HIV-TUBERCULOSIS CO-INFECTION IN CHILDREN

Authors: **Elizabeth Whittaker, Anna Turkova, Alasdair Bamford**

Date of preparation: **June 2015**

Next review date: **June 2019**

Abbreviations:

AFB	Acid fast bacillus
ART	Antiretroviral therapy
ARV	Antiretroviral
ATT	Antituberculous therapy
ATV/r	Ritonavir boosted atazanavir
DOT	Directly observed therapy
DRV/r	Ritonavir boosted darunavir
EFV	Efavirenz
IGRA	Interferon gamma release assay
IRIS	Immune reconstitution inflammatory syndrome
LFT	Liver function tests
LPV/R	Ritonavir superboosted lopinavir
LTBI	Latent tuberculosis infection
MDR-TB	Multi-drug resistant tuberculosis

NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside/nucleotide reverse transcriptase inhibitor
NVP	Nevirapine
PI	Protease inhibitor
TB	Tuberculosis
TST	Tuberculin skin test
VOT	Video observed therapy

PART 1. SUMMARY DOCUMENT

1. Screening

- All children should be screened for TB at first presentation to HIV clinic with relevant clinical history and examination, chest x-ray and TST+/-IGRA

- Further symptom based screening should be performed at each clinical review with appropriate investigations if concerns.

- Following any exposure to an infectious case of TB, all children should be - screened for active disease as above.

- All children diagnosed with TB should have an HIV test.

2. Management of Latent TB infection (LTBI) & Chemoprophylaxis

- All HIV-infected children exposed to an individual with infectious TB and all children with evidence of latent TB infection should have preventive TB treatment (once active TB disease has been excluded).

- 3 months Isoniazid and Rifampicin if not on ART
- 6 months Isoniazid if on ART

3. Diagnosis of Active TB disease

- Radiological Investigations

- Chest x-ray +/- CT chest for clarification of extent/severity of disease
- Abdominal Ultrasound for hepatosplenomegaly, lymphadenopathy
- Consider cranial imaging if any suggestion of disseminated disease
- Other imaging as clinically indicated

- Microbiological Investigations

- Children with suspected pulmonary TB should have at least two respiratory specimens collected (see Part 2 “Microbiological assays” below)
- Children with suspected extrapulmonary TB, in addition to specimens from the affected sites, should have respiratory samples collected
- All specimens should be processed for AFB microscopy, TB culture and molecular tests as available (Xpert MTB/RIF or MTB PCR)

- Immunological Investigations

- TST
- IGRA where available.

Note: negative IGRA and/or TST do not rule out active or latent TB

4. Treatment of Active TB disease

- Management of TB-HIV co-infection, especially concurrent anti-tuberculous therapy (ATT) and ART, requires selection of antiretroviral drugs with minimal drug interactions where possible, dose adjustment and careful monitoring of therapeutic drug levels and for overlapping toxicity

- All children diagnosed with TB should be started on ART. ART should be initiated within 2 and 8 weeks of TB treatment in children with severe and moderate immunosuppression respectively. ART may be deferred in patients with no/mild immunosuppression until TB treatment is completed if there are concerns regarding drug interactions, toxicities or high pill burden affecting adherence and close clinical monitoring can be assured .

- Children already on effective ART should have their regimen preserved if possible. Efavirenz-based therapy is preferable in children >3yrs of age. If efavirenz is contraindicated, children could start with nevirapine (if <3 yrs of age) or PI-based ART provided that therapeutic drug monitoring is in place to control for drug interactions. See Table 3 for ART choices in children receiving ATT.

- Children with TB co-infection should be managed jointly with/by a consultant with expertise in treatment of paediatric TB

- Children with TB-HIV co-infection should receive directly observed therapy (DOT)

- Duration of therapy in uncomplicated TB should be the same as in non-HIV infected children

- Duration of therapy in complicated TB, or in the presence of moderate to severe immunocompromise, depends on the response to treatment

- Corticosteroids may be used for the management of some complicated forms of TB, e.g. tuberculous meningitis, pericardial TB and severe airway obstruction by TB lymph glands. In tuberculous meningitis, 2-4 mg/kg/day of prednisolone (or equivalent dose of dexamethasone 0.6mg/kg/24hr) is recommended with gradual withdrawal over 4-8 weeks.

- Each child should be assessed 2 weeks after the start of TB treatment then reviewed monthly with clinical monitoring, including symptom assessment, weight measurement, assessment of adherence to treatment and enquiry about any adverse events. Dosages of anti-TB drugs and ART should be adjusted to account for any weight gain.

- If ART and ATT are co-administrated with significant drug-drug interactions, dosages of ART and ATT should be adjusted based on results of TDM.

- Screening for adverse events – patients should be monitored clinically for signs of toxicity, especially hepatotoxicity. LFTs can be performed at the time

of other monitoring bloods (e.g. HIV viral load, TDM etc.). One suggested schedule for monitoring of LFTs is: 2,4,8 weeks and then 2-3 monthly.

5. Management of Relapse, Treatment Failure and Drug Resistance

- Adherence, drug levels, drug resistance, TB-IRIS and alternative diagnoses should be considered in the event of poor treatment response, treatment failure or relapse.

- A specialist in drug-resistant TB (DRTB) should be involved in the management of DRTB contacts and cases.

- Non-tuberculous mycobacteria may present in a similar fashion to TB in severely immunocompromised children and should be considered in the event of treatment failure.

6. Immune Reconstitution Inflammatory Syndrome (TB-IRIS)

- TB-IRIS should be considered in all children who present with either an exacerbation of known TB disease or with the development of TB symptoms following commencement of ART.

- Anti-TB treatment should be continued/commenced.

- The addition of corticosteroids and referral to/joint care with a specialist centre should be considered.

7. Prevention of Tuberculosis

- BCG vaccination is not recommended in children who are known to be HIV infected.

- BCG vaccination may be given to HIV exposed infants at low risk of HIV transmission (maternal viral load undetectable at/after 36/40 gestation) if at high risk of TB exposure.

- BCG disease should be considered in infants who were given BCG vaccine prior to a diagnosis of HIV infection presenting with lymphadenopathy or other symptoms consistent with TB. Disseminated BCGosis is a rare but serious complication in HIV-infected children. Local reaction at the site of BCG is much more common and less serious, but may result in localized BCG-IRIS after starting ART.

PART 2. BACKGROUND AND JUSTIFICATION

Epidemiology and background

The UK is classified as a low TB-incidence country, with overall rates of 12-14/100,000 population, with small areas in metropolitan centres such as London and Birmingham reporting rates of >40/100,000 population.[1,2] Despite this, recent data on TB incidence from CHIPS showed that HIV-infected children in the UK/Ireland remain at substantially higher risk of TB compared to the general population.[3] This is likely to be due to a combination of environmental and immunological risk factors. The majority of newly diagnosed HIV-infected children in the UK/Ireland are foreign-born and therefore at higher risk of exposure to TB (http://www.chipscohort.ac.uk).[4] Younger age and immune status are the greatest risk factors for the development of TB disease following exposure.[5] TB decreases the CD4 count and worsens immunodeficiency.[6] Children with HIV infection are 20 times more likely to develop TB and have a 6 times greater risk of dying from TB than HIV uninfected children.[7,8] Anti-retroviral therapy (ART) has a great potential to reduce the risk of TB disease.[9] **All children diagnosed with TB should be screened for HIV** and **all children with HIV should be screened for TB disease.[10]**

Screening, Chemoprophylaxis and Management of Latent TB infection

All HIV-infected children should be screened for TB infection at HIV diagnosis with history of symptoms and possible exposure, clinical examination, TST or IGRA and chest X-ray. Further symptom screening should occur at every visit and repeat TST/IGRA and CXR should be performed following contact with an infectious TB case.[11] Preventive TB treatment has been shown to effectively reduce the incidence of TB disease in HIV-positive children exposed to an infectious TB source case.[12] All HIV-infected children exposed to an individual with infectious TB (including all those exposed to individuals with respiratory TB) and all those with evidence of latent TB infection (positive TST or IGRA) and no clinical or radiological signs suggestive of TB disease should have preventive TB treatment. A positive TST may be defined as a reaction

>5mm.[13] Either of the commercially available interferon gamma release assays (T-Spot.TB and Quantiferon) can be used.
A Cochrane review of preventive regimens in HIV infected individuals aged over 13 years found no difference in incidence of TB disease between a 6-month regimen with isoniazid monotherapy and 3 months of treatment with co-administered isoniazid and rifampicin.[14] However, the combination regimen was associated with more discontinuations because of adverse effects. Children tolerate combination therapy well and a 3 month regimen of a combination of isoniazid and rifampicin has shown to be effective.[15] Children with HIV infection exposed to TB or with LTBI who are not receiving ART can be treated with either 3 months of isoniazid and rifampicin or 6 months of isoniazid. For those on ART, the preferred preventive treatment regimen is 6 months isoniazid. Following exposure to drug-resistant TB, preventive therapy should be discussed with a drug-resistant TB expert.

Diagnosis of TB-HIV Co-infection

Clinical Presentation

Clinical presentation of TB disease among children with HIV infection is similar to that in children without HIV infection[6] although HIV infected children have higher rates of severe disease and higher rates of extrapulmonary TB compared to HIV uninfected children.[16] Most tuberculosis infection is latent and asymptomatic. Early clinical manifestations of disease may include fever, weight loss, cough, night sweats and chills, however, children with TB may have relatively few or non-specific symptoms and a high index of suspicion is required. Poor weight gain may be the only presenting feature initially.

Diagnosis of TB in HIV-infected children is notoriously challenging as the presentation may be very non-specific and the combination of clinical features frequently overlaps with other common clinical presentations in HIV. There is an overlap of radiological findings between TB and other HIV related lung disease, including lymphocytic interstitial pneumonia (LIP). Furthermore, paediatric TB is often paucibacillary, making microbiological confirmation less likely. In addition, the tuberculin skin test (TST) is less sensitive in HIV

infected children, especially at low CD4 counts.[17] The optimal approach to the diagnosis of co-infected children is still not clear, and may differ between areas of high and low TB endemicity. The challenges in diagnosing TB in HIV-infected children are multiple. The approach to the diagnosis for any child with suspected TB as recommended by the World Health Organization (WHO) is summarized in the left-hand column of Table 1.[18] The specific challenges posed to this by concurrent HIV infection are highlighted.

Table 1 Impact of HIV infection on diagnosis of TB in children

Elements of diagnosis of TB in children	**Impact of HIV infection**
Careful history including history of TB contact	*Especially important due to poor sensitivity of TST to identify TB infection*
Careful history of symptoms consistent with TB	*Lower specificity: clinical overlap between symptoms of TB and HIV*
Clinical examination including growth assessment	*Lower specificity: malnutrition is common in HIV infection*
Tuberculin skin testing	*Lower sensitivity: TST positivity decreases with increasing immunosuppression*
Bacteriological confirmation whenever possible	*Important in both HIV infected and uninfected children*
Investigations relevant for suspected pulmonary TB and extrapulmonary TB	*Wider range of diagnostic possibilities because of other HIV-related disease*

Chest x-ray may show hilar lymphadenopathy, segmental involvement, cavitation, pleural effusion or a miliary pattern. However, radiological changes may be less well-defined in HIV-infected children. CT chest may be helpful in confirming the diagnosis of TB.

Microbiological Assays

Despite being positive in less than 30% of cases, it is important to obtain microbiological confirmation of infection where possible, and ideally determine antibiotic sensitivities.

Whilst older children may expectorate and produce sputum samples, most younger children will require either gastric washings, induced sputum or broncho-alveolar lavage to aid diagnosis.[13] Non-invasive methods of specimen collection may be of value, including nasopharyngeal aspirate (NPA) and stool.[19,20] In some cases, newer techniques such as endobronchial ultrasound guided biopsy of mediastinal lymph nodes may be diagnostic. For extrapulmonary disease, tissue sampling method will be determined according to site of disease (Table 2).

Recent advances in both culture-based (MODS assay, BACTEC MGIT 960, etc) and non-culture based diagnostics (PCR based assays such as Xpert MTB/RIF (Cepheid, Sunnyvale, Ca, USA)) increase early TB case confirmation compared to traditional mycobacterial culture. PCR, although not as sensitive as conventional culture, does provide a rapid result and information about drug resistance and in the UK setting should be used in conjunction with traditional microscopy and culture. These newer types of assay may have a particular role in distinguishing MTB from atypical mycobacteria that may cause similar clinical disease patterns in very immunocompromised children. However, these tests are most effective when applied to samples in which mycobacteria have been detected microscopically. The performance of Xpert MTB/RIF, an integrated sample processing and nucleic acid amplification test for detection of Mycobacterium tuberculosis and resistance to rifampicin has shown particular promise to date in both respiratory and non-respiratory samples[19,21-24] and is recommended by WHO as first-line for diagnosis of pulmonary and extra-pulmonary TB in children with HIV in place of conventional microscopy and culture.[10] Availability of these newer assays varies greatly between centres and clinicians should liaise with their local microbiology department to ensure the best investigations are performed.[25]

Table 2 Approach to diagnosis of extra-pulmonary TB according to site of disease (adapted from WHO guidelines)

Site	Practical Approach to Diagnosis
Peripheral lymph nodes (esp. cervical)	USS, Fine needle (22G) aspiration
Intrathoracic lymph node or Miliary TB	Chest X-ray +/- CT, induced sputum or gastric aspirates, nasopharyngeal aspirate, bronchoscopy including bronchoalveolar lavage +/- endobronchial lymph node biopsy
TB meningitis	Lumbar puncture (+ CT or MRI brain) Dilated fundoscopy
Pleural effusion	Pleural tap
Abdominal TB	Abdominal USS +/- CT and ascitic fluid tap; omental or lymph node biopsy
Osteoarticular	X-ray, USS, MRI, joint tap or synovial or bone biopsy
Pericardial TB	CXR, Echocardiogram and pericardial tap

Immunological Diagnosis

TST using purified protein derivative (PPD, from Statens Serum Institute, dose 2 tuberculin units) has traditionally been used as a diagnostic tool. However, TST suffers from significant false positives and negatives. 10-20% of immunocompetent children with culture proven TB disease will have a negative TST. Sensitivity is even lower in children with HIV co-infection, particularly those with CD4 counts <15% or 200 cells/L.[26] This limits the usefulness of a negative TST result as a means of confidently ruling out active or latent TB in an HIV infected child. Specificity is also limited due to cross-reaction with BCG and non-tuberculous mycobacteria.

Interferon gamma release assays (IGRA) are currently licensed and available for use in the UK, although availability varies between institutions.[25] These assays measure interferon-gamma production by lymphocytes in response to MTB antigens not present in BCG (including ESAT-6 and CFP-10) and may allow differentiation from atypical mycobacteria and BCG. Data from children with TB disease in South Africa show better sensitivity than TST (83% and 63%, respectively), especially in HIV-infected children (73% and 36%) respectively, but they are influenced by immune suppression and malnutrition.[27] In a UK study of HIV uninfected children, for culture-confirmed active TB, the sensitivity of the TST was 83%, compared with 80% for Quantiferon Gold-InTube assay and 58% for T-SPOT.TB assay.[28] The role of these assays in identifying latent TB infection is less clear, since there is no gold standard for the presence of latent infection. Further studies are required to evaluate their use in HIV infected children in resource rich settings, but until then, they should be considered as a source of additional information but not a sole basis for decision-making regarding treatment, particularly if negative.

Treatment of Active TB disease in HIV Co-infected children

Anti-tuberculous therapy (ATT)

The basic principles of anti-tuberculous therapy do not differ between HIV-infected and uninfected children. However, issues of timing and concurrent ART complicate the picture.

It is recommended that initial empiric treatment of a child with presumed drug sensitive TB disease should consist of a daily 4-drug regimen for 2 months including isoniazid, rifampicin, pyrazinamide, and ethambutol. In the case of severe or disseminated disease such as abdominal TB, TB meningitis, spinal TB, pericardial TB or miliary TB, children should be hospitalized. Following this 2 month induction phase, treatment is completed with 2 drugs, traditionally isoniazid and rifampicin.[13] This induction phase can be extended if there is a suboptimal response to therapy, but alternative reasons for this should be sought (see below). In the case of uncomplicated pulmonary disease, 6 months total therapy is sufficient, even in HIV-co-infected children. 12 months treatment is recommended for TB meningitis. Recent work in

South Africa has demonstrated that for drug-susceptible TBM, ethionamide could be considered instead of ethambutol as it has better CSF penetration. Furthermore a prospective study of 184 children supports the use of Ethionamide as part of short intensified therapy for TB meningitis (9 months Isoniazid, Rifampicin, Pyrazinamide, Ethionamide).[29] Wider studies are required before this is recommended as standard practice. For other TB disease, duration of therapy should be determined by treatment response, which in turn may be influenced by disease severity and immunocompromise.

Anti-retroviral Therapy (ART) and concurrent administration with ATT

Co-treatment with ART and ATT can decrease morbidity and mortality in co-infected children, but management is complicated by a high pill burden, which may result in poor adherence, drug interactions or drug toxicity.

All HIV infected children diagnosed with TB should be commenced on ART, however the optimal timing of ART initiation depends on the degree of immunocompromise. Adult studies showed significant reduction in mortality and progression to AIDS with earlier ART in patients with CD4 counts <50 cells/µl.[30-32] This was confirmed in a paediatric South African study which demonstrated that a delay of ART of longer than 2 months in children with a median CD4 percentage of less than 12% was associated with increased mortality.[33] Therefore it is recommended that children with severe immunosuppression commence ART within 2 weeks of ATT and those with moderate immunosuppression within 8 weeks. There is insufficient data on children with mild immunosuppression, but extrapolation from adult data suggest that delaying ART until the end of ATT is not associated with worse outcome.[34]

Concurrent administration of ART and ATT is associated with significant drug interactions and potential adverse events. Therapeutic drug monitoring (TDM) should be performed where available. Rifampicin, a potent CYP3A4 inducer, has significant interactions with other medicines metabolized through CYP450 enzymes, reducing their blood levels. Considerable interaction occurs when rifampicin is co-administered with nevirapine (NVP) or protease inhibitors (PI's), whereas interaction with efavirenz (EFV) is less significant

and achieving therapeutic levels is possible without dose alteration. If available, rifabutin may be used instead of rifampicin to reduce drug interactions. However dosing of rifabutin in children receiving ritonavir has not been established and high rates of severe neutropaenia have been reported.[35] When co-administered with boosted PIs, the dosing of PIs and rifabutin should be TDM guided. In addition close safety monitoring for dose-related toxicity (eg neutropaenia, uveitis) should be in place. Last generation fluoroquinolones have comparable anti-TB bactericidal activity with rifamycins, therefore in children with intolerance to rifamycins, levofloxacin or moxifloxacin can be used. Adult data suggests that this practice can be adequate.[36] However substitution of rifamycins by fluoroquinolones haven't been studied in clinical trials, and therefore this cannot be recommended for routine practice.

In settings where TDM is available, dose adjusting of ART and rifampicin/ rifabutin is recommended. The choice of ART in children co-treated for TB depends on the child's age, whether the child is receiving ART or starting ART, history of previous ART exposure and availability of TDM. Recommended regimens are summarized in Table 3.

Table 3 ART regimens for children treated for TB co-infection with rifampicin containing regimens (adapted from PENTA guidelines 2015)

		<3yr	>3yrs
Initiating ART	**Preferred**	**LPV/R [1,2]+ 2NRTI** **NVP [2,3,4]+ 2NRTI**	**EFV + 2NRTI**
	Alternative	**N/A**	**LPV/R [1,2]+ 2NRTI** **DRV/r[2] +2NRTI** **ATV/r[2] + 2NRTI**
Already on ART	**Preferred**	**LPV/R +2NRTI** **NVP[2,4] + 2NRTI**	**EFV + 2NRTI**
	Alternative	**3 NRTI[5]**	**LPV/R [1,2]+ 2NRTI** **DRV/r[2] +2NRTI** **ATV/r[2] + 2NRTI** **3 NRTI[5]**

Notes:

1. Superboost LPV with increased ritonavir dose (R) to achieve lopinavir/ritonavir ratio of 1:1. Return to regular dosing once rifampicin is discontinued
2. TDM is recommended (where available) to adjust doses
3. Start NVP without lead-in dose and maximum recommended dose for age
4. Two weeks after starting NVP, consider increasing NVP maintenance dose by further 20-30%. Watch for liver toxicity. Return to regular dose once rifampicin is discontinued
5. In virally suppressed children

(N/A = not available)

There are not enough data on use of other third agents (integrase inhibitors, CCR5 inhibitors and 2nd generation NNRTIs) with anti-TB treatment to make recommendations. Advice on dose adjustments given in the Liverpool drug interactions database (http://www.hiv-druginteractions.org/) and TDM results should guide the use of these ARVs in children if necessary. There are promising phase I trial data on co-administration of dolutegravir and rifampicin: twice daily dosing of dolutegravir (50mg BD) can overcome inducing effect of rifampicin.[37] More data should be soon available from adult and paediatric trials (NCT02178592, NCT02259127).

Pyridoxine supplementation is recommended for all HIV-infected children on antiretroviral therapy treated with isoniazid to avoid peripheral neuropathy.[13,38]

Management of drug resistant TB

There are limited data on the extent of multidrug resistant (MDR) TB among HIV positive children. Several South African studies show no difference in HIV prevalence in TB compared to MDR-TB, suggesting there is no association between HIV infection and MDR-TB. Additionally, HIV was not associated with poor treatment outcome.[39] Treatment of MDR-TB in HIV infected children follows the same principles as for HIV uninfected children. Drug-resistant TB should be treated with a minimum of three effective anti-tuberculous drugs to which the isolate is susceptible. These medications should be used in consultation with an ID or TB specialist and chosen according to known bacterial drug resistance and national TB guidelines. Care needs to be taken to anticipate potential drug interactions and cumulative toxicities between ART and the TB regimen; the choice of ART may be simpler in TB regimens that do not contain rifampicin. Recent

observational studies in children with drug resistant have shown good response to treatment (90% response, median 13 months therapy).[40] It is currently recommended children with drug resistant TB receive TB treatment for 12-24 months regardless of their HIV status.[41,42]

Directly Observed Therapy

Directly observed therapy is recommended for all children with HIV infection. This is when a trained health professional, or responsible lay person supported by a trained health professional, provides the prescribed medication and observes the patient swallowing every dose. School nurses may play an important role in administering DOT. Children with excellent previous adherence to ART can receive ATT supervised within the family with training and support from health professionals. More recently, video observed therapy (VOT) has been used, this may be of particular value in the adolescent cohort. Intermittent therapy is not recommended in TB-HIV co-infection.

Use of Corticosteroid Therapy

Adjunctive treatment with corticosteroids has been shown be beneficial in children and adults with tuberculous meningitis and adults with tuberculous pericarditis. Other situations where steroids may be beneficial include complications of airway obstruction by TB lymph glands, pleural effusions, , and TB-IRIS.[13,43] In tuberculous meningitis, a dose of 2-4 mg/kg/day of prednisolone (or equivalent dose of dexamethasone 0.6mg/kg/24hr) is recommended with gradual withdrawal over 4-8 weeks.[13,43,44] Maximum dosage of 4 mg/kg/day (60 mg/day) prednisolone for 4 weeks with 4 weeks of tapering may be used in children with severe disease.[44,45] In tuberculous pericarditis, 1 mg/kg/24hr (maximum 40 mg/day), with gradual withdrawing 2–3 weeks after starting treatment.[43]

Ongoing evaluation of patients

Each child should be assessed 2 weeks after the start of TB treatment then reviewed monthly with clinical monitoring, including symptom assessment, weight measurement, assessment of adherence to treatment and enquiry

about any adverse events.[11] Dosages of anti-TB drugs should be adjusted to account for any weight gain. Adverse events caused by anti-TB drugs are much less common in children than in adults. The most important adverse event is the development of hepatotoxicity, which can be caused by isoniazid, rifampicin or pyrazinamide. Liver enzyme levels should be measured at the start of therapy and after 2,4 and 8 weeks of treatment, then 2-3 monthly. The occurrence of liver tenderness, hepatomegaly or jaundice should prompt investigation of serum liver enzyme levels and the immediate stopping of all potentially hepatotoxic drugs and replacement with less liver toxic alternatives (ethambutol, aminoglycosides, fluoroquinolones). Patients should be screened for other causes of hepatitis, and no attempt should be made to reintroduce these drugs until liver functions have normalized. An expert with experience in managing drug-induced hepatotoxicity should be involved in the further management of such cases. Early signs of ethambutol toxicity can be tested in the older child through red-green colour discrimination. Evaluation for optic neuritis can be sought early when appropriate. Potential mitochondrial toxic effects of NRTIs may post additional risk for ethambutol-related optic neuropathy.[46] Although there are insufficient data to recommend ophthalmology evaluation in every HIV-infected child on ethambutol, age-appropriate monitoring for ethambutol toxicity should be considered with prompt discontinuation of the drug if suggestive signs of optic neuropathy is present. Early toxicity is usually reversible with ethambutol discontinuation.

Management of treatment failure or relapse

In the event of progression of TB symptoms on ATT or re-development of symptoms, a number of eventualities need to be considered, including suboptimal drug levels, poor adherence, drug resistance, alternative diagnosis or paradoxical reaction/TB-IRIS. Children with severe immunosuppression may be at risk of non-tuberculous mycobacterial (NTM) infection, which can present similarly to TB, but may not respond to ATT. Microbiological culture and molecular assays may be of benefit in distinguishing between these two diseases.

Immune reconstitution inflammatory syndrome (IRIS) is the result of reconstitution of cell-mediated immunity in response to antigens and may occur to mycobacterial antigens in both TB disease (TB-IRIS) and BCG (BCG-IRIS) in young infants. It can occur following initiation of ART and also with improved nutritional status during ATT. Paradoxical worsening of TB after ART initiation. can present with fever, increase in lymphadenopathy or increase in tuberculomas. Although there are only a few studies on TB-IRIS in children, similar risk factors to those identified in adults appear to pre-dispose children to the development of this paradoxical reaction – low CD4 percentage at initiation of ATT, extensive TB disease at diagnosis, poor nutrition and additionally younger age (under one year).[47,48]. In a systematic review of the topic, median time from start of ART to IRIS diagnosis varied from 8 days to 16 weeks.[47]. Although a significant cause of morbidity, relatively few deaths were attributed to IRIS. Management includes the continuation of ATT and ART and consideration of corticosteroid treatment. In rare cases of CNS TB-IRIS, discontinuation of ART in addition to corticosteroids and other anti-inflammatory agents may be required.[49].

Prevention of TB

BCG vaccine is currently the only available vaccine for TB. It has been shown to decrease the risk of disseminated TB and TB meningitis in young infants, but has variable efficacy against pulmonary TB in studies.

BCG vaccine is not recommended in children with known HIV infection due to the increase risk of developing disseminated BCG disease. The diagnosis and treatment of BCG disease is difficult. Children with suspected BCG disease should be referred to an ID expert. *M bovis* is resistant to pyrazinamide and higher doses of other first-line TB medications are often required.

In TB endemic settings, the risk of disseminated TB disease is greater than the risk of BCG disease in HIV exposed uninfected infants, so in these areas, BCG continues to be recommended. In UK settings local BCG vaccination practices for babies of HIV infected mothers should be followed. HIV exposed

infants at low risk of HIV transmission (born to HIV infected mothers adherent to an ART regimen who have an undetectable viral load (<50 HIV-1 RNA copies/ml at or after 36/40 gestation)) with high risk of TB exposure may be considered for BCG vaccination prior to definitive exclusion of HIV infection.[50] Otherwise BCG vaccination should be delayed until confirmed HIV negative.

References:

1 Public Health England. Tuberculosis in the UK: 2014 report. www.gov.uk. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/360335/TB_Annual_report__4_0_300914.pdf (accessed 18 May2015).

2 ECDC. HIV/AIDS surveillance in Europe 2015. ecdc.europa.eu. http://ecdc.europa.eu/en/publications/Publications/tuberculosis-surveillance-monitoring-Europe-2015.pdf (accessed 18 May2015).

3 A Turkova, IJ Collins, A Judd *et al.* Tuberculosis (TB) co-infection in HIV-infected children in the UK & Ireland. Poster presentation at 32nd Annual ESPID Meeting, Dublin, May 2014

4 Cohen JM, Whittaker E, Walters S, Lyall H, Tudor-Williams G, Kampmann B. Presentation, diagnosis and management of tuberculosis in HIV-infected children in the UK. *HIV Med* 2008; **9**: 277–84.

5 Marais BJ, Gie RP, Schaaf HS, *et al.* The clinical epidemiology of childhood pulmonary tuberculosis: a critical review of literature from the pre-chemotherapy era. *Int J Tuberc Lung Dis* 2004; **8**: 278–85.

6 Swaminathan S, Padmapriyadarsini C, Narendran G. HIV-associated tuberculosis: clinical update. *CLIN INFECT DIS* 2010; **50**: 1377–86.

7 Swaminathan S. Tuberculosis in HIV-infected children. *Paediatr Respir Rev* 2004; **5**: 225–30.

8 Palme IB, Gudetta B, Degefu H, Bruchfeld J, Muhe L, Giesecke J. Risk factors for human immunodeficiency virus infection in Ethiopian children with tuberculosis. *Pediatr Infect Dis J* 2001; **20**: 1066–72.

9 Verhagen LM, Warris A, van Soolingen D, de Groot R, Hermans PWM. Human immunodeficiency virus and tuberculosis coinfection in children: challenges in diagnosis and treatment. *Pediatr Infect Dis J* 2010; **29**: e63–70.

10 World Health Organization. Global tuberculosis report 2014. *Geneva: World Health Organisation 2014* 2014; : 1–171.

11 Bamford A, Turkova A, Lyall H, *et al.* Paediatric European Network for Treatment of AIDS (PENTA) guidelines for treatment of paediatric HIV-1

infection 2015: optimizing health in preparation for adult life. *HIV Med* 2015; : n/a–n/a.

12 Schaaf HS, Cotton MF, Boon GPG, Jeena PM. Isoniazid preventive therapy in HIV-infected and -uninfected children (0 - 14 years). *S Afr Med J* 2013; **103**: 714.

13 World Health Organization. Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children, 2nd ed. Geneva, World Health Organization, 2014.

14 Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database Syst Rev* 2010; : CD000171.

15 Bright-Thomas R, Nandwani S, Smith J, Morris JA, Ormerod LP. Effectiveness of 3 months of rifampicin and isoniazid chemoprophylaxis for the treatment of latent tuberculosis infection in children. *Arch Dis Child* 2010; **95**: 600–2.

16 Hesseling AC, Westra AE, Werschkull H, *et al.* Outcome of HIV infected children with culture confirmed tuberculosis. *Arch Dis Child* 2005; **90**: 1171–4.

17 Zar HJ. Chronic lung disease in human immunodeficiency virus (HIV) infected children. *Pediatr Pulmonol* 2008; **43**: 1–10.

18 World Health Organization. Rapid Advice: Treatment of tuberculosis in children, 2010. 2011.

19 Nicol MP, Spiers K, Workman L, *et al.* Xpert MTB/RIF Testing of Stool Samples for the Diagnosis of Pulmonary Tuberculosis in Children. *CLIN INFECT DIS* 2013. doi:10.1093/cid/cit230.

20 Oramasionwu GE, Heilig CM, Udomsantisuk N, *et al.* The utility of stool cultures for diagnosing tuberculosis in people living with the human immunodeficiency virus. *Int J Tuberc Lung Dis* 2013; **17**: 1023–8.

21 Zar HJ, Workman L, Isaacs W, Dheda K, Zemanay W, Nicol MP. Rapid diagnosis of pulmonary tuberculosis in African children in a primary care setting by use of Xpert MTB/RIF on respiratory specimens: a prospective study. *The Lancet Global Health* 2013; **1**: e97–e104.

22 Nicol MP, Workman L, Isaacs W, *et al.* Accuracy of the Xpert MTB/RIF test for the diagnosis of pulmonary tuberculosis in children admitted to hospital in Cape Town, South Africa: a descriptive study. *Lancet Infect Dis* 2011; **11**: 819–24.

23 Bates M, O'Grady J, Maeurer M, Tembo J. Assessment of the Xpert MTB/RIF assay for diagnosis of tuberculosis with gastric lavage aspirates in children in sub-Saharan Africa: a prospective descriptive …. *The Lancet infectious …* 2013.

24 Maynard-Smith L, Larke N, Peters JA, Lawn SD. Diagnostic accuracy of the Xpert MTB/RIF assay for extrapulmonary and pulmonary tuberculosis when testing non-respiratory samples: a systematic review. *BMC Infect Dis* 2014; **14**: S15.

25 Tebruegge M, Ritz N, Koetz K, *et al.* PLOS ONE: Availability and Use of Molecular Microbiological and Immunological Tests for the Diagnosis of Tuberculosis in Europe. **9**: e99129.

26 Schaaf HS, Marais BJ, Whitelaw A, *et al.* Culture-confirmed childhood tuberculosis in Cape Town, South Africa: a review of 596 cases. *BMC Infect Dis* 2007; **7**: 140.

27 Liebeschuetz S, Bamber S, Ewer K, Deeks J, Pathan AA, Lalvani A. Diagnosis of tuberculosis in South African children with a T-cell-based assay: a prospective cohort study. *Lancet* 2004; **364**: 2196–203.

28 Kampmann B, Whittaker E, Williams A, *et al.* Interferon-gamma release assays do not identify more children with active tuberculosis than the tuberculin skin test. *European Respiratory Journal* 2009; **33**: 1374–82.

29 van Toorn R, Schaaf HS, Laubscher JA, van Elsland SL, Donald PR, Schoeman JF. Short Intensified Treatment in Children with Drug-susceptible Tuberculous Meningitis. *Pediatr Infect Dis J* 2014; **33**: 248–52.

30 Abdool Karim SS, Naidoo K, Grobler A, *et al.* Integration of Antiretroviral Therapy with Tuberculosis Treatment — NEJM. *N Engl J Med* 2011; **365**: 1492–501.

31 Blanc F-X, Sok T, Laureillard D, *et al.* Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med* 2011; **365**: 1471–81.

32 Havlir DV, Kendall MA, Ive P, *et al.* Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med* 2011; **365**: 1482–91.

33 Yotebieng M, Van Rie A, Moultrie H, *et al.* Effect on mortality and virological response of delaying antiretroviral therapy initiation in children receiving tuberculosis treatment. *AIDS* 2010; **24**: 1341–9.

34 Mfinanga SG, Kirenga BJ, Chanda DM, *et al.* Early versus delayed initiation of highly active antiretroviral therapy for HIV-positive adults with newly diagnosed pulmonary tuberculosis (TB-HAART): a prospective, international, randomised, placebo-controlled trial. *Lancet Infect Dis* 2014; **14**: 563–71.

35 Moultrie H, McIlleron H, Sawry S, *et al.* Pharmacokinetics and safety of rifabutin in young HIV-infected children receiving rifabutin and lopinavir/ritonavir. *Journal of Antimicrobial Chemotherapy* 2015; **70**: 543–9.

36 Bonora S, Mondo A, Trentini L, Calcagno A, Lucchini A, Di Perri G.

Moxifloxacin for the treatment of HIV-associated tuberculosis in patients with contraindications or intolerance to rifamycins. *J Infect* 2008; **57**: 78–81.

37 Dooley KE, Sayre P, Borland J, *et al.* Safety, Tolerability, and Pharmacokinetics of the HIV Integrase Inhibitor Dolutegravir Given Twice Daily With Rifampin or Once Daily With Rifabutin. *JAIDS Journal of Acquired Immune Deficiency Syndromes* 2013; **62**: 21–7.

38 Cilliers K, Labadarios D, Schaaf HS, *et al.* Pyridoxal-5-phosphate plasma concentrations in children receiving tuberculosis chemotherapy including isoniazid. *Acta Paediatrica* 2010. doi:10.1111/j.1651-2227.2010.01696.x.

39 Seddon JA, Hesseling AC, Willemse M, Donald PR, Schaaf HS. Culture-Confirmed Multidrug-Resistant Tuberculosis in Children: Clinical Features, Treatment, and Outcome. *CLIN INFECT DIS* 2011. doi:10.1093/cid/cir772.

40 Seddon JA, Hesseling AC, Godfrey-Faussett P, Schaaf HS. High treatment success in children treated for multidrug-resistant tuberculosis: an observational cohort study. *Thorax* 2014; **69**: 458–64.

41 Seddon JA, Godfrey-Faussett P, Hesseling AC, Gie RP, Beyers N, Schaaf HS. Management of children exposed to multidrug-resistant Mycobacterium tuberculosis. *Lancet Infect Dis* 2012. doi:10.1016/S1473-3099(11)70366-8.

42 Schaaf HS, Marais BJ. Management of multidrug-resistant tuberculosis in children: a survival guide for paediatricians. *Paediatr Respir Rev* 2011; **12**: 31–8.

43 National Institute for Health and Clinical Excellence. Update of CG117 Tuberculosis - clinical diagnosis and management of tuberculosis, and measures for its prevention and control, incorporating PH37 Tuberculosis - Hard to reach Groups. London, UK: NICE, anticipated publication date December 2015.

44 Thwaites G, Fisher M, Hemingway C, Scott G, Solomon T, Innes J; British Infection Society. British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. J Infect 2009; 59: 167-87.

45 Schoeman JF, Van Zyl LE, Laubscher JA, Donald PR. Effect of corticosteroids on intracranial pressure, computed tomographic findings, and clinical outcome in young children with tuberculous meningitis. Pediatrics 1997; 99: 226-31.

46 Hamzah Mustak GRCC. Ethambutol induced toxic optic neuropathy in HIV positive patients. *International Journal of Ophthalmology* 2013; **6**: 542.

47 Link-Gelles R, Moultrie H, Sawry S, Murdoch D, Van Rie A. Tuberculosis

Immune Reconstitution Inflammatory Syndrome in Children Initiating Antiretroviral Therapy for HIV Infection. *Pediatr Infect Dis J* 2014; **33**: 499–503.

48 Smith K, Kuhn L, Coovadia A, *et al.* Immune reconstitution inflammatory syndrome among HIV-infected South African infants initiating antiretroviral therapy. *AIDS* 2009; **23**: 1097–107.

49 van Toorn R, Rabie H, Dramowski A, Schoeman JF. Neurological manifestations of TB-IRIS: A report of 4 children. *Eur J Paediatr Neurol* 2012. doi:10.1016/j.ejpn.2012.04.005.

50 de Ruiter A, Taylor GP, Clayden P, Dhar J, Gandhi K, Gilleece Y, Harding K, Hay P, Kennedy J, Low-Beer N, Lyall H, Palfreeman A, O'Shea S, Tookey P, Tosswill J, Welch S, Wilkins E; British HIV Association. British HIV Association guidelines for the management of HIV infection in pregnant women 2012 (2014 interim review). HIV Med 2014;15 Suppl 4:1-77. Available: http://www.bhiva.org/documents/Guidelines/Pregnancy/2012/BHIVA-Pregnancy-guidelines-update-2014.pdf.