Challenges of Childhood TB/HIV Management in Malawi

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Abstract

The diagnosis and management of childhood tuberculosis (TB) are major challenges in countries such as Malawi with high incidence of TB and human immunodeficiency virus (HIV) infection. Diagnosis of TB in children often relies only on clinical features but clinical overlap with the presentation of HIV and other HIV-related lung disease is common. The tuberculin skin test (TST), the standard marker of *M. tuberculosis* infection in immune competent children, has poor sensitivity in HIV-infected children and is not usually available in Malawi. HIV test should be routine in children with suspected TB as it improves clinical management. HIV-infected children are at increased risk of developing active disease following TB exposure which justifies the use of isoniazid preventive therapy (IPT) once active disease has been excluded but this is difficult to implement and appropriate duration of IPT is unknown. HIV-infected children with active TB experience higher mortality and relapse rates on standard TB treatment compared to HIV-uninfected children, highlighting the need for further research to define optimal treatment regimens. HIV-infected children should also receive appropriate supportive care including co-trimoxazole prophylaxis and anti-retroviral treatment (ART) if indicated. There are concerns about concurrent use of some anti-TB drugs such as rifampicin with some ARTs.

Introduction

Malawi, like other HIV-endemic countries in sub-Saharan Africa, has among the highest incidence rates of TB in the world.[1-3] As a direct consequence, TB is common in Malawian children but this is not so well appreciated due to the difficulties of confirming TB in most children who are treated for TB. The focus on child TB has been greater in Malawi than in many other similar resource-poor countries. This review aims to highlight some of the common challenges of managing childhood TB in the HIV endemic setting of Malawi with particular reference to national data.

Epidemiology

The burden of childhood TB provides an accurate measure of the level of TB control achieved in a particular community.[4,5] A tuberculin survey of school-aged Malawian children undertaken in 1994 found an annual risk of TB infection of around 1%. A nationwide survey of TB disease was conducted by the Malawi National Tuberculosis Control Programme (NTP) in 1998.[6] Children accounted for 12% of all cases treated for TB and for 21% of all sputum smear-negative PTB cases. Consistent with reports of child TB from elsewhere, smear-negative PTB accounted for 66% of all child TB cases, smear-positive PTB for 4% and extrapulmonary TB for 30%. The commonest forms of extrapulmonary TB were TB adenitis, pleural effusion and spinal TB. Although classified as "sputum smear-negative PTB" by the NTP, most of these child cases have not had sputum examined as young children can usually not expectorate sputum and gastric lavage is rarely done in Malawi.

Children rarely develop sputum smear-positive TB[6] so may be excluded from recording and reporting practices in the resource-poor setting where TB control efforts focus primarily on the most infectious cases in an effort to contain the epidemic. Recent World Health Organization (WHO) guidelines made two important recommendations regarding recording and reporting practices; NTPs should now include HIV-related information for all TB cases[7] and information on TB in children should be broken down into 2 age groups of 0-4 years and 5 years and older.[8] Such data are now being collected routinely by the Malawi NTP and NTP guidelines are being revised with inclusion of some of the improvements suggested by WHO.[8] This will be useful for future monitoring and evaluation purposes although the uncertainty of TB diagnosis remains a problem, particularly in HIV-infected children.[9]

Evidence from clinical and autopsy studies with large numbers of African children with confirmed TB show that TB is associated with HIV infection.[10-13] This is because HIV-infected children have an increased risk of TB exposure and/or an increased risk of progression to active disease following infection.

As well as an increase in the incidence of sputum smear-positive TB, the HIV epidemic has resulted in a lower peak age-prevalence, so that the highest incidence of infectious cases now occurs among young adults who are often parents of young children.[14] The overall effect of HIV on TB transmission within communities remains uncertain. While HIV-infected adults more often have sputum smear-negative TB, they still pose a considerable transmission risk. In addition, reports from Tanzania and Botswana indicate that many are sputum smear-positive and/or are only diagnosed after a considerable period of symptomatic disease, which indicate that HIV-infected TB patients contribute significantly to TB transmission in endemic areas.[15,16]

The children most at risk of developing TB following primary infection are those that are immunocompromised either due to young age[4], malnutrition or HIV infection. In a prospective study from Côte d'Ivoire, the risk of TB was 4 times higher in children with CD4% below 15% than in those with CD4% above 15%.[17]

Diagnosis of TB and impact of HIV

The diagnosis of childhood TB presents a major challenge as bacteriologic confirmation is rarely achieved. Sputum smear microscopy is often the only diagnostic test available but most TB occurs in young children and it is difficult to get a sputum sample from younger children under 8 years. Further, PTB in young usually presents as primary complex disease with lymphadenopathy so even if sputum is available it usually has few bacilli (paucibacillary disease). Therefore, sputum smear microscopy is positive in less than 10-15% of children

with probable TB[18,19] and these are often adolescents with cavitatory disease. Because of the paucibacillary nature of disease in children, the yield from sputum will be increased by culture e.g of sputum obtained by 2-3 fasting gastric aspirate samples to about 30-40%. In Malawi, gastric aspiration is rarely done[20] and culture is rarely available. A further problem with reliance on culture is that it takes 6-8 weeks for a result yet a decision to treat for TB or not usually needs to be made well before this time. Sputum sampling by other methods such as induced sputum sampling with hypertonic, nebulised saline and chest physiotherapy or nasopharyngeal aspiration are more convenient and show a higher yield than gastric aspiration but still rely on culture facilities for highest yield.[21-23] The potential of induced sputum was first described in Malawian children[21] but its use is still limited to the research context.

In the absence of bacteriologic confirmation, the diagnosis of childhood TB is often based upon the triad of 1) close contact with an index case; 2) positive tuberculin skin test (TST); and 3) suggestive signs on the chest radiograph (CXR).[8] TST is unfortunately not usually available in Malawi although it is recommended by WHO.[8] The diagnosis of childhood TB depends mainly on clinical features and the subjective interpretation of the CXR[20] even though the CXR has well-recognized limitations. A variety of clinical scoring systems are available but they have not been validated.[24] Symptoms such as a cough of >3 weeks duration and failure to thrive are non-specific for TB[25] and also common in HIV-infected children without TB.

The diagnostic problems are more pronounced in HIV-infected children and current diagnostic algorithms perform poorly in this group.[28] Factors contributing to these additional diagnostic difficulties are that:

- HIV-infected children are more likely to be exposed to an adult index case because they live in close contact with HIV-infected adults who have a high incidence of PTB. This means that a positive contact history of TB may suggest infection with TB or HIV if the contact is the child's parent and so the clinical symptoms of the child may represent either disease or both. This underlies the importance of HIV testing rather than depending on clinical screening.
- Weight loss, failure to thrive and low grade fever are typical features of both TB and HIV.
- A persistent chronic cough as a guiding symptom is a less distinct symptom for PTB in a child with HIV related recurrent pulmonary infections or chronic lung disease.
- Rapid TB disease progression may occur in HIV-infected children, reducing the sensitivity of diagnostic approaches that focus on persistent, non-remitting symptoms.
- TST is much less sensitive than in HIV-uninfected children[29-31]
- CXR interpretation is complicated by HIV-related co-morbidity such as bacterial pneumonia, lymphocytic interstitial pneumonitis (LIP), bronchiectasis, pulmonary Kaposi sarcoma (KS) and the atypical presentation of TB in immune compromised children.[9,29]

The TST is negative in the majority of HIV-infected children with bacteriologically confirmed TB[29,30] despite using a reduced induration size cut-off of ≥5mm. The lower cut-off of 5 mm for TST is now recommended[8] although there is no evidence for this recommendation. In practice, it is probably not so important as TST reactions are usually 10 mm or more or 0 mm – a reaction of 5-10 mm is uncommon. The clinical disease presentation is usually similar to that seen in HIV-uninfected children though HIV-infected children are more prone to develop disseminated TB.[31-33] However it is more difficult to differentiate TB-related symptoms from those caused by other HIV-associated conditions. Additional clinical and radiological signs may be helpful to differentiate TB from HIV-related lung pathologies such as LIP, bronchiectasis or pulmonary KS, but there is considerable clinical overlap and co-morbidity is common in HIV-infected children.[34]

Diagnostic approach in HIV-infected child with suspected TB

The diagnostic challenges for child TB in the HIV-endemic setting have recently been reviewed.[35] It is essential to know a child's HIV status as this will assist diagnosis as well as guide clinical management. The list of possible causes of chronic respiratory symptoms is considerably shorter if the child is HIV-uninfected. If the child is HIV-infected, then effective interventions such as cotrimoxazole prophylaxis and anti-retroviral therapy (ART) need to be considered in addition to TB treatment.

The decision if and when to initiate TB treatment remains difficult until diagnostic methods that are more accurate and easier to perform are found and become available. Remaining alert and willing to reconsider a diagnosis is crucial. Table 1 shows some of the main classic features for PTB and other HIV-related lung diseases. Being a structured summary it simplifies and neglects to some extent the complexity of the problem but may help the clinician to approach the problem when confronted with a symptomatic child.

A CD4 count or CD4 percentage may help to draw diagnostic conclusions. In case of not significant or mild immunosuppression the TST is more likely to reflect a truly negative result and symptoms are more likely to be related to TB rather than to HIV infection. If advanced or severe immunodeficiency is present, TST and clinical features are less reliable and more emphasis has to be put on CXR findings and the patient's contact history. HAART should be initiated soon.

Other causes of chronic respiratory symptoms in HIV-infected children

Autopsy and bronchoscopy studies have shown that LIP is common in HIV-infected African children.[10,12,34] Clinical findings of digital clubbing, parotid swelling and persistent generalised lymphadenopathy support the diagnosis of LIP though are not always present. A careful history of TB contact is important and TST should be undertaken because a positive result is helpful. CXR is also helpful as LIP is typically characterised by diffuse bilateral reticulonodular infiltrates and bilateral adenopathy whereas PTB is usually characterised by focal parenchymal abnormalities with adenopathy. The diffuse nodular pattern of LIP can be confused with miliary TB. Table 2 lists features that can help distinguish between PTB, LIP and miliary TB.

Bronchiectasis is common in HIV-infected children and can

Table 1. Clinical and diagnostic features of TB and other lung diseases in HIV infected children

	Typical features PTB	Typical features CLD	Classic features other HIV-related pulmonary diseases	Remarks
Leading symptom	Cough >3 weeks, persistent, increasing in character no improvement on antibiotic treatment	Cough commonly for a year or longer, persistent or intermittent but no progressive character, - productive in case of bronchiectasis - dry in case of LIP, may be associated with marked increased respiratory rate or distress in severe cases some improvement but not resolving on antibiotics LIP may respond to steroids	KS: Gradually (sometimes rapid) increasing cough and respiratory distress No response to antibiotics PcP: Increasing respiratory distress, dry cough response to Cotrim depending on time of treatment initiation and co-morbidity Recurrent bacterial pneumonia: Recurrent cough with (complete) remission in between.Responding to antibiotic treatment	A change in character of cough in case of pre-existing lung pathology may mark onset of TB disease At least one, preferably two different antibiotic groups should have been prescribed in adequate dose and length of time
Contact history	Sputum positive household contact	No contact (or sputum negative)	KS /PcP / recurrent pneumonia:No contact (or sputum negative)	Chronic cough of a contact person may be undiagnosed TB
Symptoms	Low grade fever Weight loss Night sweats	Variable fever Variable weight loss No night sweats	KS: no fever PcP: low grade to moderate fever Recurrent pneumonia: fever associated with episodes of cough	
Clinical findings	Focal or generalized findings on chest examination Any age	Clubbing Generalized lymphadenopathy Parotid enlargement Age > 2 years	KS: Focal or generalized findings on chest examination, blood stained fluid in case of effusion, further KS lesions on other body sites PcP: Only mild (or no) crepitations on auscultation, marked respiratory distress, hypoxia Age: infancy Recurrent pneumonia: Respiratory distress, focal findings on auscultation	
Chest X-ray	Lymph node enlargement, primary complex, asymmetric infiltrations	Bronchiectasis: Honeycombing, commonly lower lobes LIP: Lymph node enlargement, reticulonodular infiltrations, symmetric pattern of changes	KS: effusion, nodular diffuse infiltrations PcP: diffuse, interstitial infiltrations, hyperinflation Bacterial pneumonia: focal infiltrations	Repeated Chest X-rays can be useful if taken in a not too short time distance
TST	> 5mm	negative	negative	Response altered, depending on level of immunosuppresion

complicate recurrent bacterial pneumonia, LIP and PTB.[34] Digital clubbing is typical in bronchiectasis, as in LIP, but bronchiectasis, unlike LIP, is characterised by a productive cough with copious, purulent sputum and typical focal chest radiograph abnormalities with bronchial dilatation.

The importance of other causes of chronic lung disease in HIV-infected children can vary substantially between regions.[34] Nocardiosis is described in a Malawian child[21] and also needs to be distinguished from PTB or bacterial pneumonia. Opportunistic fungal infections include pulmonary aspergillosis, candidiasis and cryptococcosis but these are rarely reported from the region. In HIV-infected Malawian children, the commonest malignancy causing chronic respiratory symptoms is pulmonary KS. At presentation, it is usual to find typical KS lesions elsewhere, especially on the palate. Outcome is poor and palliative care is important.

Treatment

Preventive Chemotherapy

Current WHO guidelines advise that all children under 5 years of age in close contact with a sputum smear-positive index case should be provided preventive chemotherapy once active TB has been excluded.[8] Symptom-based screening is adequate and TST and CXR are not required for asymptomatic children; only symptomatic children require further investigation to exclude active TB.

Table 2. Clinical and radiographic features that may differentiate pulmonary and miliary TB from LIP

Feature	PTB	Miliary TB	LIP
Clinical			
Respiratory symptoms	Common	Variable	Common
Persistent fever	Common	Common	Common
Wasting	Common	Common	Variable
Generalised lymphadenopathy	Uncommon	Uncommon	Common
Parotid enlargement	Rare	Rare	Common
Clubbing	Uncommon	Rare	Common
Chest radiograph disease			
Focal parenchymal	Common	Uncommon	Uncommon
Diffuse micronodular	Absent	Common	Uncommon
Diffuse reticular	Absent	Absent	Common
Lymphadenopathy	Common	Uncommon	Common

Isoniazid preventive therapy (IPT) has proven efficacy to prevent active disease after documented TB infection[36], though uptake and adherence is often very poor.[37,38] Only 7% of cases of sputum smear-positive cases in Blantyre presented child contacts to the paediatric TB clinic for screening.[38] Screening and IPT are important in HIV-infected children due to the high risk of disease progression and the well-documented benefits of IPT in adults with TB/HIV.[39,40] The optimal duration of IPT for these children is not known.

Curative treatment in HIV-infected children with TB

Treatment for HIV-infected children with TB was recently reviewed.[35] Present recommendations are to treat HIV-infected children with TB with the same regimens as HIV-uninfected children with TB.[8] Thiacetazone was discontinued in Malawi in 1995 because fatal Stevens-Johnson reactions were common in HIV-infected adults and children. Ethambutol was introduced to replace thiacetazone. Concerns existed about the toxicity of ethambutol in young children but a literature review at the time conclude that the use of ethambutol was safe[40] and ethambutol is now recommended even in young children at the recommended dose of 15-20mg/kg/day[41]; this is also supported by clinical experience over the last decade. Rather than toxicity, the problem for ethambutol as well as for the other anti-TB drugs may be that the current recommended doses are too low in young children[42,43] and achieving effective serum levels may be particularly important for adequate treatment response in HIV-infected children.

There is an increased risk of disease relapse in HIV-infected children[44] and consideration may need to be given to prolong treatment duration but there have been no randomized controlled trials to substantiate this. A multi-centre trial compared the use of ethambutol and isoniazid (EH) in the continuation phase to a rifampicin-based regimen and reported superior outcomes with the rifampicin-based regimen, especially in HIV-infected adults.[45] This study resulted in Malawi NTP recently substituting rifampicin for ethambutol in the continuation phase. However, interactions between anti-retroviral therapy (ART) and rifampicin remain a potential problem.

An increased risk of hepatotoxicity or cutaneous reactions and the reduction of NNRTI levels by 20-60%, especially in case of concomitant administration with Nevirapine (NVP) are of concern.[46] The risk of possible earlier development of resistance due to sub-therapeutic NVP levels and ART failure is debated. In adults NVP levels are regularly way above the minimal therapeutic level of 3µg/ml which makes a reduction less relevant.[47,48] In children the situation with regards to sufficient drug levels is less favorable.[49] Future studies have to determine whether the risk for virological failure is increased in adults and/or children in this group of patients.

Treatment Outcome

It is well documented and not surprising that HIV-infected children have a poorer response to TB treatment and higher mortality than HIV-uninfected children. Possible reasons for this include:

- higher incidence of co-infections with other pathogens
- poorer absorption and low levels of anti-TB drugs especially in the younger children or in children with gastrointestinal infection.
- misdiagnosis of TB in children with HIV-related lung disease such as LIP, bronchiectasis or KS with the possibility of missing the diagnosis in the first place, leading to late initiation of TB treatment or starting wrongly on TB treatment whereas ART is required.
- presence of underlying chronic lung disease resulting in poor penetration of drugs into fibrotic or bronchiectatic areas
- poor adherence to treatment because of chronic illness or death of the parent responsible for the child's treatment
- advanced immunosuppression and severe malnutrition

In adults and children, a large proportion of HIV/TB-related deaths occur in the first couple of months after TB therapy has commenced[3,11] but reasons for this are not well understood

Drug Interactions

TB is frequently the presenting disease in children with previously undiagnosed HIV infection who may have advanced HIV disease requiring ART. The Centers for Diseases Control and Prevention (CDC) has established guidelines for initiating ART in adults presenting with TB and for initiating anti-TB treatment for those already on ART. As both HIV and TB have their highest mortality in children under one year of age, most clinicians caring for these very young children would initiate ART early with anti-TB treatment. In older children, in the absence of severe immunosuppression, it is reasonable to complete the anti-TB treatment first, but there is a need for more data to optimally define when to initiate ART in children with TB.

Significant drug interactions occur between the rifamycins, especially rifampin, and some of the non-nucleoside reverse transcriptase inhibitors (NNRTIs) and/or protease inhibitors (PIs). The known effect of lower NNRTI levels when combined with rifampin led to a change of the Malawian guidelines for antiretroviral treatment. Patients starting ART while on a rifampin containing TB regimen are not any longer receiving a lead in phase which contains only half of the

Nevirapine dose for the first two weeks[50]. Concerns about subtherapeutic NVP levels in case of co-administration remain. Rifampin is regarded as being compatible with all nucleoside reverse transcriptase inhibitors (NRTI's) although it promotes the glucoronidation and elimination of zidovudine (AZT). Abacavir, another NRTI that has been used in triple NRTI regimens, is also eliminated by glucoronidation. Little pharmacokinetic information is available on the interaction of these drugs but numerous studies are ongoing.

Other HIV-related issues

Trimethoprim-sulphamethoxazole (TS) prophylaxis

TS prophylaxis has proven beneficial in reducing the risk of Pneumocystis jiroveci (PcP) pneumonia, invasive bacterial infections and malaria in HIV-infected adults and children.[51-54] A randomized controlled trial of TS prophylaxis in HIV-infected Zambian children of 2 years and older showed significant survival benefit.[50] Routine TS prophylaxis is now recommended by the WHO for all HIV-infected children including those with TB.[54] TS prophylaxis is also recommended for HIV-exposed infants because PCP is common in that age group.

Nutritional support

An HIV-infected child has higher caloric requirements, even in case of non-advanced immunosuppression[55]. This need rises further in case of additional consummating infections as PTB. Providing additional nutritional can be a crucial intervention for children with HIV and PTB.

Immune Reconstitution Inflammatory Syndrome (IRIS)

Transient worsening of symptoms such as fever, increasing lymphadenopathy, exacerbation of intracerebral tuberculomas, pleural effusions and even acute respiratory distress syndrome have been reported after the initiation of ART in severely immune compromised patients.[58-60] This temporary exacerbation of TB symptoms and signs is mainly ascribed to the effects of immune reconstitution, although a "hypersensitivity" reaction to antigens released by killed TB bacilli may also contribute. It does not indicate TB-treatment failure and usually subsides spontaneously, although severe cases may require treatment with corticosteroids. If a child is not yet receiving antituberculosis treatment initiation is indicated as soon as the diagnosis is made[8]. ART drugs should be continued and -if resources allow- adjustments in the ART regimen to avoid drug interaction should be made. In a recent prospective survey of 152 Thai children with low CD4 percentages (<15%), IRIS was documented in 19%, usually within 4 weeks of ART initiation. Two recent reports also documented IRIS due to M. bovis BCG in HIV-infected children initiated on ART.[62,63] The risks of IRIS, higher drug toxicity and potential drug interaction make it difficult to determine the best point in time to initiate ART if a child receives TB treatment. Advanced immunosuppression may not allow waiting until TB treatment is completed. WHO recommends to hold co-administration for a time interval of at least 2 -8 weeks; clinical HIV-stage. A CD4 count may help to guide more individual decision making.[8,63,64]

BCG vaccination

Neonatal BCG is particularly protective against disseminated (miliary) disease in young HIV-uninfected children (<2 years of age)[65,66] but does pose a risk of disseminated BCG disease.[61] WHO currently advises BCG vaccination of all asymptomatic HIV-exposed infants in TB endemic areas with careful monitoring for the development of BCG-related disease.[66-68] BCG disease occasionally presents in Malawian children. The usual presentation is in an HIV-positive infant of less than 6 months of age with marked axillary lymphadenopathy on the same side as the BCG vaccination site (usually right) and with marked failure to thrive. It can cause respiratory or more disseminated disease.

Perinatal infection

Some Malawian women in their reproductive years are dually infected with TB and HIV. Maternal TB is a cause of increased maternal mortality. Maternal TB and/or HIV also has an adverse effect on perinatal outcomes with increased prematurity, low birth weight and neonatal mortality rates, while severe and rapid progression of HIV disease have been reported in neonates co-infected with TB and HIV.[69-71] First-line TB drugs have few adverse effects during pregnancy except for streptomycin which may affect the hearing of the baby. The combination of both anti-TB medication and ART during pregnancy is more complicated but ART has proven efficacy to reduce vertical transmission of HIV and is routinely used during pregnancy in many settings. Active TB case-finding may be considered in all HIV-infected pregnant women presenting for antenatal care in an attempt to decrease the perinatal risks for mother and baby.

The management of a baby born to a mother who is co-infected with TB and HIV is complex; the first principle is to ensure that the mother is on optimal treatment and to regard the baby as being at risk for TB, HIV and other congenital infections. Counseling and preventive measures to reduce the risk of HIV transmission to the baby is needed together with appropriate HIV-related care. The possibility of active TB in the baby needs to be considered and treated. If the baby does not have active TB, then IPT is required if the mother is symptomatic or has been on anti-TB treatment for less than 2 months.

Conclusion

The diagnosis of TB infection and disease is particularly difficult in HIV-infected children. Routine HIV testing is an important part of the diagnostic work up, as knowledge of the child's HIV status will guide the clinical management. In addition to IPT or treatment for TB, the child with HIV/TB can benefit from other interventions such as cotrimoxazole prophylaxis and ART. Although there are major diagnostic and therapeutic challenges, the management of children with TB/HIV could be vastly improved by better implementation of readily available interventions.

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