The impact of HIV on respiratory disease in Malawian children
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Discussion

Each chapter of this thesis examines the various aspects of the impact of HIV infection on aetiology and clinical management of infants and children presenting with acute or persistent respiratory disease in Malawi. The findings and discussion are relevant to other resource-limited HIV-endemic settings in the sub-Saharan African region. This is the region most affected by the epidemic of human immunodeficiency virus (HIV) with high rates of mother-to-child transmission.(1) Of the estimated more than 2.3 million children living with HIV worldwide, approximately 2 million (>85%) live in sub-Saharan Africa. Most of HIV-infected children develop a respiratory disease at some point during the course of their illness and respiratory disease is the major cause of death.(3,4) Further, pneumonia is the commonest cause of death in children globally and the highest case-fatality rates due to child pneumonia are also reported from the sub-Saharan African region.(5) It is estimated that around one-half of all pneumonia-related deaths in children occur in this region. Understanding the association between HIV and childhood respiratory illness in this setting is important to inform more effective clinical case-management or preventative strategies.

Chapter 1 provides by way of introduction a perspective of the background knowledge and situational analysis when I started working in Malawi in 1995. At the time in Blantyre, antenatal HIV prevalence was very high as was the rate of mother-to-child transmission, and the consequence was that HIV infection was having a major impact on childhood morbidity and mortality. Treatment (such as ART) and preventative strategies (e.g. perinatal ART and CPT for HIV-exposed infants) were non-existent and even HIV testing of children with HIV-related disorders was not routine and not widely accepted by health care workers. It was clear that HIV was a major risk factor for incidence and treatment failure for respiratory disease (i.e. pneumonia and PTB). At the time, perceptions of the burden of respiratory disease in HIV-infected African children as either extrapolated from data from HIV-infected African adults (e.g. burden of PcP) or from data from HIV-infected children in different epidemiological settings such as USA (e.g. burden of PTB). The main focus of this PhD was to more carefully examine and describe these issues in order to provide an evidence base for more appropriate treatment and prevention strategies that could be readily implemented even in the resource-limited setting.

There has been the need for frequent revision of guidelines for management of child pneumonia and PTB in the HIV-endemic resource-limited setting over the last 15 years. The context in which studies were undertaken as part of this PhD and the relevance of the findings to national and international guidelines and practice will be particularly emphasised in the discussion below. The main findings from each subsequent chapter will be briefly highlighted. In addition, the clinical relevance and the limitations of the studies will be emphasised and include issues not mentioned or not clearly described in the published papers, mainly due to a lack of space.
Chapter 2 describes a prospective clinical study of 150 infants and children (2 months to 5 years of age) that included nasopharyngeal sampling for diagnosis of PcP. All patients were tested for HIV infection, including by PCR when appropriate as the majority were infants, and 63% were HIV-infected. HIV infection was associated with a significant three-fold increased risk of death. The immunofluorescent technique for PcP diagnosis using NPA samples was established in Department of Paediatrics at QECH in a previous study undertaken in 1995.(6) The study described in Chapter 2 was undertaken in 1996. PcP was confirmed in 11% of cases and accounted for 30% of all deaths. These two studies at QECH, Blantyre, were the first clinical studies to identify PcP as an important cause of severe pneumonia and death in HIV-infected African infants. All cases of PcP were HIV-infected, less than 6 months of age and the in-hospital case-fatality rate was 63% compared to 18% for non-PcP cases. The commonest isolates from blood culture were *Streptococcus pneumoniae* and non-typhoidal *Salmonella*. Clinical features were identified that characterised PcP by comparison with those with bacterial pneumonia. In addition to the high mortality, the morbidity associated with PcP was emphasised by severity and persistence of hypoxia. This is particularly relevant in a resource-limited setting where oxygen availability is often limited.

The findings of this prospective study were supported by earlier autopsy studies and subsequent clinical studies in the region, including from Cote d’Ivoire, South Africa, Zimbabwe, Botswana, Zambia and Uganda.(7-16) These studies all showed that PcP is an important cause of fatal pneumonia in HIV-infected African infants, as was the case elsewhere in the world prior to the introduction of routine CPT for HIV-exposed infants.(17-19) These data are in contrast to the findings that PcP is an uncommon cause of respiratory disease in HIV-infected African adults and children (over 1 year of age), supported by subsequent evidence from community-based cohort studies in Malawi and neighbouring Zambia of people living with HIV older than 1 year of age and not receiving CPT.(20,21) As it became evident that CPT improved survival for HIV-infected African adults and children, it was found that the benefit was due to a reduction in incidence of invasive bacterial disease and malaria rather than to prevention of PcP.(22) At the same time, many health workers and researchers were unaware of the importance of PcP in HIV-infected infants. Studies were being undertaken, including in Malawi, that investigated various strategies to reduce mother-to-child transmission of HIV and yet CPT was not being provided routinely for HIV-exposed or infected infants. Chapter 3 is a viewpoint article that aimed to highlight the epidemiological importance of PcP in HIV-infected African infants and prompt recognition of the need for routine CPT for HIV-exposed infants, including in HIV-endemic Africa.

Chapter 4 provides findings from an observational cohort study that aimed to document morbidity and survival for HIV-exposed (infected and uninfected) infants when using CPT from 6 weeks of age
and comparing to controls. Controls were infants born to HIV-uninfected mothers who did not receive CPT. The original proposal for this study was funded by Wellcome Trust, UK, and aimed to provide CPT for all HIV-exposed infants until 6 months of age, after which they were to be enrolled in a randomised placebo-controlled trial of CPT from 6 months until 2 years of age to examine impact of CPT on morbidity and mortality in HIV-infected infants. At the time, the effectiveness of CPT in HIV-infected children beyond the age group for PcP was uncertain and this was combined with concerns that widespread use of CPT would select for drug-resistant malarial and bacterial infections. The study also aimed to describe incidence of adverse events related to CPT compared to placebo, even though there was already substantial experience from elsewhere that CPT is well tolerated by HIV-infected children.

Enrolment commenced of infants of 6 weeks of age born to HIV-infected mothers and controls (and cotrimoxazole syrup and identical placebo were obtained and labelled by block randomisation) but before any study participants reached 6 months of age, the results of a randomised placebo-controlled trial of HIV-infected Zambian children of 1 year of age and older were communicated to me by the CHAP study Principal Investigator (Di Gibb). It could not be justified to proceed with a placebo-controlled trial in Malawian infants given the strong and significant survival benefit in the treatment arm. That study was subsequently published and is likely to remain the only RCT of CPT in HIV-infected infants and children ever conducted. (20) The trial was stopped early because of clear and significant survival benefits in those receiving CPT. The benefit of CPT on survival in Zambian children related to reduced episodes of pneumonia but not PcP. (23)

The aims of the CPT study was therefore changed from the original RCT to an observational cohort study while following what is now Malawi and WHO guidelines. (24) The study represents the only published data of the use of CPT for HIV-exposed African infants, and was conducted before the recent change in WHO guidelines (November 2009) that now recommends that all HIV-infected infants receive ART regardless of symptoms, clinical or immunological staging. The results are presented in Chapter 4. The study found that the survival for HIV-exposed but uninfected infants was equal to those that were born to HIV-uninfected mothers not receiving CPT. This is important as it has been reported from natural history data that HIV-exposed but uninfected infants have poorer survival than infants born to HIV-uninfected mothers. The incidence of malaria parasitaemia was significantly less in those receiving CPT, providing further evidence of support for the protective effect of CPT against malaria even though a related compound, sulfadoxine-pyramethamine, had been standard treatment for non-severe malaria for the previous decade in Malawi. HIV infection was associated with the poorest survival of the three groups and incidence of pneumonia and sepsis were high. The study was not able to determine if CPT had any impact on survival or morbidity such as due to invasive bacterial disease in the HIV-infected infant cohort because of change in design. There
were no cases of PcP detected in those with severe pneumonia. CPT was well tolerated and was not associated with an increase in adverse events compared to those not receiving CPT. The major limitation of the study was the low proportion of children in each group that were followed until 2 years. Lost-to-follow-up was common as was transfer of the child to another district. This was despite transport money being provided for each follow-up and a dedicated clinic available for intercurrent illness with short waiting time. This emphasises the challenges of effective implementation of a routine CPT policy in this setting. The dedicated clinic has been continued until now since cessation of the study and also serves a role as a staging clinic since ART has become increasingly available for HIV-infected children. Data are still being collected for operational research purposes but it would seem logical that compliance and attendance to such clinics would be improved if such services were positioned closer to communities in peripheral health centres rather than in the large urban hospital.

Chapter 5 provides findings from a more recent prospective clinical study of infants and children presenting to QECH with severe pneumonia that was completed in 2006. In contrast to the previous study in 1996, the study enrolled a larger cohort of infants and children aged up to 14 years, aimed to reduce selection bias for more severe cases and was conducted in a setting where Hib immunisation had been implemented since 2002, and where use of CPT and ART for HIV-infected children was more readily available. The study also attempted to increase the yield for bacterial pathogens by using lung aspiration for select cases, provide further evidence of the importance of invasive NTS disease in African children with clinical pneumonia and describe in vitro antibiotic susceptibility of bacterial pathogens. Finally, the study aimed to examine the prevalence and importance of Mycobacterium tuberculosis and respiratory viruses in Malawian infants and children with severe pneumonia.

This study again found that PcP was a major cause of death in HIV-infected infants and the clinical presentation of PcP was found to be similar as previously described in 1996 study. Also similar was the finding that S. pneumoniae and NTS were the commonest blood culture isolates. Hib vaccine had been introduced since the previous study and interestingly, the presentation of the few Hib cases suggested that protective vaccine efficacy is reduced in HIV-infected children. Lung aspirate was employed in select cases using criteria aimed to increase yield and minimise risk due to the procedure. Although culture yield was low from lung aspirate (prior antibiotic usage was very common in this study group), the use of bacterial DNA PCR found a high yield of pneumococcal DNA. This methodology has not been used before on lung aspirate and we plan to compare relationship between pneumococcal DNA load in blood to that from lung aspirate. This may provide important data as blood culture is known to have such a poor yield in children with bacterial pneumonia especially with prior antibiotic use.
NTS would be considered an unusual cause of bacterial pneumonia but it is a common blood isolate in studies of severe pneumonia in children in tropical Africa. Unlike in adults, NTS bacteraemia is usually not associated with HIV infection in children as was the case in this study. The finding that three of those with NTS had normal CXR supports the explanation that some of the children with NTS septicaemia may not have pneumonia but rather clinical overlap presenting with features consistent with pneumonia. However, in contrast there was also an HIV-uninfected child with consolidation of the left lung with a positive culture for *S. typhimurium* on lung aspirate as well as blood. This case was reported in detail. Irrespective of the pathological association, there is consistent evidence that NTS is a common blood isolate from children in tropical Africa, including Malawi, presenting with clinical features consistent with a classification of severe pneumonia. This means that recommended first-line antibiotic coverage should include coverage for NTS. The main reason for the use of penicillin and gentamicin as first-line antibiotics at QECH for severe and very severe pneumonia in this recent study was the sudden emergence in 2001 of *in vitro* resistance of NTS to chloramphenicol (27) which was associated with treatment failure when chloramphenicol was first-line antibiotic treatment, as was the case in the earlier study in 1996. The change to penicillin and gentamicin is justified by the *in vitro* susceptibility data findings from the more recent study of 2006 and by the finding that case-fatality rate was substantially lower (10% versus 26% in 1996 for 2-59 months of age group). However, the validity of such a comparison is limited by the fact that the study group in 1996 had a higher proportion of very severe cases, higher HIV prevalence and higher prevalence of hypoxaemia.

Attempts to isolate other pathogens were unsuccessful. This aetiology study funded by the Wellcome Trust provided the resources to establish mycobacterial culture at the MLW laboratories but there were difficulties identified by EQAS that suggested that culture was not reliable. There were children with a clinical diagnosis of PTB but only one child had diagnosis confirmed from sputum specimen. The importance of PTB as a cause of severe pneumonia in HIV-infected and uninfected children in this context has been suggested by regional autopsy data and by clinical data from South Africa. (12,16,28,29) Hopefully with the establishment of more and more mycobacterial culture facilities in different settings in TB endemic countries, data will emerge that describe the prevalence and presentation of PTB in African infants and children with acute severe pneumonia. NPA specimens were stored and transported to the Department of Microbiology, University of Liverpool, for intended identification of common respiratory viruses and causes of atypical pneumonia using multiplex PCR technology. The quality of the samples was poor, perhaps because NPA samples were also used on site in Blantyre for PCP and TB diagnosis. Further, the support in Liverpool to undertake the investigation ended with the sudden death of the Head of Department, Professor Tony Hart.
The main conclusion of this recent study is that HIV infection is making a major contribution to the high case-fatality rate due to childhood pneumonia in this region. PcP is a major cause of these deaths and the main impact of HIV is in infants. PcP was confirmed in infants with WHO-classified “severe” pneumonia as well as “very severe” pneumonia. The early use of high-dose cotrimoxazole therapy for presumed PcP in this recent study did not reduce PcP-related case-fatality rate compared to the earlier study. On the other hand, there were no cases of PcP among HIV-infected children receiving CPT at time of admission. Interventions such as reduced mother-to-child transmission of HIV and CPT for HIV-exposed infants have the huge potential to reduce case-fatality rate by reducing HIV prevalence in severe pneumonia and reducing incidence of PcP.

It is not possible to confirm the diagnosis of PcP in resource-limited settings where the majority of cases present. The findings from the two prospective clinical studies that investigated for PcP were utilised to identify for readily-available clinical features that most characterised a diagnosis of PcP. The findings are presented in Chapter 6. Clinical features that help differentiate PcP from bacterial pneumonia include younger age, more severe and persistent hypoxia, less febrile, clear chest on auscultation and higher prevalence of HIV infection. Using just two readily available features of age less than 6 months and being HIV-infected showed a high sensitivity and high negative predictive value as a screening tool for PcP cases among severe pneumonia cases. Addition of other features to the algorithm improved specificity but reduced sensitivity. The features are consistent with current guidelines for suspected PcP diagnosis in children with severe pneumonia. The findings would support revision of current guidelines for treatment of suspected PcP to limit empirical treatment with high-dose cotrimoxazole to infants.

Chapter 7 describes a prospective clinical study undertaken at QECH on children with suspected pulmonary TB. The study aimed to improve yield from sputum smear by using laryngeal swab in addition to self-expectoration and early morning fasting gastric lavage. Mycobacterial culture was not available at the time. The use of laryngeal swab did not improve yield as had been suggested by an earlier study in Uganda and it was observed that such a technique requires careful attention to reduce infection risk for the health worker. Gastric lavage also found a low yield – culture was not done and it was logistically extremely difficult to obtain a specimen in early morning before the child was ambulant (even by aiming to do the procedure before 5 o’clock in the morning). HIV prevalence was high in the study population including in those with confirmed or probable PTB. Tuberculin test was less likely to be reactive and digital clubbing significantly more common in HIV-infected. Other diagnoses aside from PTB were LIP, bronchiectasis and pulmonary Kaposi Sarcoma. However, the largest diagnostic category was the group in which no diagnosis was made. This group had the highest HIV prevalence and the poorest outcome despite all being treated with empirical anti-TB treatment.
This emphasizes the significant challenge of managing HIV-infected children with chronic or persistent respiratory symptoms.

The challenges of childhood TB have gained increased attention over the last decade. The majority of cases occur in the resource-limited setting and confirmation of diagnosis is rarely possible. The challenges for diagnosis and management are compounded in the context of TB/HIV. We rely heavily on one setting in the world for most of the clinical research in child TB/HIV – South Africa – where relatively large numbers of children with TB are confirmed. This may not necessarily always be representative of elsewhere and it is important to encourage the systematic collection of data from other regions. The National TB Control Programme (NTP) in Malawi has a strong tradition of conducting operational research to provide answers and hopefully possible solutions to the many challenges of improved TB control in the resource-limited setting. Malawi remains one of the very few TB endemic countries that have published NTP data of disease burden and outcome for children.(30) Chapter 8 describes the findings of a cross-sectional audit that examined what tools were used for diagnosis of PTB in children receiving anti-TB treatment as inpatients at the time in central, district and mission hospitals in Malawi. Tuberculin solution was only available in a couple of settings where specific external funding had been used for procurement. HIV testing was remarkably uncommon at the time despite that it is recognized as one of the most important investigations for children with suspected TB and should be routine. The majority of children were diagnosed clinically with the aid of a CXR. It is important to document such findings, especially when guidelines are written that do not relate to the possibilities and realities in the field.

Chapter 9 provides a recent summary of the data from the region of the burden of non-tuberculous lung disease in HIV-infected children with radiographic findings illustrated by CXRs of Malawian children. Clinical markers are listed for diagnosis of PcP in HIV-infected infants to assist with differentiation from bacterial pneumonia, and data are reviewed of other opportunistic pathogens such as CMV and their role in HIV-infected infants with pneumonia. CMV was not investigated in the studies above of Malawian children but may have been a significant pathogen in these children. CMV is often reported as a co-infection with PcP and is associated with a high case-fatality rate in South African studies.(9,12,16,31) It is often suggested, though not proven, that the limited benefit of steroids observed when used in infants with PcP may be because of the co-infection with CMV.

The chapter goes on to describe other HIV-related lung disease. Lymphoid interstitial pneumonitis (LIP) and bronchiectasis are not uncommon in HIV-infected Malawian children. Diagnosis is clinical with radiological support. LIP is a “new” disease in the region emerging largely in association with HIV infection in children. It was well described in USA (3) in that context in 1980’s and 1990’s but the spectrum has now changed with use of ART. It is important and very common as a clinical
challenge to differentiate from pulmonary or miliary TB. It can only be confirmed by biopsy and a bronchoscopy study in Durban, South Africa, found it to be the commonest cause of persistent respiratory disease in a select group of HIV-infected children.(32) To add to the complexity for diagnosis, TB is described as a co-infection in children with LIP, LIP is not uncommonly associated with secondary bacterial pneumonia and LIP is often complicated by bronchiectasis especially in those with advanced disease who did not receive early ART. The chapter reviews the epidemiology and pathogenesis of LIP as well as listing clinical and radiological features to assist with diagnosis based on clinical experience in Malawi. Finally, pulmonary Kaposi sarcoma is also described. It appears that this presentation is mainly limited to regions where Kaposi sarcoma was endemic prior to the HIV epidemic such as in Malawi, as colleagues in South Africa rarely report this presentation.(33) It is likely that the spectrum of HIV-related lung disease in children will change with earlier use of ART – but also likely that improved survival may mean that persistent/chronic lung disease will continue to be a major management challenge.

Chapter 10 reports findings from a pharmacokinetic study of anti-TB drugs in Malawian children that examined the impact of HIV as well as other factors such as age and nutritional status. The main finding of the study is that serum levels of pyrazinamide and ethambutol are particularly low in young children (aged < 5 years). Recommended dosages for anti-TB drugs in children have been extrapolated from data derived from pharmacokinetic studies in adults – this is not only the case for anti-TB drugs but for many drugs in children. Other recent studies recognize that higher dosages per weight may be needed for young children (34,35) and WHO has recently revised recommendations to increase range of dosages for the first-line anti-TB drugs including isoniazid and rifampicin as well as pyrazinamide and ethambutol.(36,37) In the past, outcome for child TB using the previously recommended dosages has been very good in HIV-uninfected children with a very low risk of serious adverse events. Outcome for HIV-infected children has been less satisfactory (38,39) and it may be that increased dosages might improve outcome in children with TB and co-infected with HIV by achieving higher serum levels. The increased dosages may lead to higher rates of toxicity although data from children when using the higher dosages suggest that they are likely to be well tolerated.(40)

Chapter 11 is a recent review of the issues of childhood TB in the era of HIV epidemic co-authored with leading experts in the field from Cape Town, South Africa. It aims to provide an up-to-date and comprehensive examination of the epidemiology, diagnostic challenges, management issues and preventative aspects. The search for new, improved diagnostics for child TB has been given a much needed boost in recent years and ironically, the challenges of TB/HIV and MDR TB (mainly in adults) has provided a lot of impetus. It would at least be a small comfort and positive legacy if the added challenges of diagnosing TB in HIV-infected adults and children resulted in improved TB diagnosis for all children with TB.
Chapter 12 is the final concluding chapter that reviews the topic of HIV-related lung disease in African children and focuses on pragmatic management issues. It aims to provide a comprehensive review and includes reference to work and experience compiled during the study of Malawian infants and children. The work associated with this PhD largely pre-dated the era of ART availability in Malawi. There is no doubt that increased uptake of CPT and ART in HIV-infected children will change the spectrum and incidence of HIV-related lung disease and improved survival is likely to increase the management challenges associated with acute and chronic respiratory disease in school-aged children and adolescents. ART is a welcome and important intervention that will reduce morbidity from respiratory disease and improve survival in HIV-infected African children. (41) In conclusion, however, it must be emphasised that there is still huge potential to reduce HIV-related morbidity and mortality from respiratory disease in Malawian infants and children by a reduction in maternal HIV prevalence as well as by implementation of effective and available strategies that identify HIV-infected pregnant women, prevent mother-to-child transmission, provide CPT for HIV-exposed infants and provide care for HIV-infected mothers. A lower incidence rate of new HIV infections in Malawian infants would substantially reduce the burden on the health services and health workers that manage all sick children in Malawi, irrespective of HIV status.
References


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