Survival rates of 70% by 6 years and 50% by 9 years were reported from prospective cohorts. In a recent analysis of over 3000 HIV-infected children participating in clinical trials in the US before highly active antiretroviral therapy (HAART) became available, serious bacterial infections (rate 15.1/100 child-years; most commonly pneumonia 11/100 child-years) which occurred during all stages of HIV infection, and PCP (1.3/100 child-years) and *Mycobacterium avium-intracellulare* complex (MAIC) (1.8/100 child-years), which occurred in advanced disease, were the most common infections. These occurred at much higher rates than among HIV-negative children. Since 1997, the availability of HAART has led to a dramatic reduction in HIV disease progression, morbidity requiring hospital admission, and death. Even before 1997, decreased progression rates were reported, attributed, in part, to the availability of double ART. Further, the revised guidelines for PCP prophylaxis in 1995 and intensive regimens for management of children with
Lymphocytic interstitial pneumonitis (LIP) and recurrent chest infections contributed to a falling incidence of PCP and chronic lung disease, respectively, before the HAART era. None-the-less, a quarter of children living with HIV are now entering teenage years and some have residual damaged lungs from respiratory illness in early childhood which HAART may not improve. Key differences in the manifestations of HIV between adults and children are shown in Table 1.

Much less is known of the incidence and aetiology of HIV-related respiratory infection in Africa than in Europe or the US and survival is far worse. Diagnostic and therapeutic options for HIV-infected African children are limited or non-existent, and those with respiratory infection are usually managed on the basis of a clinical algorithm, a limited range of available antimicrobials and without confirmation of HIV status. The majority of HIV-infected African children die by 3 years of age. However, in regions of established high HIV endemicity, it is common for HIV-infected school-aged children to present with respiratory disease. The early studies of HIV disease in African children concentrated on rates of vertical transmission and early mortality. Cohort studies showed that acute and chronic pneumonia were more common than in HIV-uninfected children, but specific aetiology was not sought. Autopsy studies provide consistent evidence that respiratory infection is the dominant cause of death, but tend to represent infections that are unresponsive to available standard treatments or that occur with advanced HIV disease. Only recently have data from prospective clinical studies emerged. Common causes of acute and chronic pneumonia in HIV-infected African children are listed in Table 2.

### Causes and management of respiratory infections

#### Bacterial pneumonia

The respiratory tract is the most common site of bacterial infections, with approximately half being lower respiratory infections. Bacterial pneumonia

Table 2: Common causes of respiratory infection in HIV-infected African children

<table>
<thead>
<tr>
<th>Organism</th>
<th>Age group</th>
<th>Impact of HIV infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial pneumonia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>All ages</td>
<td>Increased incidence</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td></td>
<td>Early relapse and higher case-fatality rate in those with AIDS</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td></td>
<td>Increased antibiotic resistance</td>
</tr>
<tr>
<td>Klebsiella spp.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmonella spp.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escherichia coli</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumocystis carinii</td>
<td>2–6 months</td>
<td>Very strongly HIV-related</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Common cause of death in HIV-infected infants</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poor outcome, especially if associated with CMV infection</td>
</tr>
<tr>
<td><strong>Viral pneumonia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory syncytial virus</td>
<td>Infants</td>
<td>Higher rates and more secondary bacterial pneumonia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Less wheeze or typical bronchiolitis</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Infants</td>
<td>Higher mortality</td>
</tr>
<tr>
<td>Measles</td>
<td>Usually after 6 months</td>
<td>More common</td>
</tr>
<tr>
<td></td>
<td></td>
<td>More severe</td>
</tr>
<tr>
<td><strong>Lymphocytic interstitial pneumonitis</strong></td>
<td>Usually after 1 year</td>
<td>Always HIV-related</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td></td>
<td>Better prognosis group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Often confused with TB</td>
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<tr>
<td></td>
<td></td>
<td>Increased recurrent chest infections and bronchiectasis</td>
</tr>
<tr>
<td><strong>Pulmonary tuberculosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>All ages</td>
<td>More common</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diagnosis more difficult</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tuberculin test less sensitive</td>
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<tr>
<td></td>
<td></td>
<td>Poorer outcome</td>
</tr>
<tr>
<td><strong>Bronchiectasis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary to above infections</td>
<td>Usually after 3–4 years</td>
<td></td>
</tr>
<tr>
<td><strong>Pulmonary Kaposi's sarcoma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human herpes virus B</td>
<td>Usually after 3–4 years</td>
<td>Strongly HIV-related</td>
</tr>
<tr>
<td><strong>Nocardiosis</strong></td>
<td>Nocardia asteroides</td>
<td>Confused with PTB</td>
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</tbody>
</table>

was common in HIV-infected children in the US before the era of HAART and was more frequent than pneumonia due to opportunistic pathogens such as *P. carinii* even before the routine use of PCP prophylaxis with trimethoprim-sulfamethoxazole (Cotrimoxazole)\textsuperscript{12,21}. Bacterial pneumonia, particularly due to *Streptococcus pneumoniae* was 5–10 times more common in HIV-infected than in HIV-uninfected children in the US and Europe\textsuperscript{12,22}. Bacterial pneumonia also occurs, albeit less frequently, in
children with relatively high CD4 cell counts, suggesting that serious bacterial infections occur at all stages of HIV infection. In addition, pneumonia has been reported with approximately twice the frequency in children with underlying LIP, with many children having repeated hospital admissions for lower respiratory tract infections. Other bacterial pathogens include *Haemophilus influenzae*, *Staphylococcus aureus* and *Salmonella* spp.

The incidence of bacterial pneumonia and associated mortality was already high in non-industrialised countries prior to the HIV epidemic and the commonest cause was *Strep. pneumoniae*. Similarly, the commonest isolate from blood culture of HIV-infected African children hospitalised with severe pneumonia is *Strep. pneumoniae*. A recent study from South Africa estimated the risk of invasive pneumococcal disease to be 40 times greater in HIV-infected children than in HIV-uninfected children. The range of other bacteria causing pneumonia in HIV-infected children is similar to that in HIV-uninfected children but also with greater frequency (Table 1). *Staph. aureus* has re-emerged as an important cause of pneumonia in South African children with HIV infection, particularly among those with a history of chronic lung disease. *Salmonella* is an important invasive pathogen in tropical Africa particularly during the rainy season and is often HIV-related. Gram-negative bacteria such as *Klebsiella pneumoniae* and *Escherichia coli*, which are common in malnourished children without HIV infection, are also common in HIV-infected children. Although the case-fatality rate for severe acute pneumonia is up to 6 times higher than in HIV-uninfected children, this mainly reflects the impact of *P. carinii* pneumonia (PCP). The outcome of pneumococcal pneumonia was similar between HIV-infected and -uninfected children except in those with advanced AIDS. HIV-infected children are also prone to recurrent bacterial disease and infection with antibiotic-resistant organisms. However, in vitro resistance does not necessarily affect treatment response for bacterial pneumonia.

In addition to prompt treatment with antibiotics, physiotherapy and nutritional support for those with chronic lung disease, strategies to reduce or prevent bacterial infections in general, and pneumococcal disease in particular, are a priority. *H. influenzae* type b (Hib) conjugate vaccine is now routinely given to children in most well-resourced countries and a study in the pre-HAART era showed that most HIV-infected children achieve Hib antibodies in the protective range, although levels were 10-fold lower than in HIV-uninfected children, and even lower in children with AIDS. Polysaccharide pneumococcal vaccine has been recommended for HIV-infected children, but there are no data from phase III trials and results of a Ugandan trial showing poor efficacy in HIV-infected adults is of concern. Pneumococcal conjugate vaccines may prove to be an important intervention for pneumococcal disease in HIV-infected children, even in the era of HAART, given the efficacy of this vaccine in preventing...
pneumococcal disease in normal children in clinical trials. Data are eagerly awaited from a current trial of a pneumococcal conjugate vaccine in South African children where HIV infection is common.

**Pneumocystis carinii pneumonia (PCP)**

There is now robust evidence from autopsy and clinical studies that PCP is a common cause of severe pneumonia and death in HIV-infected African infants. PCP should be suspected in an infant between 2–6 months of age with marked respiratory distress, often with severe hypoxia, a poor response to standard first-line antibiotics and either a clear chest or diffuse rather than focal abnormalities on auscultation. The hypoxia is less responsive to oxygen than is bacterial pneumonia. PCP is a clinical diagnosis as confirmation requires technology such as fluorescent microscopy or PCR of broncho-alveolar secretions or nasopharyngeal aspirates and these are rarely available. The commonest abnormalities on chest radiograph are hyperinflation or a diffuse interstitial pattern but these are non-specific.

Recommended treatment includes high-dose intravenous (or oral if not available) cotrimoxazole, prednisone and oxygen but outcome is very poor. Data from South Africa suggest that CMV pneumonitis not uncommonly occurs with PCP. The outcome for these infants is even worse than among those with PCP alone, and there is suggestive evidence that administration of steroids may worsen CMV pneumonitis. As mixed infections are common in HIV-infected children, initial treatment should include a recommended antibiotic for severe bacterial pneumonia even when PCP is strongly suspected.

In resource-rich countries, PCP also presents most commonly in the first 6 months of life and before the era of HAART, had a very poor outcome, despite availability of intensive supportive care with ventilation, i.v. high dose cotrimoxazole and steroids. CD4 count was shown to have limited value in predicting development of PCP in infants, which often occurred even before the diagnosis of HIV. The recognition of this led to the 1995 revised guidelines recommending universal cotrimoxazole prophylaxis in all infants born to infected women from 6 weeks of age irrespective of CD4 cell count. This has contributed to the reduced incidence of PCP observed even before the advent of HAART.

Infants who recover from PCP can now expect to do very well clinically with normal development and growth, good recovery of CD4+ cell numbers and often undetectable viral load on HAART. This contrasts with previous experience where children surviving PCP often went on to develop HIV encephalopathy and other AIDS indicator diseases. However, even in the era of HAART, some babies with PCP...
will die of their initial lung disease before HAART can be given\textsuperscript{4}, stressing the value of diagnosing HIV in women antenatally. In the UK, PCP has also been reported to occur frequently with CMV disease in infants, the occurrence of dual infection being independently associated with breast-feeding and with mothers being born in Africa\textsuperscript{4}. Survival was significantly worse for infants with dual infection and, in contrast to previous studies, use of adjuvant corticosteroids was not associated with improved survival from PCP. This finding may be partly explained by the high prevalence of CMV co-infection in this study, as corticosteroids could adversely affect the course of CMV disease\textsuperscript{34}. These data suggest that infants developing PCP should be investigated for CMV infection and retinitis, especially if they were born to African mothers and were breast-fed. In addition, anti-CMV therapy with gangcyclovir should be strongly considered in infants with PCP and evidence of CMV infection, especially in those who receive adjuvant corticosteroids.

Prophylaxis against PCP and bacterial infections
In Europe and the US, cotrimoxazole is recommended for primary prophylaxis against PCP in children born to HIV-infected women, starting at 6 weeks of age and continuing until HIV infection status is shown to be negative\textsuperscript{15}. In infected children, it is recommended to stop after 12 months of age if the CD4\textsuperscript{+} cell count is over 750 cells/mm\textsuperscript{3} or 15\% of total lymphocyte count. In Africa, UNAIDS recently made a recommendation that infants born to HIV-infected women should receive cotrimoxazole prophylaxis, as in the industrialised world\textsuperscript{35}. However, the majority of HIV-infected women currently remain undiagnosed, and although this strategy has been introduced with antenatal HIV testing programs in some areas of Africa, this is not yet standard practice in most regions. In addition, there are concerns about increasing population levels of resistance against other pathogens and further research to evaluate this alongside implementation is required.

No trials have evaluated the efficacy of cotrimoxazole prophylaxis in reducing bacterial and other infections in children after the first year of life. In the early 1990s, two trials of intravenous immune globulin (IVIG) therapy in children reported reductions in the number of bacterial infections and hospital admissions in the IVIG arm, but no effect on HIV progression or survival\textsuperscript{41,42}. This expensive and difficult therapy is no longer recommended for HIV-infected children. In the second IVIG trial, some children were also taking cotrimoxazole prophylaxis and, in a subset analysis, the benefit of IVIG was not observed. This provided some evidence of a protective effect of cotrimoxazole against bacterial infections. More recently, two placebo-controlled trials of cotrimoxazole in HIV-infected adults in West Africa reported reductions in infections caused by \textit{Isospora}
belli and malaria and decreased rates of pneumonia in the active arms\textsuperscript{43,44}. Whether these results can be extrapolated to other parts of Africa remains unclear because, unlike West Africa at that time\textsuperscript{45}, high rates of cotrimoxazole resistance to bacteria and other organisms exist in many other countries. There are also concerns that widespread use of cotrimoxazole could cause cross-resistance with sulfamethoxazole-pyramethamine (Fansidar\textsuperscript{\textregistered}) which has replaced chloroquine as first-line therapy for non-severe malaria in many African countries. Trials are ongoing in adults and children with HIV infection in Zambia where there is a high rate of cotrimoxazole resistance to common bacteria causing pneumonia in adults and children.

**Viral pneumonia**

HIV infection is associated with an increased frequency and poorer outcome with viral pneumonia such as due to respiratory syncytial virus (RSV), influenza, parainfluenza, adenovirus and measles\textsuperscript{46,47}. Characteristics of RSV infection in HIV-infected children are that the typical presentation of bronchiolitis with wheeze is less common while secondary bacterial pneumonia is more common and there is a higher case-fatality rate than in HIV-uninfected children. Cytomegalovirus (CMV) may occur with PCP\textsuperscript{4} and was a common finding at autopsy in the lungs of HIV-infected infants\textsuperscript{18,20}. CMV was cultured from respiratory secretions from 14\% of HIV-infected children with severe pneumonia in Cape Town\textsuperscript{26}. HIV-infected children with immunosuppression may develop giant cell pneumonia due to varicella, although this is rare in early stages of HIV. Autopsy and clinical studies have found that mixed viral and bacterial pneumonia is common\textsuperscript{1,26,46}.

**Pulmonary tuberculosis**

HIV-infected children are susceptible to tuberculosis (TB) but the incidence of TB is low in the US and Europe compared to other HIV-related disease\textsuperscript{12,21}. TB is very common in African adults as a result of the HIV epidemic and young children are at particular risk of developing disease following exposure to a case of smear-positive pulmonary tuberculosis (PTB). Thus, HIV-infected African children are at risk for TB because of immunosuppression and also because they are more likely to have close contact with smear-positive PTB than HIV-uninfected children because PTB is the commonest HIV-related disease in their parents\textsuperscript{1,48}.

There has been considerable difficulty in estimating the association between HIV and TB in African children for two main reasons\textsuperscript{1}. First,
the clinical and radiological picture of lymphocytic interstitial pneumonitis (see below) with secondary bacterial infection in HIV-infected older children may mimic PTB. Second, it is difficult to confirm PTB in most children in resource-poor regions and HIV infection has further reduced the sensitivity or specificity of clinical diagnostic criteria such as history of contact, chronic symptoms, reactive tuberculin test and response to antituberculosis therapy1,48,49. Consequently, HIV-infected children with chronic respiratory disease are often misdiagnosed as smear-negative PTB and occasionally vice versa. It is clear that the incidence of PTB in HIV-infected African children is lower than other HIV-related respiratory infections such as recurrent bacterial pneumonia or PCP and is also lower than the incidence in HIV-infected African adults.

Notwithstanding, childhood TB is much more common in Africa than in the US or UK and the numbers are increasing because TB control among adults has worsened. Further, there is now good evidence that in regions where childhood HIV infection is common, HIV prevalence is high among children with TB, including those with confirmed PTB25,26,48,49. The extent of TB/HIV co-infection in children varies between regions and important factors include childhood HIV prevalence, the severity of the TB epidemic among the adult population and the prevalence of TB/HIV co-infection in adults.

The clinical presentation of PTB and radiographic abnormalities are similar in HIV-infected and HIV-uninfected children1,48,49. The tuberculin test is less sensitive but may still be useful. Response to antituberculosis therapy may be poorer in HIV-infected children, particularly in those with advanced disease48. Thiacetazone should not be used as there is a high risk of a severe and often fatal Stevens-Johnson reaction. The value of prophylaxis given to HIV-infected household contacts of cases of smear-positive PTB has not been studied. None-the-less, giving isoniazid prophylaxis to young children in households with open PTB would be desirable.

*M. tuberculosis* has been reported infrequently in HIV-infected children in Europe or the US. However, PTB has been reported as the most common AIDS diagnosis in adults in the UK who acquired HIV in Africa, and children of these adults are clearly at risk. The question of BCG (Bacille Calmette-Guérin) vaccination for babies of immigrant African mothers with HIV has been debated in the UK. While the risk-benefit ratio would favour routine BCG in babies irrespective of the HIV status of the mother in the African setting, the balance would be against it in most parts of Europe and the US where the risk of BCG-osis, although small, is present for babies with rapid disease progression. However, in parts of the UK, with large African immigrant populations, and where children may be likely to travel back to Africa, the benefit may outweigh the small risk to the infected child. BCG immunisation is almost universal in African countries and yet BCG disease is rare even in HIV endemic regions.
Non-tuberculous mycobacterial infections are uncommon in the era of HAART and only occur with very low CD4 cell counts. The most common organism in this group is MAIC which causes around 90% of identified infections. It usually presents with systemic disease and rarely as respiratory disease alone. Respiratory distress with nodular infiltrates on CXR may occur.

**Lymphocytic interstitial pneumonitis**

Lymphocytic interstitial pneumonitis (LIP; Table 3) is characterised by extensive lymphocytic infiltration of the pulmonary interstitium. It occurs almost exclusively in HIV-infected children and Epstein-Barr virus (EBV) is thought to be important in the pathogenesis. LIP usually present after 2 years of age and is common in African children. LIP presents with a broad spectrum of clinical and radiological disease and is often confused with TB. Thus, many children present with chronic respiratory disease but a poor response to anti-TB therapy. Clinical features that are often associated with LIP include generalised and symmetrical lymphadenopathy, bilateral chronic non-tender parotid swelling, digital clubbing and hepatomegaly. Typical radiographic findings are diffuse bilateral reticulo-nodular infiltrates so it can be misdiagnosed as miliary TB (Fig. 1).

Confirmation of diagnosis requires a lung biopsy which is rarely undertaken. Lung histology shows considerable changes in lung architecture with invasion of alveolae with CD8 cells (Fig. 2 and Plate 2 on page 150). A bronchoscopy study with biopsy of South African children found that LIP was the commonest abnormality in HIV-infected children with chronic respiratory symptoms and was more common than PTB. Unlike PCP, LIP is associated with a favourable prognosis but secondary bacterial pneumonias and eventual bronchiectasis are common. This further confuses interpretation of chest

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**Table 3** Lymphocytic interstitial pneumonitis in HIV-infected children

- Occurs in 25–30% of vertically HIV-infected children but is rare in those infected through other routes at an older age, and in adults
- Associated with a better prognosis than many other HIV manifestations
- Associated with parotid enlargement and marked lymphadenopathy. May be associated with obstructive airways disease (which may respond to bronchodilators)
- Secondary bacterial infections and bronchiectasis occur, but wide variation from asymptomatic to severely hypoxic
- May be associated with obstructive sleep apnoea and adenoidal and tonsillar hypertrophy
- Hyperviscosity associated with very high immunoglobulin values may occur
- Has been associated with MALT (mucosa-associated lymphoid tissue) but this is rare and does not necessarily have a poor prognosis
radiographs (Plate 1 page 150). Corticosteroids, although not subjected to a controlled trial, appear to be effective in alleviating respiratory symptoms and are used for 4–6 weeks in high doses, followed by rapid weaning to small alternate day doses. It is important, therefore, to exclude PTB in these patients and to consider TB prophylaxis. Clinical studies of LIP in African children are needed to improve diagnosis and management. As HIV disease progresses, features of lymphocytic infiltration such as lymphadenopathy and parotid swelling diminish as the child’s immune function worsens and he/she becomes more wasted.

In Europe and the US, LIP has been reported to occur in approximately 20–30% of vertically HIV-infected children, but is rare in adults with HIV. Anecdotally, in these countries, it appears to be more common in children of African origin (possibly associated with an earlier acquisition of EBV). Recurrent bacterial and viral respiratory infections appear to be more common in association with LIP, but children may manifest a range of symptoms from asymptomatic to chronic hypoxia. In addition to steroids, ART improves symptoms and radiographic appearances of LIP. It

Fig. 1 This 4-month-old child presented with gradual onset of poor feeding and being generally unwell. In the past, she had recurrent oral Candida and was failing to thrive. Nasopharyngeal aspirate and bronchoalveolar lavage revealed P. carinii; see also Plate 1 (colour), page 150.
Fig. 2 Lymphocytic interstitial pneumonitis with secondary bacterial infections and bronchiates. This child, who has had several episodes of herpes Zoster (A), chronic lung disease with marked chest X-ray changes of lymphocytic interstitial pneumonitis and secondary consolidation due to recurrent bacterial infections (B). See also Plate 2 (colour) page 150. The lung biopsy shows destruction of the lung architecture and large numbers of CD8 cells.
is to be hoped that younger children who have had the benefit of receiving HAART before becoming symptomatic will have less problems with chronic lung disease associated with LIP. Many children with LIP have associated wheezing and may also benefit from the use of a bronchodilator.

Other causes of respiratory disease

Malignant lymphoma has been reported to occur approximately 1000 times more frequently than in HIV-uninfected children, and as in adults with HIV, a decline with the advent of HAART may occur. Lymphomas are usually of the B-cell type and most frequently affect the brain, but have also been reported in the nasopharynx, soft palate, and tonsillar areas. In a case-control study in Uganda, Burkitt’s lymphoma was 7.5 times more common in HIV-infected compared with uninfected children, and HIV infection was associated with a considerable increase in risk from Kaposi’s sarcoma (OR 94.9), which in this endemic form, may also affect the lungs. Mucosa-associated lymphoid tissue has been reported in association with LIP, but this is rare.

Conclusions

This review has emphasised the importance of respiratory infections in HIV-infected children. Common causes of acute pneumonia include the usual respiratory pathogens of childhood such as pneumococcus or RSV that occur more frequently and more severely, and opportunistic pathogens such as *P. carinii* and CMV, that are often fatal. LIP is a common cause of chronic, recurrent respiratory disease in HIV-infected children and PTB is common in regions of high TB endemicity. The implementation of preventive strategies has successfully and dramatically reduced mother-to-child transmission of HIV infection in industrialised countries, and the incidence of PCP in HIV-infected infants. The advent of potent ART has increased survival and changed the pattern of morbidity. Although not as well documented, data are emerging that suggest that the pattern of respiratory infections in HIV-infected children in the non-industrialised world is not markedly different from that which occurred in the industrialised world before ART was available and PCP prophylaxis to HIV-exposed infants was routine. The major differences from well-resourced countries are the scale of the problem, the frequent early morbidity and poor survival, the limited diagnostic and therapeutic options, and the inadequacy of the health care infrastructure to implement effective prevention strategies. It is to be hoped that with the recent call for therapies for HIV to be made
available at affordable prices in resource-poor countries most heavily affected by HIV, that implementation programmes and the necessary infrastructure both to reduce mother-to-child transmission and to provide, sustainably, treatment for HIV-infected children and adults will be a priority for governments, international organisations and research institutions around the world.

References

Childhood respiratory diseases

Childhood respiratory diseases

Plate 1 Nasopharyngeal aspirate and broncho-alveolar lavage revealing \textit{P. carinii} in a 4-month-old child who presented with gradual onset of poor feeding and being generally unwell. In the past, she had recurrent oral \textit{Candida} and was failing to thrive. See also Fig. 1, page 144.

Plate 2 Lung biopsy showing destruction of the lung architecture and large numbers of CD8 cells in a patient with lymphocytic interstitial pneumonitis with secondary bacterial infections and bronchiates. See also Fig. 2 page 145.

Plate 3 Grocott stain revealing \textit{Aspergillus} hyphae invading a blood vessel (centre) in lung tissue removed following pneumonectomy. See also Fig. 5 A–C in next chapter by Veys and Owens on page 163.