The impact of HIV on respiratory disease in Malawian children
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Introduction

Infection with human immunodeficiency virus (HIV) type 1 has been recorded retrospectively as occurring in Malawi since as early as 1982. (1) The first recorded case of HIV/AIDS was reported in 1985, and over the next 10 years, the community and antenatal HIV prevalence rose rapidly especially in the urban populations. By 1995, HIV prevalence had reached 30% among mothers attending the antenatal clinic at Queen Elizabeth Central Hospital (QECH), Blantyre, which is Malawi’s largest hospital.(2)

Studies of mother-to-child HIV transmission prior to any intervention showed that around one-third of babies born to HIV-infected Malawian mothers were being infected with HIV.(3) At QECH where there were around 12,000 deliveries per year, this meant that around 100 HIV-infected babies were being born each month at one hospital alone. The mortality rate per 1000 live births of infants and children of HIV seropositive mothers was substantially higher (223 at 12 months, 317 at 24 months and 360 at 30 months) than those of HIV seronegative mothers (68 at 12 months, 106 at 24 months and 118 at 30 months).(4) Although maternal prevalence was lower in rural communities, HIV was still having a major impact in that setting. The antenatal HIV prevalence in rural Mangochi, Malawi, district was reported as 5.3% in the period 1987-1990 and infant mortality rate was 235 per 1000 live births for infants born to HIV-seropositive mothers compared to 144 per 1000 live births for those born to HIV-seronegative mothers.(5) The importance of regional co-morbidities was emphasized by that study as the odds of post-neonatal mortality were substantially and significantly higher if the infant had exposure to maternal HIV infection and placental malaria rather than to HIV or placental malaria alone.

The consequences of these statistics on infant and child morbidity and mortality in Malawi and in other similar resource-poor HIV endemic countries in the region have been profound and devastating. With no specific treatment available, around 30% of HIV-infected infants died by 1 year of age and around 60-70% by 3 years of age.(6-8) Therefore, the main burden of HIV-related illness presents in infants and young children, an age group already at risk of disease-related mortality and malnutrition. Early autopsy studies, cohort and cross-sectional clinical studies in the region consistently showed that respiratory disease was the major cause of morbidity and mortality in HIV-infected children.(9-13) In Europe and USA, respiratory disease was also the major cause of morbidity although survival was much better for HIV-infected infants even prior to specific interventions.(14-17) In addition, there have been important indirect consequences of the HIV epidemic on child health. Maternal morbidity and mortality associated with HIV is associated with poorer survival of the children including those who are not HIV-infected. Further, the added burden of disease associated with paediatric HIV infection places a major strain on limited resources including human resources, drugs and equipment (such as availability of oxygen and CXR).
Malawi

Malawi is a small land-locked country in south-eastern Africa. It is densely populated with the majority living in rural areas, and the population has grown rapidly since independence in 1963 to around 13 million in 2005. The largest city is Blantyre which is a major commercial centre and the main city of the southern region. The population of urban Blantyre and per-urban Blantyre district is around 1 million while the population of the Southern Region of Malawi is approximately 6 million. Malawi is a poor country with a gross domestic product per capita of less than US$ 600 per year, Sixty-five percent of the country live below the poverty line of less than US$ 1 per day.

Female literacy is low as 57% of females in 2002 received no education or to less than 4 years of primary education. Maternal mortality rate is among the highest in the world at 1,120 deaths per 100,000 births. Infant and child mortality is high but has been steadily falling in the last decade. Infant mortality and child mortality in 2003 were reported as 127 deaths and 201 deaths per 1000 live births respectively. Immunization coverage is quite high. Common childhood diseases are pneumonia, malaria and malnutrition. Skilled human resources are very limited, for example, one physician per 101,000 people in 2003 with public health expenditure of US$ 11 per capita per annum.

HIV prevalence in the population rose rapidly between 1987 and 1997 from 1.6% to 12.2% and has since plateaued with a decrease in the incidence of new HIV infections in the last decade. The total number of HIV-infected persons in Malawi in 2003 was estimated to be 760,000. HIV prevalence is higher in the urban compared to rural population (23% versus 12.4% respectively in 2003) and highest in the southern region (19.5% in 2003). Life expectancy at birth of a Malawian fell to 39 years in the late 1990’s as a result of the HIV epidemic and is now around 45 years. It was estimated that there were 900,000 AIDS orphans in Malawi in 2005.

“Situational analysis” in 1995

The impact of HIV was an obvious challenge to improve clinical case-management of sick children presenting to the paediatric wards at QECH (where I started working in January 1995) and to a lesser extent at the rural-based district (Chikwawa, Chiradzulu and Ntcheu District Hospitals) and mission hospitals (St Joseph’s Hospital, Nguludi, and Holy Family Hospital, Phalombe) that I would visit regularly every 2-3 months. The Department of Paediatrics was established as part of the new University of Malawi College of Medicine in 1991 and was then (and continues to be) responsible for providing care for paediatric inpatients at QECH. In 1995, there was clinical research being undertaken in malaria and severe malnutrition which has been ongoing. Aside from severe malaria and malnutrition, pneumonia is the other major cause for admission and death. The Department of Paediatrics has a daily morning meeting to discuss difficult cases for the previous day and a weekly
meeting to review the deaths from the previous week. It soon became clear that the diagnosis and management of respiratory disease was a major challenge, especially in the context of two clinical dilemmas: acute severe pneumonia in infants not responding to recommended first-line antibiotics, and poor response to treatment for tuberculosis (TB) in children with chronic or persistent respiratory symptoms. It was often presumed that these clinical scenarios were HIV-related but this had not been well described. These challenges of diagnosis and management became the focus of this PhD.

Studies of aetiology of respiratory disease in the resource-limited setting are very challenging in children especially in the infant or young child, the age group also at greatest risk of morbidity and mortality. There were, however, data available of respiratory disease in HIV-infected infants and children in USA from the 1980’s prior to the use of CPT and availability of effective ART. These studies showed a high incidence of bacterial pneumonia especially pneumococcal pneumonia in HIV-infected children.\(^\text{18}\) *Pneumocystis* pneumonia (PcP) was also recognized a common in HIV-infected children, particularly in infants of 3 to 6 months of age, often as a first presentation of HIV infection in the infant and mother.\(^\text{19}\) Lymphoid interstitial pneumonitis (LIP), a systemic lymphoproliferative disease in children causing persistent respiratory symptoms, was recognized as HIV-related having been very unusual prior to the HIV epidemic.\(^\text{20}\) LIP and bronchiectasis were not uncommon while in contrast pulmonary tuberculosis (PTB) was relatively rare in children in USA.\(^\text{17}\)

*Pneumocystis* pneumonia and HIV in Africa

Studies of adults in the HIV-endemic African setting, including bronchoscopy studies which could not be done in infants and young children in the same setting, began to define the common pathogens causing lung disease in HIV-infected African adults. The common causes of acute and persistent respiratory disease were soon recognized to be pneumococcal pneumonia and PTB.\(^\text{21}\) PcP was surprisingly uncommon in contrast to the early experience with HIV/AIDS epidemic in regions such as North America, Europe and Australia. It appeared that this was not just a feature of under-recognition as it was also uncommon in autopsy studies of HIV-infected adults and clinical studies employing bronchoscopy. In contrast however at QECH in 1995, a clinical diagnosis of PcP was not uncommon in an infant with severe respiratory distress and some data began to emerge. Early autopsy studies of HIV-infected African children found that PcP was a cause of fatal pneumonia in infants.\(^\text{9,10,22}\) Further, a clinical study was undertaken in 1995 at QECH which confirmed PcP in 5 of 60 children from 2-24 months of age with severe pneumonia \(^\text{23}\) This was the first description of PcP in infants in the region, and 4 of the 5 infants died.

Tuberculosis and HIV in African children

The data from USA and Europe of co-morbidities in HIV-infected children reported that TB in HIV-infected children was uncommon.\(^\text{17,20}\) This was not particularly surprising given the very low
incidence of infectious cases of TB in the community. In the sub-Saharan African region, the incidence of sputum smear-positive TB was high and had increased significantly in the previous decade in the wake of the worsening HIV epidemic including in Malawi. (24) This meant that TB infection and disease in children in the region was also likely to be relatively common, including in HIV-infected children.

The first autopsy study in HIV-infected African children was reported from Abidjan, Cote d’Ivoire, and did not find TB to be common. (9) Autopsy data by definition has the limitation of reporting causes of fatal diseases, have inherent selection bias and provide no data of incidence of specific diseases. Nevertheless, this finding resulted in a perception oft-quoted at the time that “TB was common in HIV-infected adults in Africa but uncommon in HIV-infected children”. This perception differed greatly from early experience at QECH where I was also managing the child TB inpatient ward as well as child TB outpatient and TB contact clinics at the time. Our own clinical observation in Malawi was that HIV-exposed children were often also close household contacts of adults with smear-positive TB, and that it was not uncommon for HIV-infected children to be started on TB treatment. In contrast to the USA, TB exposure and infection was common in HIV-exposed and infected Malawian children, and it made logical sense that once infected, an HIV-infected child would be at increased risk of developing TB disease because of immunosuppression.

The difficulties in confirming TB diagnosis in infants and young children meant that there was a lack of strong evidence from clinical studies and so the actual burden of childhood TB in HIV-infected African children was uncertain. (25,26) Poor early survival of HIV-infected infants also meant that most TB disease, if present, would likely present in infants and young children of less than 5 years. This is an age group for which confirmation of pulmonary TB is particularly difficult, especially without mycobacterial culture. An audit undertaken with Malawi National TB Program data for Blantyre district showed that there had been an 8-fold increase in children being treated for TB from 1986 to 1995, although there were no data of impact of HIV infection for this retrospective analysis. (24) An original pilot study using induced sputum for the first time in the region was conducted at QECH in 1994 and confirmed TB in 8 of 29 Malawian children with suspected TB. (27)

Adding to the diagnostic challenges for TB was the emerging evidence over the previous decade that HIV was commonly associated with other causes of persistent respiratory disease such as LIP and bronchiectasis. (17,28) It was therefore likely that HIV-infected children in the region presenting with chronic cough and not responding to antibiotics were commonly misdiagnosed clinically as TB when the presentation was of other HIV-related lung disease. LIP was not a clinical diagnosis that health workers in the region were familiar with because it had only emerged as a disease entity in children with the HIV epidemic and required tissue biopsy for confirmation. (17,20,28) We reported an original
observation that digital clubbing was a clinical marker of HIV in African children (29), a finding which has subsequently been supported by other studies from the region.(30,31) Digital clubbing is common in children with LIP and bronchiectasis, and has been associated with HIV infection in children with culture-confirmed TB.(31)

One of the roles that I adopted on joining the Department of Paediatrics in 1995 was management of the child TB outpatient and child TB contact clinics as well as supervision of inpatient TB management. Referral of children to QECH who had been commenced on TB treatment but were not responding was a common scenario. Treatment adherence was also noted to be poor. The poor outcome and adherence of all Malawian children treated for TB in 1998 has since been documented. (32) Evidence was emerging at the time that co-infection with HIV was a major risk factor for poor outcome.(26,33,34) One reason for poor response to anti-TB treatment is that many of the children did not have TB but rather another HIV-related lung disease as mentioned above.(28) However, in studies such as from South Africa where culture facilities are available, co-infection with HIV is still a risk factor for poorer treatment response including in children with confirmed TB.(31) One potential reason for this was that serum levels of anti-TB drugs might be lower than necessary in HIV-infected individuals due to possible malabsorption because of HIV-related enteropathy, and because of confounding associations with malnutrition and age.(35)

HIV testing
Finally, that we reported clinical markers of HIV infection such as digital clubbing is a reflection of the fact that HIV testing was uncommon at the time. Clinicians would look for clinical indicators for suspicion rather then simply test. Health workers were often reluctant to offer testing HIV status as there was the difficult issue of poor prognosis, not being able to offer any specific therapy to improve morbidity or survival in the patient. There were also concerns about stigmatization and the potential unintended socioeconomic consequences, to which mothers and children were particularly vulnerable.(36) This is a very difficult position for any health worker to face. It was widely stated and believed that people would prefer their children not to be tested, especially because it usually meant that the mother was also HIV-infected, and often the father as well. The potential consequences of testing often seemed too challenging and difficult. The role of HIV pre- and post-test counseling was usually taken up by church-based non-governmental organizations.

At the time we undertook two surveys asking parents and guardians of their knowledge and perceptions about HIV transmission and disease, and attitudes to testing.(37,38) The majority (over 80%) of parents/guardians were open to HIV testing and these attitudes to testing did not differ between the two similar surveys, one of mothers/guardians of well children in immunization clinic and the other of mothers/guardians of children hospitalized with chronic disease suspicious of being
HIV-related. The main reason for testing was that it would help with the management of their sick child, although a minority answered that they would prefer not to know the result.

Research Capacity Strengthening

The University of Malawi College of Medicine has had a number of strong and enduring collaborative partnerships over the years, often with international institutions. These partnerships have provided direct benefit locally in a variety of ways, such as providing local evidence base for common illnesses that can improve and prioritize prevention and management strategies; that can inform teaching and training; that can provide career opportunities in clinical research. In 1995, the University of Liverpool established a tropical medicine research collaboration funded by the Wellcome Trust, UK, and this included establishment of quality microbiology facility. This presented an opportunity to embark upon clinical research to better describe aetiology and management challenges for acute and persistent respiratory disease in HIV-infected and uninfected Malawian children.

Primary objective

To determine the impact of HIV infection on aetiology, clinical presentation and outcome of Malawian infants and children presenting with acute or persistent respiratory disease

Secondary objectives

- To determine the prevalence and describe the clinical presentation of *Pneumocystis* pneumonia
- To determine the causes of bacterial pneumonia in HIV-infected and uninfected children
- To determine the impact of cotrimoxazole preventive therapy on pneumonia and survival in HIV-infected and exposed infants
- To describe the clinical presentation and management challenges of pulmonary tuberculosis in children and the impact of HIV
- To describe the clinical presentation of non-tuberculous causes of chronic lung disease in HIV-infected children
References


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