Guidance for national tuberculosis and HIV programmes on the management of tuberculosis in HIV-infected children: Recommendations for a public health approach

World Health Organization

International Union Against Tuberculosis and Lung Disease

Health solutions for the poor

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Contents

Acknowledgements

Abbreviations

AFB	Acid fast bacilli
ART	Anti-retroviral therapy
ARV	Anti-retroviral
BCG	Bacille-Calmette-Guerin
CPT	Cotrimoxazole preventive therapy
CXR	Chest X-ray
DST	Drug susceptibility testing
EPTB	Extrapulmonary Tuberculosis
DOTS	WHO/IUATLD strategy for TB control (now part of the Stop TB strategy)
FDC	Fixed-dose combination
HCT	HIV counselling and testing (includes VCT and PITC)
HCW	Health care worker
HIV	Human immunodeficiency virus
IGRA	Interferon-gamma release assay
IPT	Isoniazid preventive therapy
IRIS	Immune reconstitution inflammatory syndrome
IUATLD	International Union Against Tuberculosis and Lung Disease
MDR-TB	Multidrug-resistant Tuberculosis
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NTP	National Tuberculosis (Control) Programme
PI	Protease inhibitor
PITC	Provider initiated testing and counseling
PMTCT	Prevention of mother to child transmission
PTB	Pulmonary Tuberculosis
TB	Tuberculosis
TB/HIV	Tuberculosis and HIV infection
TBIC	Tuberculosis infection control
TBLN	Tuberculosis of the lymph nodes
TBM	Tuberculous meningitis
TST	Tuberculin skin test
VCT	Voluntary counselling and testing
WHO	World Health Organization
XDR-TB	Extensively drug resistant tuberculosis

SECTION 1. INTRODUCTION

DEVELOPING THE GUIDANCE DOCUMENT

Dual infection with tuberculosis and HIV (TB/HIV) is common especially in Sub-Saharan Africa. There is a need for a guidance document to aid health workers that provide care for children with TB/HIV. The World Health Organization (WHO) HIV department submitted an initial request to TB-CAP (Tuberculosis Control Assistance Program) for funding to develop guidelines for the management of TB/HIV in children. In the process of developing the proposal, it was decided that the Union (or IUATLD) would co-coordinate developing the proposed guidance in conjunction with WHO and KNCV Tuberculosis Foundation, The Netherlands. The proposal was submitted to TB-CAP and the necessary funding granted.

Target audience:

The aim of the proposal was to develop a guidance that would aid health care workers working in district and regional hospitals in resource-limited settings in preventing, diagnosing and treating TB in HIV-infected children. The guidance document aims to address the common management problems. The document is also for managers and staff of national TB and HIV control programmes.

Process in developing the guidance document:

The Child Lung Health Division of the Union under the guidance of Ms Penny Enarson developed the proposal, established the operating budget, organized the workshop and was responsible for completion and printing of the guidance. The Union commissioned Prof Mark Cotton to write an initial working document that would serve as a discussion document at a planning workshop. Prof Cotton approached colleagues with expertise in the field and they were responsible for each developing a chapter. The invited colleagues were responsible for reviewing the literature, providing the current evidence and writing a summary for each chapter of the working document.

Guidance planning workshop:

The Union under the guidance of Ms Penny Enarson co-coordinated the workshop. The invited delegates were chosen to represent the following constituencies: National TB programme managers from high incidence countries, National HIV/AIDS programme managers from high prevalence countries, Union, KNCV, WHO, paediatricians working in countries with high TB/HIV infection rates and experienced in management of childhood TB and childhood HIV. A three day workshop was held in Paris, 15th-17th July 2008. The working document was circulated to the attendees prior to the workshop.

The workshop was chaired by Prof Robert Gie, chair of the Childhood TB subgroup of the DOTS Expansion Working Group of the STOP TB partnership and aided by Prof Anthony Harries and Prof Don Enarson from the Union. At the workshop each of the different aspects of the treatment of TB and HIV was presented, the evidence weighed and recommendations made by consensus. The evidence was considered and recommendations made according to WHO guidelines (WHO handbook for guideline development. Draft version March 2008). The discussion and recommendations were recorded.

Writing the guidance:

At the workshop a writing committee was selected that rewrote the chapters of the guidance in accordance with the recommendations of the delegates to the workshop and added chapters thought to be necessary by the workshop attendees. The rewritten chapters were then circulated to the members of the workshop for comment. The writing committee met in Paris on 15th-16th October 2008 to consider the changes recommended by the workshop members. The proposed changes were then debated by the writing committee and included in the relevant sections of the guidance. The chapters were then revised and sent out to the wider audience including members of the Childhood TB subgroup of the DOTS Expansion Working group of the STOP TB Strategy for comment. Comments were then accommodated in the final guidance which was submitted to the WHO and Union technical committees for ratification.

Recommendations:

All recommendations in this guidance document are current recommendations already published in guideline documents for management of TB and HIV. Every effort has been made to be consistent with current international guidelines and references to these

documents are provided in each case. No new recommendations were made but important issues highlighted as a summary at the end of each chapter. Areas in need of further evidence were identified, discussed with references and included in the final chapter.

Note that there are differences between this on-line website version and the printed, published version that relate to the publication in late 2010 by WHO of the new TB treatment recommendations for children. The differences are largely confined to section 4 and appear as an addendum in the 2010 print version of these guidelines.

Potential conflict of interest:

All workshop members and writing committee signed the Declaration for the Conflict of Interest using WHO format – there were no conflict of interest declared by any member**.**

Updating of the Guidance.

The Union and WHO will review and update this document after 3–5 years or as needed when new evidence, treatment regimens or diagnostic tests become available.

SECTION 2. EPIDEMIOLOGY OF TB/HIV IN CHILDREN

Tuberculosis (TB) is a common cause of morbidity and mortality in children in TB-endemic countries (1). A lack of routine reporting of childhood TB cases by National TB Programmes (NTPs) and the difficulties of confirming diagnosis make it difficult to estimate the true burden of childhood TB globally. The World Health Organization (WHO) has estimated that children comprise 11% of the annual caseload of TB globally but some regions report much higher proportions (1,2). The incidence of TB in children will be influenced by various factors including: the incidence of infectious TB in the community; the effectiveness of TB case-finding and management; BCG coverage; and the prevalence of risk factors for TB disease in children. Recent WHO guidelines recommend that all NTPs routinely report child TB cases (3). This should provide valuable data for future monitoring and evaluation.

The highest TB incidence rates occur in sub-Saharan Africa and South-East Asia. Infants and children of less than 3 years are particularly at risk of developing TB disease following exposure and infection (4). Other important risk factors for infection and disease in children include poverty, overcrowding, malnutrition and more recently HIV infection. HIV infection has increased the burden of childhood TB, complicated clinical diagnosis and management of TB in children, and is associated with poorer outcomes (5).

What is meant by TB exposure, infection and disease?

Exposure – A child is exposed to *Mycobacterium tuberculosis* when he/she comes into contact with an infectious TB patient, also referred to as a source case. In TB/HIV endemic regions, HIV-infected children are at greater risk of exposure because they are more likely to be in close contact with HIV-infected adults (i.e. usually parents) who have a high prevalence of infectious TB.

Infection – The risk of becoming infected is determined by the infectiousness of the source case as well as by the closeness and duration of contact. Infection is usually indicated by a positive tuberculin skin test (TST) or interferon-gamma release assay (IGRA). Children with *M. tuberculosis* infection but without active disease (TB) have latent TB infection. They do not have symptoms suggestive of TB. Repeated exposure to *M. tuberculosis* with possible re-infection can occur and may be common in TB-endemic areas. Although the risk associated with re-infection is poorly quantified, both primary and re-infection contribute to the total disease burden.

Disease – Most children with infection will not develop symptoms of active TB disease. The groups at greatest risk for developing disease and for disseminated disease are children

younger than three years of age, HIV-infected children, malnourished children and those not vaccinated with BCG.

The burden of TB in HIV-infected children

Childhood HIV infection is particularly common in regions of sub-Saharan Africa where antenatal HIV prevalence is high and interventions to prevent mother-to-child transmission (PMTCT) of HIV infection are not widely implemented. The prevalence of HIV is therefore particularly high among infants and young children, an age group also at-risk for TB. In this region endemic for TB/HIV,(5-7) the increased burden of TB among HIV-infected children is explained by:

1) Increased TB exposure and infection

The HIV epidemic has resulted in a marked increase in the incidence of both sputum smear-positive and sputum smear-negative PTB. The HIV epidemic has also resulted in a significant lowering in the peak age-prevalence of TB so that the highest incidence of infectious TB cases now occurs among young adults (20-40 years) in TB/HIV endemic regions. These adults are often parents of young children exposing their children to an increased risk of infection with TB, HIV or both.

2) Increased risk for TB disease

There is a markedly increased risk of TB disease in HIV-infected children compared to HIV-uninfected children and that this risk is influenced by the degree of immune suppression (8,9). The risk for developing confirmed TB in HIV-infected infants in a TB endemic setting was over 20 times higher than in HIV-uninfected infants (10). This explains the high prevalence of HIV infection in children with TB in TB/HIV endemic regions (5,6) and the potential of antiretroviral therapy (ART) for reducing risk of TB. A retrospective observational study from South Africa showed a significant reduction in incidence of childhood TB cases following the introduction of ART (11).

3) Increased risk for TB-related death

As for adults, there is strong and consistent evidence that the response to TB treatment and outcome are poorer for HIV-infected children when compared to HIV-uninfected children (5-7). A substantial proportion of deaths in children with TB/HIV occur in the first two months following commencement of TB treatment (7). Biomedical risk factors for poor treatment response and mortality include severe malnutrition, co-infections, severe immuno-suppression and high viral load. Poor outcomes present challenges for optimal anti-TB drug

dosages and regimens, management of co-infections, implementation of cotrimoxazole preventive therapy (CPT) and the optimal use of ART (12,13).

Summary

- **TB is common in HIV-infected children in regions endemic for TB/HIV**

- **HIV infection is common in children with TB in regions endemic for TB/HIV**

- **HIV-infected children are more likely to be exposed and infected with *M,tuberculosis* than HIV-uninfected children**

- **HIV-infected children are at increased risk of TB disease if infected with TB and this risk is related to degree of immunosuppression**

- **Response to TB treatment is poorer in HIV-infected children than in HIV-uninfected children**

Current WHO recommendation [refs 13,14]

HIV testing is recommended for all children who are TB suspects or TB patients

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SECTION 3.   DIAGNOSIS OF TB IN HIV-INFECTED CHILDREN

The diagnosis of pulmonary TB (PTB) is a common clinical challenge in TB-endemic regions. Bacteriological confirmation is rarely achieved in resource-limited regions where most cases present and where culture facilities are unavailable. Infants and young children are particularly susceptible to disease. They often have paucibacillary disease. In the absence of bacteriologic confirmation, diagnosis depends on a combination of clinical features (non-remitting chronic cough, weight loss or failure to thrive, history of a close contact with a TB case), a positive tuberculin skin test (TST) and suggestive signs on the chest radiograph (CXR). The diagnosis of common forms of extrapulmonary TB (EPTB) in children such as TB lymph nodes (TBLN), pleural effusion, spinal TB is usually more straightforward.

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 3.1 (1). If the child is HIV-infected then this may have a major impact on diagnosis of TB (2). Problems of TB diagnosis in HIV-infected children (2) are also highlighted in Table 3.1:

- Clinical symptoms "consistent with PTB" are common in HIV-infected children due to other diseases and therefore lack specificity for a diagnosis of TB.
- Most HIV-infected children are infected by mother-to-child transmission. The peak age prevalence for HIV is therefore in infants and young children (< 5 years), also the most difficult age group in which to confirm cause of acute or chronic lung disease including TB.
- TST is less sensitive in HIV-infected children than in HIV- uninfected children.
- HIV-infected children have a very high incidence of acute and chronic respiratory disease caused by pathogens other than TB (Table 3.2).
- HIV-infected children may have more than one cause of lung disease (co-infection) which can mask response to therapy.
- Overlap of radiological findings between TB and other HIV-related lung disease.

Therefore, it is important and clinically relevant to perform HIV testing in any child with suspected TB. Other interventions such as CPT are recommended and ART often indicated for children with TB/HIV (3,4).

Table 3.1   Impact of HIV on recommended approach to diagnosis of TB in children

Recommended approach to diagnose TB in children (1)	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 with TB or HIV*
Tuberculin skin testing	*Lower sensitivity: TST positivity decreases with increasing immunosuppression*
Bacteriological confirmation whenever possible	*As important for HIV infection*
Investigations relevant for suspected pulmonary TB and suspected extrapulmonary TB	*Wider range of diagnostic possibilities because of other HIV-related disease*
Chest X-ray findings	*Lower specificity: overlap with HIV related lung disease*

Recommended approach to diagnosis

It is well recognized that studies of the clinical presentation of TB in children are limited by the lack of a gold standard for TB diagnosis and the need for culture facilities (not widely available) for greatest diagnostic yield. The overlap between the clinical presentation of children with TB and HIV highlights the importance of robust data from studies that include large numbers of HIV-infected children with confirmed TB from a variety of settings endemic for TB/HIV (5-11). Overall, the clinical presentation of TB in HIV-infected children in these studies was similar to that in HIV-uninfected children. Important consistent differences were

that HIV-infected children had reduced sensitivity of TST and were more likely to be malnourishesd. In most settings, it is difficult to confirm TB diagnosis and a clinical diagnostic approach is relied upon. This section examines the challenges with this approach in HIV-infected children.

CXR is important for diagnosis of PTB or miliary TB and may be the only diagnostic tool available for young children unable to provide specimens for culture (12). The differentiation of TB from other HIV-related lung diseases (the relative importance of which varies between regions) is a common diagnostic challenge in HIV-endemic regions - Tables 3.2 & 3.3 (13). Further, PTB can be one of multiple pathologies in children with acute or chronic lung disease, compounding the diagnostic challenge (7,13,14).

1.   *Careful history*
a. Positive TB contact

Close contact is defined as living in the same household as or in frequent contact with a source case with sputum smear-positive PTB (1). Source cases that are sputum smear-negative but culture-positive are also infectious, but to a lesser degree. If there is no known contact with a TB source case, enquire further about anyone with a chronic cough and/or other symptoms suspicious of TB in regular contact with the child. A contact history is as important for HIV-infected children as it is for HIV-uninfected children (5,9). TB is common in HIV-infected adults of child-bearing years and so a child born to a family living with HIV is at increased risk of TB as well as HIV.

b. Symptoms

A careful history of the character and duration of the cough is important. PTB commonly presents with a progressive unremitting cough not improving on broad-spectrum antibiotics. The characteristic cough is more common and specific for TB in children over 3 years of age (15). PTB can present as acute pneumonia in HIV-infected children (7,16,17) and so needs to be considered in pneumonia cases not responding to broad-spectrum antibiotics. Other symptoms such as fever, night sweats, weight loss or failure to thrive, and fatigue are common in HIV-infected children with TB (5-11) but lack specificity for TB diagnosis as they are also not uncommon in HIV-infected children without TB.

Table 3.2   Causes of lung disease in HIV-infected infants (<1 year of age)

Cause	Importance	Clinical features	Management (a,b)
Bacterial pneumonia e.g. pneumococcus, staphylococcus, Gram negatives	Very high incidence	Acute onset of cough, fever and fast breathing Can be very severe with hypoxia	Broad-spectrum antibiotics including coverage of Gram-negative organisms
PcP	Common cause of severe, fatal pneumonia especially in 2 to 6 months age group	Severe respiratory distress with hypoxia not improving with broad-spectrum antibiotics; Often afebrile; CXR: diffuse interstitial infiltration or hyperinflation	Add high-dose cotrimoxazole Consider steroids
CMV pneumonitis	Common co-infection with PcP but few data from resource-poor setting	Severe respiratory distress with hypoxia not improving with broad-spectrum antibiotics and high-dose cotrimoxazole	Add ganciclovir
Viral pneumonia e.g. RSV	Common and associated with bacterial co-infection	Acute onset of cough, fever, fast breathing; Wheezing less common than in HIV-uninfected	Broad-spectrum antibiotics if suspect bacterial co-infection
Tuberculosis	Depends on prevalence of TB/HIV in adult population	TB contact usually identifiable, often mother; Presentation often acute and severe or disseminated	Anti-TB treatment
Mixed infection	Common problem: PcP, bacterial pneumonia, viral, TB	Consider when poor response to first-line empiric management	Anti-TB treatment plus treatment for additional and presumed respiratory infections
Measles	In communities with poor measles immunization coverage	Conjunctivitis, typical rash, fever and cough, respiratory distress	Broad-spectrum antibiotics Vitamin A
LIP	Uncommon in infants and associated with bacterial co-infection	Generalised lymphadenopathy, clubbing, parotid enlargement. CXR: diffuse reticulonodular pattern	If symptomatic and close follow-up, steroids and broad-spectrum antibiotics

PcP = *Pneumocystis* pneumonia; CMV = cytomegalovirus; RSV = respiratory syncitial virus; LIP = lymphoid interstitial pneumonitis
(a) Oxygen may be indicated irrespective of cause; (b) CPT and ART when indicated for all cases

Table 3.3 Causes of lung disease in HIV-infected children (1-14 years)

Causes	Importance	Clinical features	Management (a,b)
Bacterial pneumonia e.g. pneumococcus, staphylococcus, Gram negatives	Very high incidence Often recurrent	Acute onset of cough, fever and fast breathing Can be very severe with hypoxia	Broad-spectrum antibiotics including coverage of Gram-negative organisms
Tuberculosis	Common in TB-endemic regions	See text. Persistent respiratory symptoms and often poor nutritional status; positive TB contact especially in younger children; CXR: focal abnormalities and perihilar adenopathy	Anti-TB treatment
LIP	Common especially around 2-6 years and bacterial pneumonia is a common complication	Persistent or recurrent respiratory symptoms Generalised lymphadenopathy, clubbing, parotid enlargement. CXR: diffuse reticulonodular pattern and bilateral perihilar adenopathy	If symptomatic, steroids and broad-spectrum antibiotics
Bronchiectasis	Common Complicates recurrent bacterial pneumonia, LIP or TB	Cough productive of purulent sputum; clubbing; CXR: honeycombing usually of lower lobes	Broad-spectrum antibiotics Physiotherapy
Viral pneumonia	Associated with bacterial co-infection	Acute onset of cough, fever, fast breathing; Wheezing less common than in HIV-uninfected	Broad-spectrum antibiotics if suspect bacterial co-infection
Mixed infection	Common problem: bacterial pneumonia, viral, LIP, TB	Consider when poor response to first-line empiric management	As above
Measles	In communities with poor measles immunization coverage	Conjunctivitis, typical rash, fever and cough, respiratory distress	Broad-spectrum antibiotics Vitamin A
Kaposi sarcoma	Especially in tropical Africa	Characteristic lesions on skin or palate	Chemotherapy
PcP	Rarely described from African region in this age group	Severe respiratory distress not improving with broad-spectrum antibiotics; CXR: diffuse interstitial infiltration	High-dose cotrimoxazole Consider steroids
Other fungal pneumonia e.g. cryptococcosis, candidiasis	Little clinical data but data from autopsy studies suggests rare		
Penicilliosis Melioidosis	Older children in South-East Asia		

PcP = *Pneumocystis* pneumonia; LIP = lymphoid interstitial pneumonitis; TB = tuberculosis
(a) Cotrimoxazole preventive therapy and HAART when indicated for all cases

2. *Clinical examination including growth assessment*

Childhood TB is usually associated with weight loss and/or failure to thrive. Regular documentation of weight is an invaluable tool in children suspected of TB as it is unusual for a child with TB to thrive. HIV infection is also characterized by weight loss and/or failure to thrive due to chronic illness, poor intake or both. Many populations in countries endemic for childhood TB/HIV are also chronically food insecure and HIV-infected children are at particular risk of insufficient nutrition when their parents are chronically ill or have died. A poor response to nutritional support of a malnourished child is a clinical marker of TB or HIV. Clinical studies have found that HIV-infected children with TB are more likely to be malnourished at presentation than HIV-uninfected children with TB, and that degree of malnutrition is related to degree of immune suppression as measured by CD4 count (5-11).

There are no specific features on clinical examination that can confirm that the presenting illness is due to PTB. However, careful clinical examination is worthwhile - Box 3.1. There are clinical signs that should prompt investigation into the possibility of EPTB e.g. non-painful asymmetrical lymphadenopathy in TBLN, gibbus of recent onset for spinal TB, or distended abdomen with painless ascites for peritoneal TB - Table 3.4.

Box 3.1 Important clinical points in assessment of a child with suspected PTB

1. Note and record nutritional status. Look for failure to thrive on the Road-to-Health Chart (longitudinal growth chart) and record the weight at each visit
2. Think of PTB if abnormalities on examination of respiratory system are focal, marked and persistent in an ambulant child not in respiratory distress
3. Think of PTB if radiological abnormalities are focal, marked and persistent in ambulant child not in respiratory distress
4. Negative TST (or IGRA) does not exclude PTB
5. Examine for clinical markers of HIV infection
6. Exclude abnormalities of the cardiovascular system (e.g. cardiomyopathy)
7. PTB can superimpose on other chronic lung disease and is more likely to be recurrent in HIV-infected children, so check for documentation of previous clinical presentations

Adapted from WHO Guidance for NTPs on management of TB in children (1).

Table 3.4 Approach to diagnosis in forms of EPTB in children

Site	Practical approach to diagnosis
Peripheral lymph nodes (especially cervical)	Fine-needle (22G) aspiration
Miliary TB	Chest X-ray
TB meningitis	Lumbar puncture (and computerized tomography brain scan where available)
Pleural effusion	Pleural tap
Abdominal TB	Abdominal ultrasound and tap ascitic fluid tap
Osteoarticular	X-ray, joint tap or synovial biopsy
Pericardial TB	Cardiac ultrasound and pericardial tap

Adapted from WHO Guidance for NTPs on management of TB in children (1).

Documentation of other HIV-related clinical features is important for clinical management and staging. Generalized lymphadenopathy and finger clubbing are commonly described in HIV-infected children with confirmed TB (7,10,11) but are not useful clinical markers for a diagnosis of TB as they are more commonly found with other HIV-related lung disease such as lymphoid interstitial pneumonitis (LIP) or bronchiectasis (13). Always examine the cardiac system to exclude pericardial TB and HIV-related cardiomyopathy causing cardiac failure that presents with persistent cough, failure to thrive and fatigue. Chronic lung disease is associated with pulmonary hypertension and cor pulmonale.

3. Evidence of infection with TB

a. Tuberculin skin test

The TST provides important additional information in assessing a child with suspected TB, especially if there is no positive contact history. A positive TST indicates infection with mycobacteria, usually *Mycobacterium tuberculosis.* It is not a marker of disease activity. In settings highly endemic for TB where BCG is given at birth and not repeated, a positive TST (≥10 mm) has quite high specificity for infection with *M.tuberculosis* (18). The main limitation of TST in the diagnosis of TB in HIV-infected children is variable sensitivity. Important clinical causes of false negative results include severe malnutrition, severe TB disease and HIV infection.

The recommended method is the Mantoux test using either 5 tuberculin units of tuberculin purified protein derivative (PPD)-S or 2 units of tuberculin PPD RT23 (1). Health-care

workers (HCWs) must be trained in performing and reading a TST (Annex 1, reference 1). A positive or reactive TST is defined as follows (1):

- ≥10 mm diameter of induration when read 48-72 hours after administration irrespective of BCG immunization
- ≥5 mm is considered significant or positive if the child is HIV-infected or severely malnourished

There is no evidence to support this lower cut-off and data from adults show no gain in sensitivity by using a 5 mm cut-off (19). In practice, an induration between 5-10 mm is uncommon, including in HIV-infected children (6-8).

In children with active TB disease, TST is more often negative in HIV-infected than in HIV-uninfected children (5-9). Among children with TB/HIV, TST is more likely to be negative in those with more advanced immune suppression and/or malnutrition (6,10). While some studies reported that only around 20% of HIV-infected children with confirmed TB were TST positive (6-8), other studies reported that 50-60% were TST positive (9-11). Therefore, TST remains a useful tool in HIV-infected children, especially if there is not a positive contact history. A major challenge is implementation especially in peripheral health facilities because of problems of cost and procurement, and the need for cold chain storage. TST is therefore often unavailable in resource-limited settings where TB/HIV is common (12).

b. Interferon-gamma Release Assays (IGRAs)
Recently, novel blood-based immune diagnostic tools, measuring the amount of Interferon-gamma produced by T cells in response to *Mycobacterium tuberculosis*-specific antigens have been developed. Similar to the TST, the IGRA cannot discriminate between *M. tuberculosis* infection and active TB disease.

The use of T cell based IGRAs for diagnosis of TB infection has been the subject of recent reviews (20,21). IGRAs show excellent specificity for *M.tuberculosis* infection and unlike TST, are unaffected by prior BCG vaccination or exposure to environmental mycobacteria. Household contact tracing studies and outbreak investigations show good correlation between TB exposure and IGRAs (22-24). There are encouraging data showing that an IGRA is more sensitive than TST in HIV-infected children, including those with a low CD4 count and/or malnutrition (25-27).

New guidelines in some resource-rich settings include IGRAs in addition to TST in routine TB screening programmes for adults and children. These are usually settings with a low prevalence of TB infection in the community. Studies from the high TB prevalence setting

of South Africa have reported encouraging results supporting the use of an IGRA in children with TB/HIV. More evidence is needed however especially in young children of less than 3 years before general recommendations can be made for the resource-limited, TB endemic setting. There are other studies ongoing in a variety of settings that will hopefully provide a stronger evidence base for correct application of these new assays in the future. Further, if recommended, important barriers to implementation in most TB/HIV endemic settings will be cost, the need for access to specific laboratory equipment and the need for a venous blood sample.

4.   *Bacteriological confirmation whenever possible*

It is always advisable to confirm diagnosis of TB in a child using whatever specimens and laboratory facilities are available (1). Appropriate specimens for the suspected sites of involvement should be obtained for microscopy and, where facilities are available, for culture. Appropriate clinical samples include sputum (by expectoration, gastric aspiration or sputum induction), fine-needle aspiration of enlarged lymph nodes, pleural fluid or ear swab from chronically discharging ears (Annex 2, reference 1). Diagnostic yield is greater for culture than microscopy. Current recommendations advise gastric aspiration only when culture is available as smear-positivity on microscopy is low and it causes distress to the child (1). Induced sputum can be used including in young children, does not require hospital admission and yield is greater than for gastric aspirate. Infection control measures are important when collecting samples especially when techniques are used that induce cough (section 6.3).

Bacteriological confirmation is especially important for children who have (1):
- Suspected drug-resistant TB
- HIV infection
- Complicated or severe disease

HIV-infected children are at greater risk of recurrent disease following previous TB treatment due to poor adherence, drug-resistant TB or complicated disease. In addition to increasing the yield of confirmed cases, mycobacterial culture can differentiate *M. tuberculosis* from BCG and other nontuberculous mycobacteria. BCG disease is not uncommon and associated with significant morbidity and mortality in HIV-infected infants (28). Studies show that HIV infection and degree of immune suppression do not reduce the yield from smear microscopy for acid-fast bacilli in children with TB (7,9,10).

5.　Investigations relevant for suspected pulmonary TB and suspected extrapulmonary TB

a. Suspected pulmonary TB

CXR is useful in the diagnosis of TB in children and practical guides for interpreting CXRs have been developed (29,30). The commonest abnormalities in children, HIV-infected and HIV-uninfected with confirmed PTB are persistent opacification with enlarged perihilar lymph nodes (6,9,11). Cavity formation is unusual in young children and more common in older children or adolescents. Cavities on CXR are more common in HIV-infected children than HIV-uninfected children (6,9). CXR on presentation to assess baseline changes is also a useful tool for follow-up assessment on treatment for TB and HIV.

Using CXR to diagnose TB in HIV-infected children is complicated by other HIV-related lung diseases – Tables 3.2 & 3.3. The chronic radiological changes caused by repeated bacterial infections in an HIV-infected child are easily confused with PTB as the changes often do not completely resolve after a course of antibiotics. LIP typically causes diffuse bilateral reticulonodular infiltration and bilateral adenopathy while PTB and bronchiectasis typically cause focal abnormalities. Miliary TB presents typically with a diffuse bilateral micronodular pattern which can sometimes be difficult to differentiate from LIP. Table 3.3 lists other clinical features that may help differentiate LIP or bronchiectasis from TB but it is recognized that multiple pathologies can occur in HIV-infected children.

b. Suspected extrapulmonary TB

Table 3.4 shows the investigations usually used to diagnose the common forms of EPTB (1). The diagnostic approach to suspected EPTB in HIV-infected children is similar to that for HIV-uninfected children. Children with more clinically advanced HIV disease are more likely to have a combination of EPTB and PTB (10). The presentation of axiliary lymphadenopathy on the same side as the BCG should alert to the possibility of BCG disease.

c. Other tests

Serological and nucleic acid amplification tests are not recommended for routine diagnosis of childhood TB (1). These tests have been inadequately studied in children and have performed poorly especially in smear-negative PTB and EPTB (31-33). Blood culture for mycobacteria also has very low yield in children compared to adults. Computerized chest tomography and bronchoscopy are helpful in children with chronic lung disease of uncertain diagnosis or multiple pathology but are of limited availability and their most appropriate use is in specialist referral centres.

Scoring systems

As a result of the difficulty of confirming TB in children, a variety of scoring systems have been proposed to assist the clinician. Scoring systems usually use a combination of abovementioned clinical features and investigations but are difficult to validate because of a lack of a diagnostic gold standard (34). For reasons listed in Table 3.1 and outlined above, scoring systems perform poorly as a diagnostic tool for TB in HIV-infected children (35).

A "favourable response to TB treatment" is used as part of some scoring systems. However, a "trial of treatment" should never be used as a diagnostic test for TB in children. When diagnosis is uncertain, it may be tempting to start TB treatment and monitor for resolution of symptoms over the next 1-2 months. However, once anti-TB treatment is commenced, then the patient needs to complete the full course of therapy. Further, an inadequate clinical response to anti-TB therapy does not exclude TB disease especially in HIV-infected children. Treatment response is an important measure of outcome but not a diagnostic tool.

6.   HIV testing

The approach to HIV testing and counselling (HCT) in infants and children should follow recommended WHO guidelines (36). In many settings, it can be difficult to confirm the HIV status in HIV-exposed infants. If an infant (< 18 months) is HIV-seropositive with non-resolving pneumonia, manage as if HIV-infected until HIV status is confirmed.

Summary

- **The current approach to clinical diagnosis of TB in HIV-infected children is similar to that recommended for HIV-uninfected children**

- **TST is an important diagnostic tool for children with suspected TB including HIV-infected children but a negative test does not rule out TB infection**

- **IGRAs are more specific and appear to be more sensitive than TST to identify TB infection in HIV-infected children but are expensive and require laboratory support**

- **IGRAs should be considered in addition to TST for diagnosis of TB in HIV-infected children**

- **CXR is an important diagnostic tool for HIV-infected children with suspected PTB to help differentiate TB from other HIV-related lung diseases**

- **Every effort should be made to obtain appropriate specimens for culture**

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Resource

Stop TB Partnership's New Diagnostics Working Group produced a website resource in 2009 called *Evidence-based Tuberculosis Diagnosis*, available at:

http://www.tbevidence.org

Several agencies, groups and individuals have contributed to the development of this comprehensive resource and include the Foundation for Innovative New Diagnostics (FIND), the Special Programme for Research and Training in Tropical Diseases (TDR), the Global Laboratory Initiative (GLI), and the Public Health Agency of Canada (PHAC).

This aim of the website is to provide the most comprehensive single source of evidence syntheses, policies, guidelines and research agendas on TB diagnosis. It provides access to all published systematic reviews on TB diagnostics (grouped by various test types or platforms), all the relevant policies, guidelines and research agendas on TB diagnosis, and several reports, monographs and training modules and slide presentations on TB diagnostics.

SECTION 4.   TREATMENT

4.1 TREATMENT OF TB IN HIV-INFECTED CHILDREN

As explained in previous chapters, HIV-infected children are at greater risk for TB infection and TB disease than HIV-uninfected children (1,2). HIV infected children also have a poorer response to TB treatment and higher rates of mortality associated with TB disease (2-4). There are a number of likely reasons for poorer outcome which may overlap and include: severity of immune suppression; malnutrition; HIV-related co-infections and chronic lung disease; immune reconstitution inflammatory syndrome (IRIS); and greater problems of adherence to TB treatment. As for adults, the majority of deaths in HIV-infected children being treated for TB occur in the first 2 months of TB treatment during intensive phase (3).

As explained in section 3, a trial of anti-TB treatment should not be undertaken in any child, including HIV-infected children, and the use of one or two drugs for TB treatment should never be done. A decision to commence anti-TB therapy must be carefully considered and once this decision is made, a full course of treatment completed. If a child is critically ill with suspected TB such as with TBM or very severe pneumonia, there is more urgency to start treatment as soon as possible - this applies irrespective of HIV status. However if clinically stable, it is at least as important in HIV-infected children as it is for HIV-uninfected children to try to get specimens before starting treatment, including for culture. Confirmation of diagnosis and information of drug susceptibility will provide important additional information for the HIV-infected child if there is poor response to TB treatment or relapse.

In addition to anti-TB treatment, children co-infected with TB/HIV should routinely receive cotrimoxazole preventive therapy (CPT) and be considered for ART according to WHO guidelines (5,6).The timing of commencement of ART in a child being treated for TB is dealt with in the following Section 4.2. There are potential problems of drug interactions and the commencement of ART is associated with a risk of developing IRIS in children with low CD4 counts and high viral loads.

Anti-TB drug regimens in HIV-infected children
Recommendations for TB treatment in HIV-infected children or children with TB living in an HIV-endemic setting, irrespective of HIV status, have recently been revised from those listed in the 2006 WHO Guidance document (7,8). The new patient regimen for all HIV-infected children with all forms of PTB and EPTB has four drugs in the intensive phase (2HRZE) as currently listed in the first row of Table 4.1.1 (8). The continuation phase in new patient

regimen remains as 4HR for all HIV-infected children except those with TB meningitis or osteo-articular tuberculosis. A 10-month continuation phase is now recommended for TB meningitis and osteo-articular TB. Streptomycin is no longer recommended in any first-line treatment regimens for children (8).

Children with TB/HIV are more likely to have severe disease with extensive parenchymal involvement and cavities on CXR and so require the addition of ethambutol to the intensive phase. TB treatment in HIV-infected children should be given daily (7 days per week) during the intensive and continuation phases of therapy. Drug dosages depend on the body weight of the child, rounded off into weight bands, and need to be increased as the child gains weight. If there is poor response to therapy (no weight gain, persistent symptoms) children should be referred to the next level of care for urgent assessment. Specimens for culture and drug susceptibility testing (DST) should be collected in children who respond poorly to treatment (7). Drug-resistant disease should be managed according to schedules described in Section 5.2.

Revised Table 4.1.1 Recommended treatment regimens for HIV-infected children (WHO, 2010: ref 8)

TB cases and diagnostic category	Anti-TB drug regimens	
	Intensive phase	**Continuation phase**
New Patient Regimen Smear-positive PTB Smear-negative PTB with or without extensive parenchymal involvement All forms of EPTB except TB meningitis and osteo-articular TB	2HRZE	4HR
New Patient Regimen TB meningitis and osteo-articular TB	2HRZE	10HR
MDR Regimen MDR-TB	Individualized regimens (Section 5)	

H: isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol

HIV-infected children who require treatment for a second episode of TB, due to reactivation or re-infection disease, need careful consideration of what treatment regimen should apply. There are new guidelines for the treatment of adults with TB(9), and the recommendations within these guidelines need to be considered for children with previously treated TB.

All children with previously treated TB should ideally have specimens obtained for culture and DST before or at the start of treatment. DST should be performed for at least isoniazid and rifampicin. In settings where rapid molecular-based DST is available, the results should guide the choice of regimen. In settings where rapid molecular-based DST results are not routinely available to guide the management of individual patients, empiric treatment should be considered as follows:

- TB patients who have failed treatment with their first treatment course should be considered for an empiric MDR-regimen, provided factors such as poor drug quality and poor DOT have been ruled out and provided there is evidence from country-specific drug resistance data to suggest high levels of MDR. If country-specific drug resistance data suggest low levels of MDR-TB, then patients should be considered for a standard retreatment regimen

- TB patients returning after defaulting or relapsing from their first treatment course should be considered for an empiric retreatment regimen containing first line drugs (2HRZES/1HRZE/5HRE) if country-specific drug resistance data show low or medium levels of MDR in such patients or if such data are not available. However, in areas with known high MDR amongst these patients, empiric treatment shoud be considered with an MDR-TB treatment regimen

If and when DST results become available, regimens should be adjusted appropriately. ART would be indicated as well if not already being received

Children with severe disease should be hospitalized during the intensive phase of therapy. Conditions that merit hospitalization include: a) severe forms of EPTB such as TBM, miliary TB, spinal TB, pericardial TB; b) any child with respiratory distress; c) children with severe adverse reactions such as hepatotoxicity; or d) if is not possible to ensure good adherence to treatment due to social or logistical reasons.

Many experts recommend a longer duration of treatment for TB in HIV-infected children, e.g. 9 or 12 months. There are currently no randomized trials comparing the outcomes after longer treatment. Consequently, anti-TB treatment for all children, including HIV-infected children, should be for duration of 6 months. After 6 months of treatment, ensure that there has been complete resolution of TB. If there has been inadequate response to therapy continuation of treatment may be required. The correct treatment of TBM also remains uncertain (see Annex 4 in reference 1).

Recommended dosages

Current evidence supports the recommendations by WHO in 2009 to increase doses of anti-TB therapy for children, including for HIV-infected children, because serum drug levels are lower when compared to adult patients (10-12). The recently revised and accepted WHO daily dosage (range) recommendations (Table 4.1.2) are: rifampicin 15 (10-20) mg/kg; isoniazid 10 (10-15) mg/kg; pyrazinamide 35 (30-40) mg/kg; and ethambutol 20 (15-25) mg/kg. These recommendations have recently been published (8). Daily dosages are recommended and intermittent regimens not recommended for HIV-infected children.

Table 4.1.2 Recommended dosages of first-line anti-TB drugs for children (8)

Drug	Daily dosage in mg/kg Range (maximum)
Isoniazid (H)	10-15 (300 mg)
Rifampicin (R)	10-20 (600 mg)
Pyrazinamide (Z)	30-40 (2000 mg)
Ethambutol (E)	15-25 (1200 mg)
Streptomycin (S)	12-18 (1000mg)

Pill burden is a major challenge for adherence for HIV-infected children when receiving treatment for TB, often in addition to CPT and ART. There are quality assured fixed dose combination (FDC) TB medicines available. Unfortunately, none of the currently available FDCs that exist is ideal for children. The WHO Expert Committee on Selection and Use of Essential Medicines have proposed FDCs containing rifampicin, isoniazid, pyrazinamide and ethambutol that would be the ideal product for the treatment regimen for the intensive phase of treatment in children between 5 and 30 kg (13). However, no quality assured versions of such products are currently known to exist.

Rifampicin induces cytochrome P450, and therefore interacts with many ARVs. Despite this, rifampicin is the most effective anti-TB drug and should be utilized to treat all drug susceptible disease. Rifapentine and rifabutin, potentially have fewer drug-drug interactions but are presently unavailable in most regions and there are no data on their use in children.

Monitoring of therapy

It is recommended that all children with TB/HIV receive directly observed therapy (DOT) in accordance with the NTP guidelines and that this should be for the complete duration of therapy. Parents and caregivers need to be counselled about the importance of adherence for

the entire duration of treatment and the potential adverse effects of drugs. This counselling should be repeated at each follow-up visit.

Each child should be assessed at 2 weeks after treatment initiation, at the end of intensive phase, and every 2 months until treatment is completed. The assessment should include a symptom assessment, weight measurement, an assessment of adherence to treatment and an inquiry about any adverse events. TB treatment and ART dosages should be adjusted to account for weight gained. Adherence is assessed by reviewing the treatment card. A follow-up sputum microscopy at 2 months should be obtained for any child who was sputum smear-positive at diagnosis and children who respond poorly to anti-TB treatment. Follow-up CXRs are not routinely recommended. Many children have a radiological response which lags behind the clinical response to treatment. CXR is therefore most useful in follow-up if the child is not symptomatically improving despite good adherence to anti-TB treatment.

A child not responding to TB treatment (poor weight gain, persistent cough etc) should be referred to the next level of care for further assessment and management. These children may have drug-resistant TB, an unusual complication of PTB, other causes of HIV- related lung disease, problems with treatment adherence or virological failure. Good communication is necessary between the NTP and clinicians treating children for TB. Outcomes of children with TB should be reported using the standard outcome definitions – Section 8.1.

Infants (0 - 3 months of age) with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis should be promptly treated with the standard treatment regimens as described above. Treatment may require dose adjustment to take into account the affect of age and possible toxicity in young infants. This should be done by a clinician experienced in the management of paediatric TB.

Children tolerate anti-TB treatment better then adults and have fewer adverse reactions. The commonest serious adverse event due to anti-TB therapy in children is hepatotoxicity. For HIV-infected children, there is also the risk of IRIS, and serious hypersensitivity reactions such as Stevens-Johnson syndrome due to ART or CPT. Adverse events should be reported to the NTP.

Adjunctive therapy
Prednisone at a dose of 2 to 4mg/kg/d (max: 60mg/day) is of benefit in cases of TBM and TB pericarditis (7,14).

Summary

- **It is recommended that all HIV-infected children are treated with a fourth drug (ethambutol) during the intensive phase**

- **HIV-infected children should not be treated with intermittent regimens**

- **Children with TB/HIV must be followed up regularly and have dosages adjusted for weight gained**

- **Recommended dosages for anti-TB treatment in children have been revised**

- **HIV-infected children being treated for TB must be started on cotrimoxazole preventive therapy and must be also considered for ART**

Current WHO recommendation [ref 8]

HIV-infected children are treated with a fourth drug during the intensive phase and require daily treatment for the entire treatment regimen.

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4.2 ANTI-RETROVIRAL THERAPY IN CHILDREN WITH TB/HIV

The goals of antiretroviral therapy (ART) in HIV-infected children are to: improve the length and quality of life, reduce HIV-related morbidity and mortality by reducing the incidence of opportunistic infections including TB, suppress the viral load, restore and preserve immune function and preserve normal growth and development. WHO has published standardized recommendations for ART in infants and children in resource-limited settings (1,2). These serve as the basis of these current guidelines. However, the field of ART is changing rapidly, and one caveat is that guidelines can be out-dated soon after publication.

ART will reduce mortality in HIV-infected children with TB (3,4) and may reduce the destructive effects that TB has on the lungs and elsewhere. ART should also reduce the risk of recurrent TB following completion of anti-TB treatment but there are no data to confirm this. ART decreases the risk of TB disease in HIV-infected children who are TB-exposed and infected (5).

The co-management of TB/HIV with anti-TB drugs and ART is complicated by the high pill burden and therefore potential for non-adherence, overlapping drug toxicities and drug-drug interactions leading to altered pharmacokinetics. There is also the possibility of IRIS, which is a paradoxical worsening of symptoms and signs consequent upon initiation of ART.

Guidelines for use of ART: general principles

1. Standard ARV drugs

The rationale for recommended first-line and second-line regimens are comprehensively dealt with in the WHO Guidelines (1,2). A general summary of the different regimens is provided below.

The first-line ART regimen

The preferred first-line regimen for infants and children in the resource-limited setting consists of two nucleoside reverse transcriptase inhibitors (NRTI) and one non-nucleoside reverse transcriptase inhibitor (NNRTI). An alternative regimen of three NRTI drugs is also recommended for cases where it is necessary to simplify the management of toxicity, co-morbidity and drug-drug interactions with rifampicin, although it is recognised in adults that this regimen is less effective than other regimens.

In infants, the choice is complicated by whether there has been prior exposure to maternal or infant NNRTI drugs as part of a PMTCT strategy. Strategies for PMTCT include either single

dose nevirapine to mother and child at the time of labour and birth, or longer and more complicated regimens which also include nevirapine. Prior maternal or infant exposure to nevirapine can cause the infant to be infected with drug-resistant virus (6,7). In these situations, the use of a NNRTI based regimen results in suboptimal clinical and laboratory efficacy and so a preferred ART regimen is one that uses a protease inhibitor (PI) instead of an NNRTI (7,8). Use of a PI in the first line regimen for infants is complicated by the fact that a) it may not be available, affordable or feasible in many settings, and b) it is generally reserved for second-line ART.

The regimens in these different scenarios are shown in Table 4.2.1

Table 4.2.1 Recommended first-line ART regimens for HIV-infected children (1)

Children (≥1 year) and infants with no known prior exposure to maternal or infant NNRTI

Regimen of 2NRTI plus 1NNRTI:	AZT + 3TC + NVP[1]/EFV[2]
	D4T + 3TC + NVP[1]/EFV[2]
	ABC + 3TC + NVP[1]/EFV[2]

Infants with known prior exposure to maternal or infant NNRTI

Where protease inhibitors are available, feasible or affordable

Regimen of 2NRTI plus 1PI:	AZT + 3TC + LPV/r
	D4T + 3TC + LPV/r
	ABC + 3TC + LPV/r

Where protease inhibitors are not available, feasible or affordable

Regimen of 2NRTI plus NVP:	AZT + 3TC + NVP[1]
	D4T + 3TC + NVP[1]
	ABC + 3TC + NVP[1]

Infants / children with issues of toxicity, co-morbidity and drug-drug interactions

Alternative regimen of 3 NRTI:	AZT + 3TC + ABC
	d4T + 3TC + ABC

AZT = zidovudine; 3TC = lamivudine; NVP = nevirapine; EFV = efavirenz; ABC = abacavir; LPV/r = lopinavir with ritonavir (boosted PI)

[1] NVP should be avoided in post pubertal adolescent girls with baseline CD4 count > 250 cells/mm^3

[2] EFV is not currently recommended for children < 3 years of age or < 10 kg, and should be avoided in post pubertal adolescent girls who are either in the first trimester of pregnancy or are sexually active and not receiving adequate contraception

The second-line ART regimen

The preferred second-line ART regimen for infants and children in the event of treatment failure of the first line nevirapine-containing regimen consists of two nucleoside reverse transcriptase inhibitors (NRTI) and one protease inhibitor (PI).

Examples include: ddI + ABC + LPV/r if first line regimen contained AZT or d4T

ddI + AZT + LPV/r if first line regimen contained ABC

[ddI = didanosine; ABC = abacavir; AZT = zidovudine; LPV/r = lopinavir/ritonavir]

Continuation of 3TC in second-line regimens may be considered as this may result in a more poorly replicating virus which in turn causes less immune dysfunction.

2. Eligibility for ART

Eligibility criteria are comprehensively dealt with in the WHO Guidelines (1,2). An important recent revision is the recommendation that all infants (<12 months of age) with confirmed HIV infection should be started on ART, irrespective of clinical or immunological stage (2). This has significant survival benefit including in infants without clinical or immunological markers of advanced HIV disease (2,9) For children older than 12 months, clinical and immunological thresholds should be used to identify those who need to start ART. A general summary of eligibility criteria is shown in Table 4.2.2

Table 4.2.2 Summary of eligibility criteria for ART for HIV-infected children by age (2)

Criteria to start ART	Age			
	< 12 months	**12-35 months**	**36-59 months**	**5 years and above**
Clinical criteria based on WHO Staging				
WHO Clinical Stage 4	Treat all	Treat all		
WHO Clinical Stage 3	Treat all	Treat all, but use CD4 count if available to decide on TB, LIP, OHL, thrombocytopaenia*		
WHO Clinical Stage 2	Treat all	Guided by CD4 count (see below)		
WHO Clinical Stage 1	Treat all	Guided by CD4 count (see below)		
Immunological criteria based on CD4 count or CD4 percentage				
CD4 count	Treat all	$<750/mm^3$	$<350/mm^3$	$<350/mm^3$
CD4 percentage	Treat all	<20%	<20%	<15%

* LIP: lymphoid interstitial pneumonitis; OHL: oral hairy leukoplakia

ART in HIV-infected infants and children with TB

1. Eligibility for ART

Children with PTB and TB adenitis are categorised as WHO Clinical Stage 3 and children with all other forms of EPTB are categorised as WHO Clinical Stage 4 (1).

Eligibility for ART in HIV-infected children with TB is as follows:
- All infants with a diagnosis of TB (PTB or EPTB) should be started on ART
- All children with a diagnosis of EPTB (with the exception of TBLN) should be started on ART irrespective of CD4 count.
- All children with a diagnosis of PTB or TBLN should be considered for ART as follows: i) if CD4 measurements are available, the thresholds in Table 5.2 should be used to guide the decision; ii) if CD4 measurements are not available, then children should be started on ART.

2. Timing of ART

The optimal timing for initiation of ART during TB treatment is not known, although the evidence from adults favours an early start rather than a delayed start (10,11). In children with EPTB (WHO Stage 4) it is recommended that ART is started between 2 to 8 weeks after the start of anti-TB treatment. In children with PTB and TBLN (WHO Stage 3) whose CD4 counts are below the thresholds shown in Table 5.2 it is recommended that ART is started between 2 to 8 weeks after the start of anti-TB treatment. In children with PTB and TBLN (WHO Stage 3) whose CD4 counts are above the thresholds shown in Table 2, it is recommended that ART can be delayed until the end of TB therapy provided there is an excellent response to anti-TB treatment. If there is no improvement, ART can be started (1). In children with PTB and TBLN (WHO Stage 3) in whom CD4 measurements are not available, ART can be commenced between 2 and 8 weeks after the start of anti-TB treatment. However, if the response to anti-TB treatment is excellent and there is no evidence of immune suppression other than TB, ART can be delayed until the end of TB therapy. These recommendations are shown in Table 4.2.3

Table 4.2.3 Timing of ART initiation in relation to clinical stage of TB

Clinical Stage of child with TB	Timing of ART following initiation of TB therapy
EPTB (except TBLN) [WHO Stage 4]	Start ART between 2 and 8 weeks after start of TB treatment
PTB and TBLN [WHO Stage 3]	CD4 measurements available: If CD4 counts and percentages are below threshold values shown in Table 2, start ART between 2 and 8 weeks after start of TB treatment If CD4 counts and percentages are above threshold values shown in Table 2, consider delaying ART until later or after end of TB therapy provided there is an excellent response to Tb treatment No CD4 measurements available: Start ART between 2 and 8 weeks after start of TB treatment. However, if there is an excellent clinical response to TB therapy, ART can be delayed until end of TB treatment

3. ART regimen in infants and children already started standard anti-TB treatment

The choice of regimen and drugs is complicated by the fact that rifampicin interacts with the NNRTI and PI classes. These drugs have similar routes of metabolism and elimination, and extensive drug interactions can lead to sub-therapeutic ART drug levels, increasing the risk of drug resistance and ART treatment failure (1,12,13).

Rifampicin decreases EFV levels by 20%, but the serum levels still remain above those necessary to suppress HIV *in vitro*. As this is thought to have little clinical effect on ARV, EFV is the preferred NNRTI to be used concurrently with rifampicin. However, EFV cannot be used in children <3 years or <10Kg. Rifampicin decreases NVP levels by 20-55%. However, the decreased serum levels of NVP usually exceed those necessary to suppress HIV *in vitro*, and several cohort studies have shown high rates of viral suppression. NVP can therefore be used, although virological outcomes may be compromised compared with patients who are not taking rifampicin (14). Increasing the dose of NVP may be associated with an increased risk of NVP toxicity and is generally not advised. Rifampicin decreases standard PI regimens by 90%, whether or not they are boosted with low-dose ritonavir.

The preferred ART regimen in conjunction with rifampicin is a triple NRTI. Alternative regimens must be used when a triple NRTI regimen is not available:

- *In children over the age of 3 years or > 10 Kg*, the regimen is 2NRTI plus EFV. In adults the standard dose of EFV is used in conjunction with rifampicin, and reports indicate adequate virological and immunological responses. Therefore in most paediatric clinics the standard dose of EFV can be used. However, in specialist centres consideration may be given to increase the dose of EFV.

- *In children under the age of 3 years* or < 10 Kg *and in infants with prior exposure to NNRTI,* the regimen is 2NRTI plus super-boosted LPV/r. LPV/r needs to be boosted with added ritonavir to reach mg equivalence (0.75ml ritonavir per ml LPV/r). If LPV/r is not available, feasible or affordable or there are concerns about its use outside of second line ART, the regimen is 2NRTI plus NVP.

In a child who has started TB therapy the ART regimen choices are shown in Table 4.2.4

Table 4.2.4: ART regimen choices in a child who has started TB therapy

Preferred first line ART regimen:	
Regimen of 3 NRTI:	AZT + 3TC + ABC
	d4T + 3TC + ABC
Alternative first line ART regimen:	
Children over 3 years of age or > 10 Kg	AZT + 3TC + EFV
Regimen of 2 NRTI plus EFV:	d4T + 3TC + EFV
Children under 3 years of age or < 10 Kg and infants with prior exposure to NNRTI Regimen of 2NRTI plus LPV/r[a] or NVP:	AZT + 3TC + LPV/r (or NVP)
	d4T + 3TC + LPV/r (or NVP)

[a] LPV/r needs additional boosting with ritonavir to reach mg equivalence (0.75ml ritonavir per ml LPV/r)

Notes:

- NVP should be started at full dosage in children receiving rifampicin. A lower lead-in dose of NVP should be avoided because this results in sub-therapeutic NVP levels.

- The effects of rifampicin on ART metabolism lasts for 2 weeks after rifampicin is stopped

- When there is no PI available, and NVP is being used the drug should be dosed at the maximum which is based on 200mg/m^2 rather than mg/kg

4. ART regimen in infants and children already on therapy for MDR-TB

Mortality rates in children co-infected with HIV and MDR-TB are very high, even in specialised management programmes. ART should improve the prognosis of HIV-related drug-resistant TB, although there are no data to confirm this. In view of the high mortality risk, ART should also probably be initiated at an earlier stage than that recommended for drug-sensitive TB, although again there are no data to confirm this.

Second-line anti-TB drugs are associated with considerable adverse effects which overlap with those of ARV drugs (see Section 5.2 on monitoring of drug-related side effects), although the absence of rifampicin from the regimens does simplify the issue to some extent (12). Drug-drug interactions occur between fluoroquinolones and buffered formulations of didanosine (ddI) and, for this reason, ddI as a once daily medication should be given six hours before or two hours after fluoroquinolone administration. However, the enteric-coated formulation of ddI can be used concomitantly without this precaution.

5. Management of infants and children who develop TB while already on ART

TB disease can occur in HIV-infected children receiving ART even though the risk is reduced. Management depends on whether the infant or child is on first-line or second-line ART.

Infant or child on first-line ART

Anti-TB tretament should be started and ART should be continued. However, the ART regimen should be reviewed and may need adjustment (see Table 4.2.5).

Table 4.2.5 Recommended changes to ART management when commencing anti-TB treatment

Child over the age of 3 years or > 10 Kg and on 2NRTI plus NVP:

- Change NVP to EFV
  (and in specialist centres, consider increasing the dose of EFV)
- Continue with NVP but consider dosing at maximum ($200mg/m^2$)

Child under the age of 3 years or < 10 Kg and on 2NRTI plus NVP:

- Change NVP to LPV/r (and boost with added ritonavir to reach mg equivalence: 0.75ml ritonavir per ml LPV/r)
- Continue with NVP but consider dosing at maximum ($200mg/m^2$)

Infant or child on second-line ART

Anti-TB treatment should be started. The choice of ART regimen is more difficult because of likely resistance to first-line NRTI drugs and varying interactions between rifampicin and the PI drugs. The second- line NRTI drugs should be continued. LPV/r should be maintained if it is the PI being used. If another PI is being used this should be changed to LPV/r. In both cases, LPV/r should be further boosted by added ritonavir to reach mg equivalence (add 0.75ml ritonavir per ml LPV/r).

6. Monitoring of response and side effects

Clinic visits should be monthly and, in general, monitoring done clinically. At each visit, the child must have height and weight measured and plotted on a child growth chart, a history obtained about inter-current illnesses and a physical examination performed. Dosages of ART drugs, based usually on weight, need to be recalculated at each visit. Laboratory tests are performed according to national guidelines - Table 4.2.6 (1).

Table 4.2.6 Laboratory tests schedule adapted from WHO guidelines (1)

Laboratory tests	Baseline at entry into care	At initiation of 1st or 2nd line ARV regimen	Every 6 months	As required
HIV diagnostic test	X			
Absolute CD4 count or percentage	X		X	X
Haemoglobin	X	X		X
WBC and differential	X	X		X
Pregnancy test in adolescent girls	X			
Chemistry sich as liver function tests, renal function tests, glucose, lipids, amylase and electrolytes				X
Diagnostic tests for co-infections e.g. malaria, PcP, hepatitis, cryptococcal meningitis				X

7. Management of adverse drug reactions

ARV drugs and anti-TB drugs may cause overlapping toxicity (12,13). The types of adverse reaction and their management are shown in Table 4.2.7.

Table4.2.7 Adverse reaction and their management

Adverse reaction	Main ARV drug involved	Main anti-TB drug involved	Management
Peripheral neuropathy (early or late side effect)	Stavudine Didanosine	Isoniazid Cycloserine	Pyridoxine given as preventive therapy and treatment for isoniazid toxicity
Hepatitis (usually early side effect)	Nevirapine PI	Pyrazinamide Rifampicin Isoniazid Ethionamide	STOP all drugs: once resolved restart with TB therapy
Gastrointestinal dysfunction [diarrhoea, abdominal pain] (early or late side effect)	All	All	Symptomatic
Skin rash (usually early side effect)	Nevirapine Efavirenz Abacavir	Rifampicin Isoniazid Pyrazinamide Cycloserine	Anti-histamine if mild: if severe STOP all drugs: once resolved restart with TB therapy
Central nervous system dysfunction (early or late side effect)	Efavirenz	Isoniazid Cycloserine	Pyridoxine given as preventive therapy and treatment for isoniazid toxicity
Anaemia (usually early side effect)	Zidovudine	Rifampicin	Change from zidovudine to stavudine

Severe hypersensitivity reaction to ART drugs such as NVP and ABC such as Stevens-Johnson syndrome can occur usually within the first 6 weeks of treatment and require cessation of treatment. This reaction is extremely rare with anti-TB drugs but can also occur due to CPT.

Immune Reconstitution Inflammatory Syndrome (IRIS)

It has long been known that anti-TB treatment in HIV-negative children can be associated with a transient worsening of clinical disease a few days or weeks after starting therapy (15). The frequency of these reactions is increased in the presence of ART (16). In well-resourced countries IRIS has been reported in up to 30% of cases, but in Africa the reported frequency is less at 10%. In children, the frequency has been less well documented and is not well described. IRIS was seen in 19% of children in a cohort from Thailand where ART was initiated with a CD4 count below 15%, and the median onset was 4 weeks (17). In the CHER study BCG-IRIS was seen in 9% of infants, but was less common in infants starting ART under 3 months of age (9,18).

The pathogenesis of these IRIS reactions is believed to be due to the reconstitution of cell-mediated immunity in response to mycobacterial antigens. IRIS usually occurs within 3 months of starting ART, and most commonly within the first month. It is unusual for it to occur after 6 months. Risk factors for IRIS include: low baseline CD4 count; extensive TB; early initiation of ART; and rapid immunological and virological responses to ART.

This increasingly recognised phenomenon of IRIS causes diagnostic and management challenges. With respect to TB, there are two main presentations: a) exacerbation of known TB disease in an HIV-infected child started on anti-TB treatment and ART; and b) development of active TB in a child starting ART for another reason.

Exacerbation of known TB in an HIV-infected child started on anti-TB treatment and ART
Exacerbation of known TB manifests as: fever; enlarging lymph nodes and the development of fistulae and cold abscesses; central nervous system disease due to enlarging cerebral tuberculomas; TB serositis with enlarging pleural, pericardial and peritoneal effusions; increased tuberculin hypersensitivity with, for example, phlyctenular conjunctivitis or erythema nodosum; and worsening respiratory symptoms and signs and radiographic deterioration. ART started months to years after BCG immunisation can result in local complications such as ulceration at the BCG site or lymph node abscess in the axilla on the same side as the BCG site.

Alternative explanations for these clinical manifestations need to be ruled out. These include: progressive TB disease due to non-adherence with therapy, malabsorption of drugs or initial TB drug resistance; a new opportunistic infection or neoplasm as a result of continued immune suppression or even primary ART drug resistance; and adverse reactions of anti-TB drugs and ARV drugs.

A recently proposed clinical case definition of paradoxical TB-associated IRIS is shown in Table 4.2.8 (19). Further support for the diagnosis of IRIS would come from an increase in CD4 counts and a decrease in viral loads since start of ART.

Management of TB-IRIS is not yet evidence-based. Some patients with TB-IRIS die, but these patients are often already severely immunosuppressed. There is in fact no evidence to show that the development of IRIS is associated with an increased mortality risk. In general, anti-TB therapy and ART should be continued. Non-steroidal anti-inflammatory drugs such as

ibuprofen should be administered and corticosteroids given for severe reactions, with the dose adjusted upwards to account for the increased steroid metabolism induced by rifampicin.

Table 4.2.8 Proposed clinical case definition of paradoxical TB-associated IRIS (19)

Antecedent requirements:	Both of the following requirements must be met:- Diagnosis of TB in line with WHO recommendations is made before starting ART A good initial response to TB therapy is observed before the patient started ART
Clinical criteria:	The onset of TB-associated IRIS should be within 3 months of starting ART with at least one major criterion and two minor criteria: Major criteria: • New/enlarging lymph nodes or other focal tissue enlargement • New/worsening radiographic features • New/worsening CNS tuberculosis • New/worsening serositis Minor criteria: • New/worsening constitutional symptoms such as fever • New/worsening respiratory symptoms such as cough • New/worsening abdominal pain
Alternative explanations for clinical deterioration excluded:	• Poor adherence to TB therapy • Failure of TB therapy due to TB drug resistance • Another opportunistic infection or neoplasm • Drug toxicity or drug reaction

 Development of active TB in a child starting ART for another reason
There are three possible reasons why a child might develop active TB after starting on ART: unmasking of asymptomatic, subclinical TB due to IRIS; failure to diagnose TB disease at the time of ART initiation; and co-incidental development of TB. It can be particularly difficult to diagnose PTB if baseline CXR is abnormal due to HIV-related chronic lung disease.

It may be difficult to diagnose which of these reasons is correct although the unmasking of subclinical TB due to IRIS would be suggested by the lack of any features to suggest TB before the start of ART and the development of active TB within 3 months of starting ART. Management has been described previously and includes starting TB therapy and continuing with ART.

Summary

- **ART is indicated for all HIV infected infants with TB**

- **The use of ART in children (> 12 months) with TB is according to the HIV clinical staging and/or CD4 count**

- **Drug –drug interactions are common when children are treated with ART and anti-TB regimens containing rifampicin**

- **All children with suspected or confirmed multidrug resistant TB receive ART at an early stage**

- **Children must be followed regularly and drug doses for ART and anti-TB treatment adjusted for changes in weight**

- **IRIS is especially common in severely immuno-suppressed children and usually occurs within 3 months of starting ART**

Current WHO recommendations [refs 1, 2]

ART is indicated for all HIV-infected infants with TB

All HIV-infected children > 12 months who develop TB should start on ART unless their CD4 lymphocyte count is above the threshold value for starting ART – if CD4 counts are unavailable then they should start ART

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4.3 COTRIMOXAZOLE PREVENTIVE THERAPY IN CHILDREN WITH TB/HIV

Cotrimoxazole, a fixed-dose combination of sulfamethoxazole and trimethoprim, is a broad-spectrum antimicrobial agent which targets a range of aerobic gram-positive and gram-negative organisms, fungi and protozoa. The drug is widely available in both syrup and solid formulations at low cost in most settings, including resource-limited settings.

In well resourced countries, cotrimoxazole has been part of the standard of care for preventing *Pneumocystis jiroveci* pneumonia (PcP) (formerly *Pneumocystis carinii* pneumonia) and toxoplasmosis since the 1990s. Despite a provisional statement in 2000 from WHO/UNAIDS on the use of cotrimoxazole preventive therapy (CPT) in sub-Saharan Africa(1), most countries have not scaled up or implemented this intervention widely. Reasons for slow implementation have included: a) differences in aetiology and burden of HIV-related infections between well resourced and resource-limited settings; b) limited evidence for efficacy, especially in areas with high levels of bacterial resistance to the drug; c) the potential for drug resistance; d) concerns about accelerating resistance in *Plasmodium falciparum* to sulphadoxine-pyramethamine which was standard treatment for malaria in some countries; and e) lack of guidelines.

PcP is a leading cause of death in infants with HIV infection not receiving CPT (2). Evidence is now available on the efficacy and effectiveness of CPT in reducing all cause morbidity and mortality among children living with HIV, including those with TB (3-8). There are no data from resource-limited setting on the risk of stopping CPT amongst HIV-infected children even once there is immune recovery on ART.

The recommendations outlined below for children exposed to or infected with HIV-who are also diagnosed with TB are based on the WHO Guidelines for CPT among children, adolescents and adults published in 2006 (9).

Recommendations on use of CPT for children with TB in resource-limited setting
Recommendations are shown in Table 4.3.1 and doses are shown in Table 4.3.2. The recommendations for CPT use in HIV-exposed or infected infants and children are the same whether the child has TB or not. CPT is recommended for all HIV-infected infants and children including those with TB. CPT is also recommended for HIV-exposed infants starting from 4-6 weeks of age (or at the first encounter with the health care system), and continued until HIV infection is excluded. An infant of an HIV-infected mother is considered to continue to be HIV-exposed while still breast-feeding and requires CPT, irrespective of whether the infants has TB

or not. HIV infection can be excluded by testing six weeks or more after complete cessation of breast feeding. If HIV infection is then excluded, CPT can be stopped. HIV infection is excluded by HIV antibody testing (beyond 18 months of age) or virological testing (before 18 months of age).

Table 4.3.1: Recommendations for CPT in infants and children in relation to HIV status including those with TB (9)

HIV-exposed	HIV-infected
CPT is recommended, starting at 4-6 weeks of age and maintained until cessation of risk of HIV transmission and exclusion of HIV infection	CPT is recommended and continued indefinitely

Table 4.3.2: Recommended doses of cotrimoxazole by age (9)

Recommended daily dosage based on age or weight (see legend)		Suspension (5ml syrup of 200mg/40mg)	Child tablet (100mg/20mg)	Single strength adult tablet (400mg/80mg)	Double strength adult tablet (800mg/160mg)
< 6 months	< 5 Kg	2.5 ml	One tablet	¼ tablet	-
6 months to 5 years	5-15 Kg	5ml	Two tablets	Half tablet	-
6 – 14 years	15-30 Kg	10ml	Four tablets	One tablet	Half tablet
> 14 years	>30 Kg	-	-	Two tablets	One tablet
Recommended frequency = once a day					

Daily dosages based on age or weight:
< 6 months or < 5 Kg   *– 100mg sulfamethoxazole / 20mg trimethoprim*
6 months - 5 years or 5- 15 Kg   *– 200mg sulfamethoxazole /40mg trimethoprim*
6-14 years or 15-30 Kg   *– 400mg sulfamethoxazole /80mg trimethoprim*
> 14 years or> 30Kg   *– 800mg sulfamethoxazole / 160mg trimethoprim*

Contraindications to CPT

Children with a history of severe adverse reactions to cotrimoxazole, to other sulfonamide drugs and with known glucose-6-phosphate dehydrogenase deficiency should not be given CPT. In resource-limited setting, routine testing for glucose-6-phosphate dehydrogenase deficiency is not recommended

If children cannot take cotrimoxazole, then dapsone is an alternative (dose 2mg/kg once daily or 4 mg/kg/week). However, dapsone is less effective as an alternative in preventing PcP and it also lacks the broad antimicrobial and antimalarial activity of cotrimoxazole (10,11). If children cannot tolerate cotrimoxazole or dapsone, there are no alternative drugs in most resource-limited settings.

Timing of Primary CPT

CPT should be started as soon as it is indicated.

Clinical and laboratory monitoring of CPT

The safety of CPT has been established. Drug-related adverse reactions are rare. If they do occur, they typically present in the first few weeks of starting prophylaxis. Clinical monitoring should be carried out with particular interest paid to skin reactions and symptoms such as nausea, vomiting and jaundice. No specific laboratory monitoring is required over and above that required for ART and anti-TB treatment.

Treatment of bacteria and opportunistic infections in children on CPT

Despite lack of data, it is recommended to use an alternative antibiotic for treating breakthrough bacterial infections, for example pneumonia, in children already receiving CPT (9). In children diagnosed with PcP and toxoplasmosis, it is recommended that CPT be suspended and full active treatment with high-dose cotrimoxazole be started according to national guidelines. CPT should be re-instituted after the course of treatment has been completed.

Treating malaria in children on CPT

If children on CPT develop malaria, then treatment for malaria should be given with therapy that does not include sulfadoxine/pyrimethamine. There are no data of the efficacy of sulfadoxine/pyrimethamine in treating malaria in children on CPT. Artesunate combination therapy would be the treatment of choice.

Discontinuation of primary CPT

HIV-exposed infants and children confirmed to be HIV-uninfected

CPT can be discontinued when HIV infection has been definitely excluded by a confirmed negative HIV virological test six weeks after completed cessation of breastfeeding in an infant less than 18 months of age or a confirmed negative HIV antibody test in a child aged 18 months or older and six weeks after completed cessation of breastfeeding.

Children living with HIV in the context of ART

The general recommendation is that HIV-infected children in resource-limited settings where there is a high risk of bacterial infections and malaria should be continued on CPT indefinitely irrespective of immune recovery.

Discontinuation based on adverse effects of cotrimoxazole

Severe adverse reactions to cotrimoxazole are uncommon. However, if there is an extensive exfoliative rash, Stevens Johnson syndrome or severe anaemia or pancytopaenia, then cotrimoxazole will need to be discontinued.

In adults and adolescents who have reacted to cotrimoxazole, a protocol for desensitization can be followed (rechallenge with low doses of cotrimoxazole and gradual dose escalation). However, there are insufficient data on cotrimoxazole desensitization in children to recommend its use in resource-limited setting.

Dapsone is an alternative prophylactic drug (dose 2mg/kg once daily). However, dapsone is less effective as an alternative in preventing PcP and it also lacks the broad antimicrobial and antimalarial activity of cotrimoxazole.

Summary

- **CPT prevents PcP in HIV-exposed and HIV-infected infants**

- **CPT improves survival and reduces morbidity in HIV-infected children**

- **HIV-infected children at high risk for bacterial infections or malaria are likely to benefit from CPT even when already receiving ART with immune recovery**

Current WHO recommendation [ref 9]

All infants and children with TB/HIV should receive CPT provided there are no contraindications to cotrimoxazole

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SECTION 5. SPECIAL CIRCUMSTANCES

5.1 NEONATE BORN TO A MOTHER WITH TB/HIV

The burden of TB in pregnant women has increased substantially since the onset of the HIV epidemic (1). The prevalence of TB in pregnancy is higher in HIV-infected than in HIV-uninfected women. Around 2% of HIV-infected pregnant mothers are diagnosed with TB in TB endemic settings. Pregnancy occurs at an age when the prevalence of TB/HIV is high. Infants born to HIV-infected mothers are more likely to have TB than those born to HIV-uninfected mothers (2). The perinatal outcomes of infants born to women with tuberculosis are significantly worse with an increase in prematurity, low birth weight and perinatal deaths (3,4).

Management of TB in pregnancy

The presenting symptoms of TB are similar in pregnancy as compared to non-pregnant women with the commonest form of TB being PTB (5). Pleural effusion is a common form of EPTB with miliary and TBM occurring in 5-10% of pregnant woman suffering from TB (6). It is the disseminated forms of TB that are a particular risk factor for congenital TB (7). TB is often undiagnosed in the mother prior to TB being suspected or confirmed in the neonate (8).

All pregnant women in regions endemic for TB/HIV should be screened for TB and HIV. If HIV-infected and with symptoms suggestive of TB, they should be managed according to national guidelines. Equally important is for pregnant woman with confirmed TB to have their HIV status determined.

The pregnant woman may develop infectious or non-infectious, drug-susceptible or drug-resistant tuberculosis either during pregnancy or the puerperal period. If TB is diagnosed, therapy must be commenced promptly to prevent transmission and improve outcome. WHO recommends that anti-TB treatment in pregnant women is similar to that for non pregnant women (9). The first line drugs, isoniazid, rifampicin, ethambutol and pyrazinamide, freely cross the placenta (10). However, risk of not starting or continuing with anti-TB treatment in pregnancy is greater than possible adverse effects of drugs used (11). In a recent report from Peru, outcomes were satisfactory even with treatment for MDR TB during pregnancy (12). Aminoglycosides such as streptomycin can cause ototoxicity in the fetus (4).

Management of TB and HIV infection in pregnancy

Pregnant women co-infected with TB/HIV require treatment for both diseases. In all cases, standard first line anti-TB treatment with four drugs for the intensive phase should be

commenced immediately (9,11). Wherever possible, TB treatment should be given for at least 2 weeks and preferably for 2 months before commencement of ART. The pill burden, the risks of drug interactions and potential teratogenicity are good reasons for delaying the commencement of ART. Pregnant women are treated with ART according to WHO guidelines (13). Co-infection with TB is an additional indication for commencing ART. ART is usually commenced after the 14th week of pregnancy to avoid teratogenic effects to the fetus but may be intiated sooner if the woman is critically ill or if the CD4 count is <50cells/mm.

Standard first line anti-TB therapy should be commenced as soon as the diagnosis of TB is confirmed (9). ART should be continued according to the guidelines recommended by WHO(13). Care should be taken to detect possible drug–drug interactions and adverse drug reactions.

Summary

- **The prevalence of TB is increased in HIV-infected pregnant women**

- **Anti-TB treatment improves outcome for mother and fetus**

- **Standard treatment regimens are recommended in pregnancy**

- **ART should be commenced after 14 weeks of pregnancy if possible to avoid possible teratogenic effects**

Neonatal TB

Congenital TB is when the neonate acquires TB in-utero through haematogenous spread via the umbilical vessels, or at the time of delivery through aspiration or ingestion of infected amniotic fluid or cervico-vaginal secretions. Congenital TB usually presents in the first week of life and mortality for congenital TB is high (14). Neonatal TB is when the newborn is infected after birth by being exposed to an infectious case of TB which is usually the mother or may be another close contact. It is often difficult to distinguish between congenital and neonatal TB and management is the same for both. Both forms will be referred to as neonatal TB. The TB-exposed neonate may be asymptomatic or symptomatic. Breast feeding does not transmit TB.

Symptoms of TB in the neonate are usually non-specific and include lethargy, poor feeding, low birth weight and poor weight gain. The clinical signs are also non-specific and can include

respiratory distress, non-resolving pneumonia, hepatosplenomegaly, lymphadenopathy, abdominal distension with ascites, or a clinical picture of "neonatal sepsis" with disseminated tuberculosis (1,15). The diagnosis of TB should be included in the differential diagnosis of chronic neonatal infection with a poor response to antimicrobial therapy, congenital infections and atypical pneumonia(16,17). The most important clue to the diagnosis of TB in the newborn is a maternal history of TB or HIV infection (1). Critical points in the maternal history include non-resolving pneumonia, contact with an index case of TB and recent commencement of anti-TB treatment.

Management of the asymptomatic neonate exposed to maternal TB/HIV

TB disease should be excluded in a neonate born to a mother with suspected or confirmed TB. Maternal infectiousness and drug susceptibility should be determined. Bacille Calmette-Guérin (BCG) should not be given to neonates exposed to TB while screening for active disease or latent TB infection. It is not necessary to separate the neonate from the mother if the mother does not have MDR TB. It is not necessary to stop breast-feeding.

The main reason for not giving BCG is because it will interfere with interpretation of TST used for diagnosis of infection, thus reducing effectiveness of the TST. BCG is therefore delayed until TB disease or infection have been diagnosed and managed. Further, BCG should not be given if the newborn or infant is confirmed to be HIV-infected.

Asymptomatic neonates born of mothers with infectious drug-susceptible TB should receive isoniazid (10mg/kg) for 6 months once active disease has been excluded (18). The infant should be regularly followed up to ensure active TB does not develop. At the end of 6 months, if the infant remains asymptomatic, treatment with INH is stopped and a TST performed. BCG is given after 2 weeks if the tuberculin skin test remains non-reactive and the baby is HIV-uninfected (Section 6.1). If the mother is non-infectious, the infant should be screened for TB. If there is no evidence of TB infection, then the infant should be regularly followed up to ensure that that active disease does not develop.

If the diagnosis of TB is confirmed or the infant develops clinical signs suggestive of TB, treatment should be started according to WHO guidelines (18). BCG is given 2 weeks after completing therapy if the infant is HIV-uninfected. BCG is not given if HIV-infected.

Neonates born to mothers with MDR or XDR-TB should be referred to a local expert in the management of this complicated problem. Infection control measures are required to reduce likelihood of transmission from mother to child such as wearing mask (section 6.3). If the

mother has infectious TB due to a drug-resistant strain of *M. tuberculosis* and the drug susceptibility is known and the infant has no evidence of active disease, the infant should receive prophylaxis based drugs selected according to the mother's drug susceptibility pattern. If the drug susceptibility pattern is unknown then isoniazid (10-20 mg/kg), ethionamide and a flouroquinolone are usually recommended. There are no published trials demonstrating the safety and efficacy of this approach to neonates born to mothers with infectious MDR tuberculosis.

Management of the neonate with TB disease

The treatment of congenital and neonatal TB is the same. A complete investigation of mother and neonate should be undertaken. CXR and specimens from appropriate sites should be collected to confirm the diagnosis of TB in the neonate. Anti-TB therapy should be commenced on suspicion while awaiting bacteriological confirmation as TB progresses rapidly in the neonate. Standard WHO recommended drug regimens for drug susceptible and drug resistant tuberculosis are used (18) and dosages are as listed above in Section 4.1.

Infants (0 - 3 months of age) with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis should be promptly treated with the standard treatment regimens as described above in Section 4. Treatment may require dose adjustment to take into account the affect of age and possible toxicity in young infants. This should be done by a clinician experienced in the management of paediatric TB.

A favourable response to therapy is indicated by increased appetite, weight gain and radiological resolution. Breast feeding is recommended irrespective of the TB status of the mother. The risk of transmission of TB through breast milk is negligible and although anti-TB drugs are excreted into breast milk in small amounts, there is no evidence that they induce drug resistance. Separation from the mother is not an option especially in the resource-limited setting where establishment of breast-feeding can be critical for child survival.

Summary

- **Neonatal TB can be difficult to distinguish clinically from causes of congenital infection or neonatal sepsis**

- **A high index of suspicion for the presentation of TB in the mother will assist early diagnosis**

- **BCG is not given to neonates who are being treated for possible TB infection or disease until management is completed and HIV infection excluded**

- **Neonates with suspected TB must be started on anti-TB treatment with standard TB regimens promptly as disease progression can be rapid**

- **Asymptomatic neonates exposed to an infectious mother or other contact receive IPT (INH 10 mg/kg/day) after TB is excluded**

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5.2 DRUG-RESISTANT TB IN HIV-INFECTED CHILDREN

Drug-resistant TB, including multidrug-resistant TB (MDR-TB) is as common in HIV-infected as in HIV-uninfected children, even though HIV-infected children are more likely to have had previous anti-TB treatment (1). MDR-TB is defined as resistance to both isoniazid and rifampicin with or without resistance to other drugs. Extensively drug-resistant TB (XDR-TB) is resistance to isoniazid, rifampicin, any fluoroquinolone and a second-line injectable (kanamycin, amikacin or capreomycin).

There are several reasons apart from drug resistance why HIV-infected children may have a poor response to anti-TB treatment or experience recurrent TB episodes such as:

- Non-adherence to anti-TB or ARV treatment
- Incorrect treatment regimen prescribed
- Irregular treatment due to poor drug supply
- Re-infection with TB
- Severe immunosuppression
- Failure of the ART
- Poor absorption of anti-TB drugs
- Incorrect diagnosis e.g. other HIV-related lung disease

Diagnosis of drug resistant TB in an HIV-infected child

There are no clinical or radiological differences between drug-susceptible and drug-resistant TB in children except that a child with drug-resistant TB is more likely to have a history of contact with a source case of drug-resistant TB. The diagnosis is a laboratory diagnosis. Drug-resistant TB is suspected when there is contact with a drug-resistant confirmed or suspected index case, or poor response to treatment in index case. Specimens from all available sources must be obtained and sent for mycobacterial culture and DST. In children with advanced HIV disease, the mycobacterial load may be high allowing for the culture yield to be higher. Where laboratory facilities and expertise are available, rapid methods for identification of drug resistance could be done on *M. tuberculosis* isolates or in some cases on smear-positive specimens. Rapid methods are increasingly being developed and used and an update is provided in resource below (www.tbevidence.org).

Diagnostic approach will therefore depend on resource availability and approach to culture and DST shopuld follow national guidelines as these will differ depending on the prevalence of MDR TB

Indications for MDR TB treatment

In most resource-limited, high TB burden countries, laboratory facilities for culture and susceptibility testing are not readily available. Under these circumstances, drug-resistant TB should be suspected in the following cases:

- A child who is a close (household or close contact e.g. caregiver or grandparents) contact with an infectious drug-resistant/MDR-TB case
- A child who is a contact of a TB patient who died while on treatment and there are reasons to suspect the patient had drug-resistant/MDR-TB
- Children with bacteriologically proven TB or probable TB not responding to first-line anti-TB treatment where adherence to therapy is ensured

Health care workers should be guided by national guidelines for when to start treatment for MDR TB as indications differ according to prevalence of MDR TB in the community when known.

Treatment

MDR-TB is curable when promptly and correctly treated with drugs to which the isolate is susceptible. Host factors, especially those related to cell-mediated immunity e.g. HIV infection or malnutrition should be treated in conjunction with MDR-TB treatment. Experience of treating XDR-TB in children is limited, but outcome in adults with XDR-TB/HIV is poor (2). The most important principle in management of any patient with possible or confirmed drug-resistant TB is *never* to add a single drug to a failing regimen. Recommended daily dosages and possible adverse events including those of second-line drugs are listed in Table 5.2.1.

Treatment of isoniazid-resistant TB

In the case of isoniazid mono-resistance, if the diagnosis is made before treatment is initiated (DST confirmation on the child's isolate or adult source case's isolate), a four-drug initial phase followed by a three-drug continuation phase first-line anti-TB drug regimen is recommended. The duration of the recommended regimen is 6-9 months using 2HRZE in the intensive phase and 4-7 HRE in the continuation phase. HIV-infected children should preferably receive a total of 9 months of treatment. High-dose isoniazid (15-20 mg/kg) is recommended for the majority of primary or new cases (no previous anti-TB treatment or treatment for <1 month) as resistance is low-level and can be overcome by a higher dose of isoniazid.

If isoniazid monoresistance is diagnosed after the initiation of standard TB regimen, there is a small risk that additional drug resistance might have developed. In this scenario, if the child is

responding to treatment, the regimen is completed using high-dose isoniazid. If the child is not responding well to treatment, MDR TB should be considered, and investigated and managed according to guidelines.

Table 5.2.1 Drug doses for treatment of drug-resistant TB and possible adverse events

Anti-TB drug	Drug doses (mg/kg daily)	Maximum dose (mg)	Important adverse events
First-line drugs			
Isoniazid	15-20	400	Hepatotoxicity, skin rash, peripheral neuropathy
Rifampicin (only if not resistant)	10-20	600	Hepatotoxicity, thrombocytopenia
Pyrazinamide (often not tested and given as additional drug)	25-35	2000	Hepatotoxicity, arthralgia
Ethambutol	25 (20-25)	1200	Optic neuritis
Streptomycin (high rate of resistance in MDR TB cases – use only if no other injectable available)	15-30	1000	Ototoxicity, nephrotoxicity
Second-line drugs			
Fluoroquinolones			Arthralgia, insomnia
Ofloxacin	15-20	800	
Levofloxacin	7.5-10	750	
Moxifloxacin	7.5-10	400	
Ethionamide/Prothionamide	15-20	750	Gastrointestinal upset, hypothyroidism, gynaecomastia in boys
Aminoglycoside			Ototoxicity, nephrotoxicity
Kanamycin	15-30	1000	
Amikacin	15-22.5	1000	
Capreomycin (injectable)	15-30	1000	Ototoxicity, nephrotoxicity
Para-aminosalicylic acid (PAS)	150	12 000	Gastrointestinal upset, hypothyroidism

NB. Thiacetazone should <u>NOT</u> be used in HIV-infected children because of the risk of severe muco-cutaneous reaction (Stevens-Johnson syndrome)

Treatment of MDR TB

Treatment regimens for children with MDR-TB follow the same principles as in adults:

1) Use any oral first-line agent to which the isolate (child or source case) is susceptible – for the duration of therapy

2) An injectable agent (an aminoglycoside or capreomycin) normally given for a minimum of 6 months (preferably second-line aminoglycoside – kanamycin or amikacin; do not use streptomycin unless neither another aminoglycoside nor capreomycin are available) and for 4 months after culture conversion

3) A fluoroquinolone (not ciprofloxacin) for the duration of therapy

4) Two to three second-line agents (ethionamide/prothionamide, para-aminosalicylic acid or cycloserine/terizidone) for the duration of therapy

This algorithmic approach of adding drugs to a regimen based on the susceptibility pattern of the child or source case's strain in order of potency creates a standardized approach. The number of drugs needed to treat MDR-TB in children has not been prospectively evaluated. Early (paucibacillary) disease, e.g. mediastinal or hilar lymphadenopathy with or without limited lung infiltrates could be treated with three to five drugs to which the child's or source case's strain in susceptible. Extensive pulmonary TB with or without cavitation, and disseminated disease should be treated with 5 or more drugs as the first treatment is the best and only chance of achieving cure. Children with MDR-TB generally receive ethambutol and pyrazinamide if the isolate is susceptible or of unknown susceptibility to which a fluoroquinolone and up to three additional second-line drugs are added for the duration of therapy. Additionally, children should receive an injectable agent for a minimum of 6 months. The duration of therapy for MDR-TB in HIV-infected children should be 18 to 24 months (or at least 18 months after the first negative culture). All treatment should be given daily and under direct observation.

Rifampicin resistance cannot be overcome by increasing the dose. Therefore, rifampicin has no role in treatment of rifampicin-resistant TB. Rifampicin-mono-resistant TB, rare in most countries, should be managed as an MDR-TB case. New (primary) isoniazid resistance is often low-level and high dose isoniazid (15-20mg/kg/day) could add value in the treatment of children with MDR-TB, but should not replace another drug in the regimen (3).

Second-line drugs in children

Adverse effects occur less frequently in children than in adults. Careful consideration of the risks and benefits of each drug should be made when designing a regimen. Caregivers should be made aware of possible adverse events and told to immediately report any possible adverse event. No secondary anti-TB drugs are absolutely contraindicated in children. Second-line drugs should not be withheld from a child unless hypersensitivity or an intractable

adverse reaction has been documented. Children who have received treatment for DR TB generally tolerate the second-line drugs well. Regular monitoring of the child's weight is important as the drug doses need regular adjustment as the child gains weight.

Additional drugs used in the treatment of drug- resistant TB
HIV-infected children with drug-resistant TB should receive in addition:
- Pyridoxine (1-2 mg/kg/day) especially if on high-dose isoniazid and/or malnourished
- CPT
- ART should be initiated as early as possible but timing should be individualized. It is preferable to wait two to eight weeks to prevent the risk of IRIS and minimize confusion with overlapping adverse events of the two drug regimens (Section 4.2). Drug doses of antiretroviral agents do not need adjustment if rifampicin is excluded.

The use of corticosteroids are as for drug susceptible TB and for IRIS.

Adherence
Adherence is critical for both anti-TB and ART. Some drugs in both regimens have a vile taste and many of the drugs can cause nausea and vomiting. The number of drugs taken orally is a further complicating factor. If home treatment is possible, injectables should then be given daily at the local health clinic. DOT for MDR-TB treatment is essential. In some cases, hospitalization until completion of injectables is necessary. Vomiting can often be overcome by initially splitting the daily dose, but when vomiting stops, single daily dose should be reinstituted. Families need to be screened for other TB cases. Social and psychological support is needed and support groups have shown to be efficient.

Nutrition
Malnutrition is a common underlying factor in both TB and HIV-infection. Delay in the diagnosis and the initiation of appropriate therapy for MDR-TB is further cause for poor nutrition (Section 7.1).

TB preventive therapy for contacts of drug-resistant TB cases
Close contacts of drug-resistant TB patients who develop TB disease most commonly have drug-resistant disease. All children with an infectious TB contact should be screened for TB disease, including HIV-infected children. For HIV-infected children, screening should ideally include a CXR even if asymptomatic (Section 6.2). HIV-infected children with no evidence of TB disease but in contact with an index case with drug-resistant-TB should receive appropriate

TB preventive therapy and/or close follow-up. In case of isoniazid mono-resistance, for example, rifampicin alone or a combination of rifampicin and pyrazinamide would be appropriate choices. When in contact with a confirmed rifampicin-monoresistant case, isoniazid for 6 months is recommended.

The current WHO guidelines on MDR-TB recommend no specific chemoprophylaxis for contacts of MDR-TB patients other than isoniazid. The rationale for this is that child might be infected by drug susceptible bacilli due to contact with drug susceptible index cases in addition to the MDR-TB index case in high TB incidence areas (4). Failure of IPT in isoniazid-resistant and MDR-TB contacts has been documented (5). No randomized- controlled trials have been done of the efficacy of treatment of latent TB infection in MDR-exposed adults or children. Despite the lack of evidence, a two-drug regimen is recommended for latent TB infection in USA when exposed to MDR-TB: pyrazinamide and ethambutol or pyrazinamide and ofloxacin/levofloxacin (if isolates from the index are susceptible to these drugs) (6).

The alternative to chemoprophylaxis in MDR-TB contacts (and therefore also XDR-TB contacts) is careful clinical follow-up, every 2-3 monthly for the first 6 months and thereafter 6-monthly for at least two years (4). If active disease develops, prompt initiation of treatment with a regimen designed to treat MDR-TB and using the index case's DST pattern is recommended.

Chemoprophylaxis for XDR-TB contacts is debatable – the only possibility is high-dose isoniazid (15-20 mg/kg daily for 6-9 months) because of the possibility of low-level isoniazid resistance. There are no data to support this approach or to evaluate its effectiveness. Initiating ART should be considered even if treatment criteria are not yet met.

Summary

- **Drug-resistant TB occurs in HIV infected children**

- **Drug-resistant TB is a laboratory diagnosis and as many specimens as possible must be obtained from children for culture and DST**

- **Children with drug-resistant TB are treated using the same principles as adults**

- **Drug-resistant TB requires daily treatment**

- **HIV-infected children requiring treatment for drug-resistant TB should also receive ART**

- **HIV-infected children exposed to an infectious case of drug-resistant TB are at high risk of developing disease**

- **The role of preventive therapy in children after exposure to or infection with MDR and XDR-TB is unclear**

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Resource

Stop TB Partnership's New Diagnostics Working Group produced a website resource in 2009 called *Evidence-based Tuberculosis Diagnosis*, available at:

http://www.tbevidence.org

SECTION 6. PREVENTION

6.1 BCG FOR THE PREVENTION OF TB IN HIV-ENDEMIC REGIONS

Bacille Calmette-Guérin (BCG) is a live attenuated *Mycobacterium bovis* vaccine that is recommended to be given soon after birth in TB-endemic countries or populations (1).
BCG is particularly protective against disseminated TB such as miliary TB or TBM in young HIV-uninfected children (2). The protective effect against PTB in children and adults is inconsistent (3) and appears to have limited impact on the control of ongoing TB transmission. HIV infection severely impairs the BCG specific immune response (4). BCG may therefore provide reduced vaccine-induced benefit in HIV-infected infants but there are as yet no data from clinical trials. A recent study of South African infants who had had neonatal BCG vaccination reported a much higher incidence of confirmed TB among HIV-infected compared to HIV-uninfected infants (5).

BCG is safe in HIV-uninfected infants, and very rarely causes serious complications. However, in HIV-infected infants the risk for disseminated BCG is high (6-9). Therefore, BCG vaccination appears to offer limited benefit to HIV-infected infants and children, while carrying a risk of serious adverse events.

WHO recommended in 2007 that BCG should not be given to infants or children with known HIV infection (10). The practical implementation of this recommendation is complex. HIV infection cannot reliably be determined at birth and the majority of infants born to HIV-infected mothers will be HIV-uninfected. HIV-exposed but uninfected infants, not at risk for disseminated BCG disease, will be at increased risk of disseminated TB disease if not vaccinated with BCG. Therefore, BCG should continue to be given to infants born to HIV-infected mothers in settings endemic for TB/HIV unless the infant is confirmed as HIV-infected (11). Important factors that could determine the balance of risks and benefits of such an approach and that might lead to a change in BCG vaccination policy for HIV-exposed infants would be:

- Coverage and success of the PMTCT programme
- Capacity of the Expanded Programme on Immunisation (EPI) to defer BCG vaccination in HIV exposed infants until HIV infection status has been established
- Availability of diagnosis of HIV infection in infants

Improved surveillance on TB and BCG adverse events in HIV-infected infants and children is important to inform future vaccination and preventive strategies (11-13).

Summary

- **BCG is likely to have reduced protective effect against disseminated TB in HIV-infected infants but this has not been clearly established**

- **HIV-infected newborns are at risk of disseminated BCG disease**

- **In resource-limited settings, it is difficult to confirm HIV infection in neonates and to implement a policy to withhold BCG for an at-risk minority**

- **Improved surveillance of BCG disease in TB/HIV endemic settings is important**

Current WHO recommendations [ref 10]

Neonatal BCG vaccine should continue to be given routinely in TB endemic regions

Known HIV-infected infants and children should not receive BCG

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6.2 CONTACT SCREENING AND MANAGEMENT FOR PREVENTION OF TB IN HIV-INFECTED CHILDREN

In regions endemic for TB/HIV, the age group when HIV and PTB are most prevalent is between 20 to 45 years of age i.e. in early adulthood. This is also the usual age for parenthood of young children. Therefore, HIV-infected children are more likely to be exposed and infected with TB than HIV-uninfected children because they are more likely to be a close household contact of a case with active TB disease (1). Further, if infected with TB, HIV-infected children are more likely to develop TB disease than HIV-uninfected children (2). Young age (less than 2 years) is an important risk factor for developing TB disease after infection in children (3). HIV-infected children are at increased risk at any age. Preventive therapy to reduce the risk of TB disease following TB exposure and infection is therefore an important potential intervention for HIV-infected children (4).

Contact screening and case-finding

Screening of all children in close contact with an infectious TB case is recommended (5). Children of any age with symptoms suggestive of TB should be further investigated for possibility of TB disease irrespective of HIV infection status as recommended in Section 3.

For asymptomatic children, isoniazid preventive therapy (IPT) may be indicated. Recommendations for use of IPT in resource-limited settings differ depending on HIV status of the child and are outlined below.

There are no guidelines for HIV testing of children who are close contacts of an infectious case of TB. If the source case is HIV-infected and is also the parent of the child, provider initiated testing and counseling (PITC) of the child is important and indicated. Ideally, in HIV endemic regions, all child contacts of TB cases should be screened for HIV if status is unknown because having HIV infection greatly increases the risk of disease following infection with TB. All HIV-infected children who are a close contact of a TB case require CPT and assessment for ART in addition to management of TB risk with IPT or anti-TB treatment.

Active case-finding should also be undertaken if the child is the index case with diagnosis of TB. If TB is diagnosed in any child, including HIV-infected child, the source case must be sought, especially amongst household members, to provide care and prevent further transmission. Enquiry about possible exposure to TB should be made at every visit. In regions where there is a high prevalence of TB, children might be infected outside the household. A careful history needs to be taken to ensure there is not a source case outside the household especially amongst family members, friends or caregivers.

Excluding TB prior to initiation of preventive therapy

It is important to exclude TB disease as carefully as possible in child contacts, especially in HIV-infected children prior to starting preventive therapy. HIV-infected children with a positive TB contact and symptoms or abnormal clinical findings that support a diagnosis of TB, even clinical features overlapping with other forms of HIV-related lung disease, should not receive IPT but rather anti-TB treatment.

Symptoms alone are recommended for screening to exclude active disease in HIV-uninfected children (5). This is a pragmatic approach for resource-limited settings where TST is often unavailable and availability of CXR is limited. The likelihood that CXR will diagnose active TB requiring treatment In HIV-uninfected child contacts with no symptoms is very low. Further, difficulty to access CXR and cost can be a barrier to implementation of IPT. On balance, therefore, the use of symptoms alone is an appropriate approach for child TB contact management of HIV-uninfected children in resource-limited setting.

 HIV-infected children with a positive TB contact should if possible have a CXR in addition to careful history for symptoms. TB disease can be relatively asymptomatic in HIV-infected children (6). CXR on screening may show evidence of PTB which would require anti-TB treatment instead of IPT. Further, other causes of lung disease are common in HIV-infected children and a CXR on initial screening might provide baseline information that will be useful for future follow-up assessments. In contrast, TST remains of limited use in this setting. A positive result does not add much when there is already a positive contact history. Further, it has very poor sensitivity for excluding TB infection in HIV-infected children and does not distinguish between TB infection and disease.

Although ART significantly reduces the risk of TB in HIV-infected children and adults, due to immunological reconstitution, the risk of developing TB still remains higher than in HIV-uninfected children (6,7). Therefore, IPT is also indicated for asymptomatic HIV-infected children already receiving ART if they are a close contact of an infectious TB case, regardless of their degree of immune recovery. All HIV-infected children should also receive CPT (Section 4.3).

Preventive therapy

Preventive therapy against TB disease is effective in HIV-uninfected children and HIV-infected adults (4,8) and there is some evidence that it is also effective in HIV-infected infants and children (9). WHO recommends isoniazid preventive therapy (IPT) for 6 months after TB

exposure or infection to all infants and children less than 5 years of age, and to all HIV-infected children without evidence of TB disease irrespective of age (5). Recommendation for dosage of IPT in children was revised in 2008 from previous recommendation of 4-6 mg/kg/day (5) to current recommendation of 10-15 mg/kg/day (10). There is debate as to the value of continuing beyond 6 months in HIV-infected children but there is no evidence to support such a strategy.

Shorter combination strategies (such as isoniazid with rifampicin) are not currently recommended. There is the issue of interaction of rifampicin with ART and the concern that if the HIV-infected child subsequently develops active TB disease, then it is more likely to be with a strain resistant to rifampicin. There are no data on this for rifampicin but data related to isoniazid usage suggests that it is a valid concern (11).

Section 5.2 discusses recommendations concerning preventive therapy for children exposed to or infected with drug resistant strains. Section 5.1 discusses the management of neonates born to mothers with TB/HIV.

Follow-up

Adherence counseling and monitoring should be done at each clinic visit. Adherence to IPT is known to be unreliable especially after the first 2 months. It can be challenging to convince families (and the child) of the need for continued IPT for a child who is obviously well. History of recent contact, weight and clinical monitoring are important at each follow-up visit. Any child who has become symptomatic including failure to thrive or weight loss should be investigated for the possibility of active TB disease and may require anti-TB therapy.

TB contact register

WHO guidelines suggest a TB contact register to accompany TB treatment card of the index case being treated for TB (5). This can serve as a reminder of the importance of contact screening as well as provide important information on contacts such as age, HIV status and management. As yet, there is no information on implementation of such a mechanism but again we suggest that a record be kept that contact screening has taken place and the outcomes. See example in previous guidance (5).

Summary

- **HIV infected children are more likely to be exposed to an infectious case of TB**

- **HIV infected children infected with TB have an increased risk of developing TB disease irrespective of age**

- **All child contacts should be screened for symptoms suggestive of TB irrespective of age or HIV status and those with suspected TB should be appropriately investigated for TB disease.**

- **All child contacts who are HIV infected should receive IPT (10 mg/kg/day) irrespective of age and immune status once TB disease is excluded**

Current WHO recommendations [ref 5]

All children irrespective of age need to be screened for TB disease after exposure to an infectious case of drug susceptible or drug resistant TB.

If TB disease is excluded, all child TB contacts of less than 5 years of age receive IPT (10mg/kg/day) for 6 months with regular follow-up

If TB disease is excluded, all HIV-infected child TB contacts irrespective of age receive IPT (10mg/kg/day) for 6 months with regular follow-up

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6.3 INFECTION CONTROL IN TB/HIV ENDEMIC REGIONS

In countries with a high prevalence of TB/HIV there is a high risk that HIV-infected children managed in settings such as inpatient wards or health facilities offering HIV counseling and testing (HCT), CPT, ART and/or PMTCT will be exposed to infectious cases of TB (1-5). This chapter will specifically address infection control measures to prevent nosocomial TB in relation to children living with HIV. When discussing child TB/HIV, it is necessary to regard the child and their primary care giver as one unit. TB is the commonest opportunistic infection in HIV-infected adults of the child-bearing/parenting age-group.

There are many risk factors responsible for the nosocomial spread of TB in high-burden TB/HIV settings: poverty; stigmatisation; side-effects of treatment resulting in poor adherence; weak healthcare systems; high patient loads resulting in long waiting times, crowded wards and outpatient clinics; lack of scale up of implementation of ART and IPT; poor DOTS implementation: poor ventilation due to inappropriate design of facilities; shortage of human resources; and inadequate education of staff by NTPs and inadequate understanding by patients.

Children with TB are often not considered to be infectious and therefore not likely to transmit TB. However, some children do transmit TB (6,7) and infection control is therefore important even in health facilities or areas dedicated only to the management of sick children. The clinical presentation of TB in children is variable and often overlaps with the presentation of pneumonia, HIV and malnutrition so that infection control measures are relevant to all outpatient and inpatient areas where sick children are seen. A particular area of concern is the malnutrition/re-feeding/nutritional rehabilitation ward.

The TB Infection Control Subgroup (TBIC) of the Global TB/HIV Working Group in collaboration with the HIV/AIDS and Stop TB Departments at WHO has developed the following 10 point plan for the essential actions for effective TB control without stigma. The 10 point plan summarizes the essential steps needed to implement an infection control programme - Table 6.3.1 (8).

Table 6.3.1 Essential actions for effective TBIC safety without stigma (8)

1. Include Patients and Community in Advocacy Campaigns
2. Develop an Infection Control Plan
3. Ensure Safe Sputum Collection
4. Promote Cough Etiquette and Cough Hygiene
5. Triage TB suspects for "fast-track" or separation
6. Assure Rapid Diagnosis and Initiation of Treatment
7. Improve Room Air Ventilation
8. Protect Health Care Workers
9. Capacity Building
10. Monitor infection control practices

Principles of infection control

Infection control guidelines have been developed for prevention of transmission of TB in a variety of health-care settings (9-12) The guidelines developed for high income countries are neither practicable nor feasible for most resource-limited settings and more appropriate strategies have been proposed (13). There needs to be practical, affordable and effective measures introduced to reduce TB transmission which make up the TBIC plan. This plan should be developed and implemented locally with ownership by the management team and staff of the health facility, overseen by a TBIC Steering Committee.

The main goals of a TBIC plan are to detect TB disease early, to isolate promptly and to treat people who have TB disease quickly to prevent TB spreading to others. The TBIC guidelines for the prevention of air borne infection should be an integral part of, not in place of, Universal Precautions Guidelines (9) for the prevention of transmission of HIV and other blood borne infections.

There are three actions that even in resource-limited settings can reduce TB transmission:

1. Administrative control measures
2. Environmental control measures
3. Respiratory-protection control measures

1. Administrative control measures

Work practice and administrative control measures have the greatest potential impact on TB transmission within facilities caring for HIV-infected children. They serve as the first line of defense and aim to:

- prevent TB exposure to staff and patients
- reduce spread of infection by ensuring rapid investigation and treatment of patients and staff suspected or known to have TB.

Step 1: Form a TBIC Steering Committee within the health facility which is responsible for developing, implementing and managing the TBIC plan. This committee should be an integral part of a wider Infection Control Committee. The TBIC committee should include, if possible, persons with expertise in infection control, planning, architecture and engineering. A designated person should be appointed to be responsible for implementation of the TBIC Plan.

Step 2: Carry-out a risk assessment to identify the level of risk of TB transmission in each area of the facility. This assessment should include screening for active TB in health care workers (HCWs) by areas e.g. HIV clinics, TB clinics, PMTCT clinics, ART clinics and paediatric wards.

Step 3. The TBIC Steering Committee should draw up a TBIC Plan based on the findings from the risk assessment in collaboration with management and staff (1).

Step 4: Implementation of the TBIC Plan which needs to be supervised, monitored and reassessed annually by the TBIC Steering Committee.

The written protocols, policies and practices, addressing both the child and adult at risk, should include but not be limited to the following:
- triage - potentially infectious family members or others that accompany or visit the child should be screened upon arrival for prolonged cough to allow prompt early recognition of suspected TB cases**.**
- education on cough etiquette - instructing child/family members/or accompanying others with prolonged cough on respiratory hygiene/cough etiquette – provision of a face mask (e.g., surgical mask) or tissues to cover their mouths and noses. Tissues are less expensive and less likely to identify people with suspected TB so reducing the risk of stigma
- separation of child/family members/or accompanying others with suspected or confirmed TB disease:
    - at the out-patient level registering them ahead of other persons waiting in line so decreasing the amount of time spent in the facility
    - placing them in a separate, well ventilated waiting area – eg a sheltered open-air space in warm climates

- at the inpatient paediatric ward level children with suspected or confirmed TB should be isolated by placing them in a separate well ventilated room. If this is not possible in busy paediatric general wards in resource-poor countries, then they should be placed in a separate ward area ideally well away from HIV-infected children

- referral mechanism - prompt referral of patients/visitors with suspected TB disease for investigation

- investigation of TB suspects should be conducted in the OPD rather than the In-patient facility wherever and whenever possible

2. Environmental control measures (1)

The second line of defence for preventing the spread of TB is environmental control. In low resource countries the most effective environmental measure to reduce TB transmission is proper ventilation. The opening of doors and windows on opposite sides of an area maximizes natural ventilation, is freely available, maintenance free and appropriate in most high burden TB/HIV settings. This type of ventilation can be used in most of the clinical areas where there is a high risk of transmitting TB to HIV-infected children positive children such as inpatient wards, outpatient clinic waiting rooms for PMTCT, ARV etc, emergency departments, radiology facilities and especially in rooms used for sputum collection and cough-inducing procedures.

Propeller fans, either mounted in ceilings or in a window opening are an inexpensive way to increase the effectiveness of natural ventilation. Propeller fans increase air mixing as well as assisting in the direction of natural air movement by pushing or pulling of the air. The window mounted fan can be used to direct air flow in a high-risk area but it is important to ensure that air flows across the room. The diagram below demonstrates the correct set-up of a room naturally ventilated to reduce the risk of transmission to HCWs.
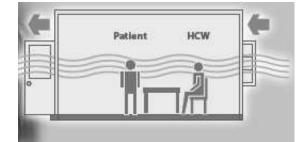
Figure. Correct direction of natural ventilation in work location

Sputum collection/induction procedures are high risk procedures for TB transmission. The ideal place for these activities is outdoors in a designated area away from other patients. If a

small room is designated for these activities there should be written instruction on how to correctly carry out the collection and the patient should remain in the room until they stop coughing. Before the room is used for another sputum collection enough time should be allowed to pass for at least 99% of the airborne contaminants to be removed. The time needed between collections will depend on the number of estimated air changes per hour in the collection room, which is in turn dependent on the air circulation in that room (10).

If sputum collection from children using cough inducing procedures, such as nebulised hypertonic saline, and other high risk procedures such as bronchoscopy, autopsy, wound irrigation and pulmonary surgery is being carried out at any facility then all staff, including maintenance workers, involved are at risk and need personal respiratory protection. See section below on respiratory-protection control measures.

For environmental measures in the laboratory handling sputum specimens for acid-fast bacilli consult the International Union against Tuberculosis and Lung Disease (The Union) Guidelines Priorities for Tuberculosis Bacteriology Services in Low-Income Countries (14).

3. Respiratory-protection control measures

Use of a face mask does not protect HCWs, other staff, patients, or visitors against TB. It is therefore not recommended that HCWs and other staff or visitors in HIV care settings wear them.

Face masks should be provided to patients with active TB disease when they leave isolation areas to undergo procedures in other areas of the health facility such as radiology. They can also be given masks to wear when HCWs attend to them. These can be cloth masks that can be sterilized and re-used.

The use of respirators,(see below) a special type of closely-fitted mask to protect HCWs from inhaling infectious droplet nuclei, are expensive and require training and specialized, individual fitting to ensure a proper seal. The protection afforded by the respirator is mosteffective if administrative and environmental control measures are being properly implemented and followed.

The risk of exposure to Multi-drug resistant TB (MDRTB)[i]

Due to the risk to HIV-infected persons from MDRTB, children and adults with confirmed

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[i] For more detailed information, please refer to reference 12 pages 45-48.

MDRTB or XDRTB should receive routine care outside of the normal HIV/TB care settings – usually at the referral level facility.

In such specialized treatment centers the use of personal respiratory protection such as the U.S.-certified N95 (or greater) or EU-certified FFP2 (or greater) respirator should be included in the IC plan.   The Global Fund could be a source of funding for the training, equipment for testing and the masks for these specialized areas.

The management of the HIV-infected HCW and support staff
HIV-infected HCWs and support staff are at increased risk of infection with TB and at increased risk of active disease because of frequent exposure to persons with infectious TB disease in the workplace. It is extremely important for HCWs to know their HIV and TB status as they in turn can be a source of transmission of TB in the workplace (15-17).

The level of risk of nosocomial transmission of TB to HCW and support staff will depend on a number of factors such as the area of the facility in which they work, their job category and how close a contact they have with TB infectious patients. It is essential that known HIV-infected personnel do **NOT** work in high-risk areas within a facility where:
- there is contact with patients being assessed for, but not yet diagnosed as having active TB such as OPD waiting rooms and Emergency Departments,
- sputum collection and bronchoscopy procedures are carried out
- laboratory tests for diagnosing TB are routinely done
- autopsies are carried out and
- TB patients are managed.

It is essential in high burden TB/HIV settings for all HCWs to know their HIV/TB status and for health facilities to encourage them to do so by providing the following services:
- workplace program providing confidential assistance to staff including HIV counseling and testing
- referral for assessment of, and adequate access to ART
- management of HIV-infected including CPT, ART and IPT as indicated
- screening for active TB

Patients, patients' families and the community in advocacy programmes:
TBIC cannot be done in isolation but should include patients, patients' families and community members in the programme. They should be aware of the value of knowing their HIV status

and the preventative measures available to them. They should be educated to understand how TB is transmitted and the need for coughing etiquette, wearing of face masks and the use of well ventilated patient areas.

Summary:

- **Transmission of TB takes place in health care facilities especially in areas where patients with suspected TB are being investigated.**

- **Transmission of TB from health care workers, care givers or visiting parents to children occurs in health care facilities.**

- **Children can be responsible for the transmission of TB to other children especially in areas where TB, HIV or malnourished children are being nursed.**

- **Every health care facility must develop a TBIC plan which ensures that patients suspected of having TB are rapidly investigated, appropriately isolated and rapidly treated to prevent TB transmission.**

- **Administrative control measures have the greatest impact on TB transmission to other patients, children or health care workers.**

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SECTION 7. SUPPORTIVE SERVICES

7.1 NUTRITIONAL SUPPORT FOR CHILDREN WITH TB/HIV

Nutritional status is an important host factor to resist TB disease (1). Malnourished children have impaired immune function with reduced cell-mediated immunity increasing susceptibility to infections such as TB. At the same time, infection can cause nutritional stress and weight loss. If a child is infected with TB, malnutrition increases the risk of active TB disease, and active TB disease makes malnutrition worse because there is catabolism which leads to further weight loss and wasting. Failure to thrive and weight loss are important clinical features in the diagnosis of TB in children. Similarly in HIV-infected children, wasting is associated with increased morbidity and poorer survival and nutritional disorders are more common.(2- 5)

Risk of malnutrition among TB/HIV co-infected children

Several observational studies have documented an increased risk of malnutrition among children with TB if also HIV-infected. Studies (4-6) report that patients with active TB are more likely to be malnourished and that wasting is associated with increased mortality in TB patients. In one Ethiopian study (6), 41% of the HIV-infected TB patients died, compared with 7% of the HIV-negative TB patients. Age and low weight-for-age were the only variables predicting death in the HIV co-infected group. The lowest weight-for-age scores were amongst the youngest children, who also had the highest mortality (6-8).

Clinical and anthropometric assessment

The systematic evaluation of nutritional status, diet and nutrition-related symptoms, is important including in the monitoring of progression of TB/HIV disease, and treatment efficacy. HIV-infected infants should be measured monthly, ideally with the use of standardized growth curves. Thereafter, children should be weighed at each review and full nutritional assessments should be made every three months.

Severe growth problems in HIV-infected children (i.e. growth failure and severe malnutrition/wasting criteria for clinical stage 3 and 4 disease, respectively) not attributable to inadequate nutritional intake are indications for ART. Growth is also useful in the evaluation of the response to ART. Conversely, potential adverse effects of ARV drugs or opportunistic infections may affect food intake and nutrition in general, with limited improvements in growth and/or adherence to therapy as a consequence.

Regular and careful assessment of the child's growth is vital. Assessment can be made by measuring weight, height, mid-upper arm circumference or observing for signs of malnutrition

such as oedema or severe wasting. The criteria for defining severe malnutrition are available in WHO guidelines for an integrated approach to the nutritional care of HIV-infected children aged 6 months to 14 years (9)

Nutritional Management

For all the reasons outlined above, a proactive approach to nutritional support in HIV-infected children is important. Nutritional support should include early efforts to continue breastfeeding where possible, ensure adequate nutrient intake on the basis of locally available and affordable foods and a daily intake of micronutrients equivalent to one recommended daily allowance (RDA) (10, 11). It is recommended to increase the energy intake of HIV-infected infants and children by 10% of the RDA for their age and sex if they are asymptomatic and by 20–30% of the RDA if they are symptomatic or recovering from acute infections (12). Increased protein requirement exceeding that required in a balanced diet to satisfy the total energy requirements (12 to 15% of the total energy intake) is not needed (12).

In children experiencing growth failure (i.e. failure to gain weight, or weight loss between regular measurements) or feeding difficulties, more targeted support may be necessary. The identification of the underlying cause of growth failure may provide valuable information on further support strategies. This may include the treatment of underlying illness, the evaluation of the need to start or switch ART, family education about locally available food choices and referral to food programmes, preferably with support for the whole family. In addition the selection of specific palatable high-energy foods for children with conditions that interfere with normal ingestion or digestion (e.g. sore throat or mouth, oral thrush, diarrhoea) may both alleviate symptoms and ensure sufficient energy intake (13)

Expert opinion advises that HIV-infected children with severe malnutrition be stabilized before decisions are made on the initiation of ART. (10, 11) The initial treatment of severe malnutrition lasts until the child has stabilized on this treatment and appetite has returned. Following successful initial treatment of severe malnutrition and any underlying infections or conditions, the clinical condition should be re-evaluated to decide the initiation of ART. The presentation of severe malnutrition in an HIV-infected child is associated with poor survival and so is an indication to commence ART early rather than delaying. Initiation of ART is indicated in HIV-infected infants and children with unexplained severe malnutrition that does not respond to standard nutritional therapy and treatment of underlying co-infections (13).

The energy and protein needs of TB/HIV co-infected children depend on their age, and the growth status at assessment. TB/HIV co-infected children need 20-30% extra energy each

day (9). Additional energy is best given through additional household foods, provided as part of a balanced varied diet. If this not possible, then specific nutritional supplements should be offered until the child is stabilized and TB is effectively managed. All children with severe malnutrition urgently require therapeutic feeding. These children need 50-100% extra energy each day until weight is recovered. Details of total caloric needs are available in a WHO guideline (9).

Support with micronutrients among TB/HIV co- infected children

Current evidence is inconclusive about the effects of micronutrient supplementation on the transmission and progression of HIV infection. However, evidence from randomized clinical trials in HIV-infected children confirms results from studies in HIV-uninfected individuals indicating that vitamin A supplementation reduces overall morbidity and diarrhoeal morbidity as well as all-cause mortality (14, 15, 16). Vitamin A supplements should be given in accordance with the WHO recommended high-dose prevention schedule for children at high risk of vitamin A deficiency (17). Zinc supplementation is also important children with TB/HIV infection and is likely to reduce incidence and severity of diarrhoea. The counseling of mothers about breastfeeding and of all children and their caregivers about food and water hygiene are further core elements of nutritional support.

Summary:

- **Children with TB/HIV are usually malnourished and often more severely malnourished than children with TB or HIV**

- **Malnutrition is a consistent risk factor for poor survival**

- **Regular monitoring of weight and growth status is an important part of management**

- **Nutritional supplementation is needed as energy demands are greatly increased**

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7.2 PATIENT AND FAMILY SUPPORT FOR CHILDREN WITH TB/HIV

The family unit bears the impact of the attendant stigma, discrimination, economic and psychological stress, as well as the burden of caring for HIV-infected children during physical illness and death.[1] In the past, HIV care-models have focused primarily on the needs of individuals and not addressed the family needs. This chapter will use the model of family-centred care, an approach that focuses on the continuum of care for the whole family rather than the individual. This requires a multidisciplinary approach to address all the needs of the family. The basic principles of continuum of care are shown in Box 13.1.

BOX 13.1 Principles in continuum of care[2]

1. *Integration of care with prevention for the provision of a comprehensive, holistic system of HIV management*
2. *Provision of non-discriminatory/judgmental care and prevention*
3. *Maintaining confidentiality and respect for basic rights*
4. *Provision of clinical and nursing care to alleviate symptoms of HIV and AIDS and prevention of opportunistic infections*
5. *Provision of counseling and psychosocial support services. Active listening to people living with HIV and his/her family, and enable them to plan for their future*
6. *Provision of support for home care*
7. *Community mobilization of resources for cost-effective comprehensive and holistic care.*
8. *Provision of education, supervision and support for staff*[ii]

The child as the "index" case of TB or HIV

When a child is diagnosed as HIV-infected, it is almost certain that the mother is also HIV-infected, probably the father and possibly other siblings as well. When a child is diagnosed with TB, it is common to find others in the family with TB that may also need further assessment. Assessment for TB and HIV testing and counseling should therefore be recommended to parents and siblings of children with TB/HIV in the form of couples or family HIV counseling and testing. HIV infected members need to be referred to other HIV services.

UNAIDS/UNICEF/WHO [3] [4] recommends the following action:

Institutionalize a family-centred approach and secure HIV testing for all additional family members once an index case is identified.

[ii] To access other WHO Fact Sheets go to : http://www.searo.who.int/LinkFiles/Publications_FactSheet-HIV-AIDSNurses.pdf Accessed 26 September, 2008.

Voluntary counseling and testing (VCT) as the entry point for to HIV prevention and care[iii]

HIV counseling is defined by WHO as, "Confidential dialogue between a person and a care provider aimed at enabling the person to cope with stress and make personal decisions related to HIV/AIDS. The counseling process includes an evaluation of personal risk of HIV transmission and facilitation of preventive behavior." [5] VCT is usually the entry point in the continuum of HIV prevention and care. It is at this point that the family receives the results of HIV testing of family members, discuss the results and learn about what ongoing services are available and how to access them. Therefore health care workers should be knowledgeable of the support services available in their community and the referral mechanisms to access them. The approach to HIV counseling and testing in infants and children should follow WHO/UNICEF recommended guidelines.[3]

Continuum of care

HIV is a life-long chronic condition which requires ongoing, uninterrupted care, counseling and access to support services. The care will take place in different types of health-care settings depending on the course of the illness. This will span a continuum of care from tertiary to home-based care.

It is essential that these services are available and that the family is fast tracked through the system and not lost to care. To ensure the continuum of care is delivered the following elements need to be in place:

- *appropriate Information, education and communication materials to promote care seeking and de-stigmatize the disease;*
- *community mobilization programmes to develop community care programmes;*
- *partnerships between government agencies and NGOs interacting with health, social and community-based health care activities;*
- *referral procedures between hospitals and peripheral health care centres;*
- *referral procedures between patients and their families and social support institutions or NGOs;*
- *health systems strengthening;*
- *monitoring and evaluation mechanisms;*
- *procedures for supervision of staff in health facilities and at peripheral levels including volunteers.*[6]

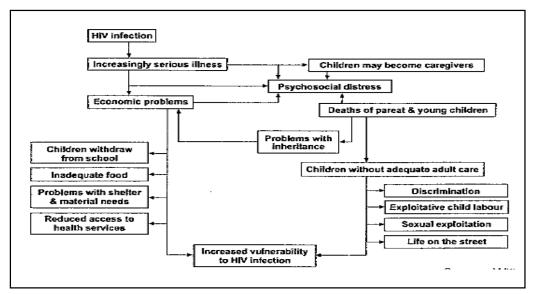[iii] See Additional Resource Section for further information.

Support for the family

The planning process for the HIV/AIDS affected family begins with identifying their needs and WHO has produced a tool to assist with this which outlines the practical steps required.[7] The ability of a family to care for a child with TB/HIV will depend on a number of aspects: socioeconomic status, parents' health/HIV status, knowledge and attitudes to HIV infection.

The health care worker needs to determine what care can be expected from family members and what care must be obtained from other sources. To determine this they need to ascertain the following information:

- What the family know about TB and HIV infection
- Has the family acknowledged that the child has TB and is HIV-infected
- What is the parents' state of health and their psychological condition
- Are they capable of providing physical care for the child
- All individuals who can offer support to this family and their age and health status.
- Are identified individuals willing and able to help care for the child.
- Social services available to the family in their community.
- The family's economic situation.
- The condition and type of family housing.
- The type and availability of food for the child and family.
- The availability of clean drinking water and sanitation

Figure 12.1 Problems experienced among children and families affected by HIV/TB

Source: UNICEF 2004

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In practical terms, support for a family with a child with TB/HIV should include:

- psychological support to family members receiving the test results that their child is HIV-infected and has active TB. This must allow time for the family to grieve and ask any questions they may have regarding the diagnosis
- an assessment during post-test counselling of what psychological, social and economic support the family requires
- support in assisting the family in understanding about their child's HIV/TB co-infection through contextually appropriate information and educational materials about the treatment. This should include the following:
  - the actual treatment for TB and HIV that the child will receive
  - the frequency and duration of treatment
  - what health services are available for both HIV and TB treatment
  - what is required from the family in relation to on-going care
  - planning a schedule of monitoring/counselling visits
  - planning regular clinical and laboratory monitoring
- support to help address issues for older children and adolescents with TB/HIV
- referral for screening for TB of other family members, especially siblings, and other close contacts
- provision of IPT as indicated
- referral for CPT and ART as indicated
- counselling on nutritional needs of infant or young child and other affected family members
- in collaboration with the family, develop a plan of support which should include identifying the support services required. The plan should include identification of all care-givers involved, their roles and what type of support they will provide, when and how, e.g. each family member looking after the child on a certain day so that the mother is not the only care-giver.
- make referrals and appointments to the identified services before the family leaves the facility

Community support

The usual approach to managing TB/HIV has been specialized care delivered at tertiary health care facilities. However, not all people with TB/HIV require referral hospital-based investigations and care. Decentralization and delivery of care at the community level when

appropriate and available through an integration of family and child services allows the following:

- All family members requiring care for TB/HIV and services can receive them at the same time and place
- Saving of both time and money when care is provided closer to home
- Continuity of care between the patient's home, community, and local health centre
- It increases support from the community which may lead to better adherence to treatment and can be instrumental in overcoming barriers to long-term care [2]

It is also important to involve local schools to assist them through education of the teachers and other staff at school to the needs of children with TB/HIV and why they need frequent visits to the clinics and the importance of taking drugs regularly. This may aid in reducing stigma in schools.

Integrate community-based approaches into child health preventive and HIV/TB programming strategies

Community-based strategies provide an important way of optimizing continued care, support and treatment for children who are exposed to or who have HIV (TB), particularly for families living far from health centres. Interventions in the community are particularly important for children who depend on caregivers within the community to access services that benefit these children. Interventions that are based in the community and use community resources can not only aid in case-finding, improve basic care and provide support for treatment adherence but can also play a vital role in addressing stigma, incorporating the voice of people living with HIV in programming and improving treatment literacy.[3]

Summary

The management of children with TB/HIV should be integrated so that all family members are counseled and tested for HIV and screened for TB

The specific needs of each family need to be determined and a plan of action developed to ensure that the family receives comprehensive care using all the services in the community

Each family needs a continuum of care which is delivered in the community

References:

[i] Newell M-L et al. Mortality of infected and uninfected infants born to HIV infected mothers in Africa: a pooled analysis. *Lancet*, 2004, 364:1236–1243.

[2] WHO. Fact Sheets on HIV/AIDS for Nurses and Midwives. Adapted from WHO Geneva Publication 2000. World Health Organization, Regional Office for South-East Asia, New Delhi, India. 2002

[3] UNICEF/WHO. Scale up of HIV-related Prevention, Diagnosis, Care and Treatment for Infants and Children: A Programming Framework. United Nations Children's Fund (UNICEF) and World Health Organization (WHO), New York, Geneva 2008: page 38.

[4] WHO. Priority interventions: HIV/AIDS prevention, treatment and care in the health sector, September 2008. World Health Organization, Geneva, 2008.

[5] World Health Organization/Global Programme on AIDS. Counseling for HIV/AIDS: A key to caring. For policy makers, planners and implementors of counseling activities. Geneva: WHO/GPA, May 1994.

[6] WHO. Planning,and implementing HIV/AIDS care programmes:A step-by-step approach. WHO Project: ICP OCD 041. (Second print) World Health Organization, Regional Office for South-East Asia, New Delhi, India. May 2000. SEA/AIDS/106 :page 10.

[7] WHO. Group interview techniques to assess the needs for people with AIDS. World Health Organization, Geneva, 1995. (WHO/GPA/TCO/HCS/95.2).

ADDITIONAL RESOURCES

Web Sites
UNAIDS: http://www.unaids.org
UNICEF: http://www.unicef.org/aids
WHO: http://www.who.int

Technical and policy documents

Best practices and HIV/AIDS
One of UNAIDS' main tasks is to identify practices around the world that work in responding to the HIV/AIDS epidemic, and to examine how and why they work. Once these practices are identified, UNAIDS and its cosponsors promote the sharing of these practices, including through such means as documentation and widespread distribution of the lessons learned.
http://www.unaids.org/en/KnowledgeCentre/Resources/Publications/bestPracticesArchivePage1.asp

The WHO HIV counselling and testing E-Library
This site provides an extensive bibliography of links to abstracts from scientific conferences or peer-reviewed articles on results of provider-initiated HIV testing and counselling, as well as policies, guidelines and training materials on all models of HIV testing and counselling.
http://www.who.int/hiv/topics/vct/elibrary/en/index.html

Prevention of Mother-to-Child Transmission

WHO/UNICEF/Inter-Agency Task Team on Prevention of HIV Infection in Pregnant Women, Mothers and their Children: Guidance on Global Scale Up of the Prevention of Mother-to-Child Transmission of HIV, November 2007
http://www.unicef.org/aids/files/PMTCT_enWEBNov26.pdf

WHO/UNICEF/Inter-Agency Task Team on Prevention of HIV Infection in Pregnant Women, Mothers and their Children and the South African Ministry of Heath: PMTCT High-Level Global Partners Forum, Meeting Report, November 2007
http://www.unicef.org/aids/files/Global_Partners_Forum_Final_Report.pdf

Consensus Statement on Achieving Universal Access to Comprehensive Prevention of Mother-to-Child Transmission Services, Global Partners Forum, November 2007
http://www.unicef.org/aids/files/consensus_statement.pdf

UNICEF, the Expanded Inter-Agency Task Team on Prevention of HIV Infection in Pregnant Women, Mothers and their Children: A Report Card on Prevention of Mother-to-Child Transmission of HIV and Paediatric HIV Care and Treatment in Low-and Middle-Income Countries: Scaling Up Progress from 2004 to 2005, February 2007
http://www.unicef.org/aids/files/PMTCT_Report_Card_2006_final.pdf

WHO:Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants in Resource-Limited settings: Recommendations for a public health approach, 2006
http://www.who.int/hiv/pub/guidelines/pmtctguidelines3.pdf

United States Department of Health and Human Services, Centers for Disease Control and Prevention, Global AIDS Programme, in collaboration with the Department of HIV/AIDS at the World Health Organization, United Nations Children's Fund and United States Agency for International Development and their implementing partners:Testing and Counselling for Prevention of Mother-to-Child Transmission of HIV (TC for PMTCT): Support Tools, December 2005
http://www.womenchildrenhiv.org/wchiv?page=vc-10-00

Protection and Support of Children Affected by HIV/AIDS

UNICEF, the Working Group on Social Protection for the IATT on Children and HIV and AIDS: Expanding Social Protection for vulnerable children and families: learning from an institutional perspective, March 2008
http://www.unicef.org/aids/files/Expanding_Social_Protection.MTemin.May2008.pdf

UNICEF: Evidence base for Programming for children affected by HIV and AIDS in low prevalence and concentrated epidemics, March 2008
http://www.unicef.org/aids/files/OVC_final.pdf

UNICEF: Inter-Agency Task Team (IATT) on Children and HIV and AIDS: Working Group on Food Security and Nutrition: A Consensus Statement, January 2008
http://www.unicef.org/aids/files/Consensus_Statement_pp5_final.pdf

UNICEF: Enhanced Protection for Children Affected by AIDS, March 2007
This publication serves as a companion paper to *The Framework for the Protection, Care and Support of Orphans and Vulnerable Children Living in a World with HIV and AIDS* .
http://www.unicef.org/publications/index_39192.html

UNICEF: Africa's Orphaned and Vulnerable Generations: Children Affected by AIDS, 2006
http://www.unicef.org/publications/files/Africas_Orphaned_and_Vulnerable_Generations_Children_Affected_by_AIDS.pdf

UNICEF: The Framework for the Protection, Care and Support of Orphans and Vulnerable Children Living in a World with HIV and AIDS, July 2004
http://www.unicef.org/aids/files/Framework_English.pdf

International HIV/AIDS Alliance and Family Health International: Orphans and Other Vulnerable Children Support Toolkit: A CD-Rom and Web Site for NGOs and CBOs. 2004
This toolkit from Family Health International and the International HIV/AIDS Alliance offers a Website and CD-Rom with over 300 downloadable resources and supporting information on how to assist orphans and other vulnerable children.
Subject areas include: Introduction; Running a Programme; Health and Nutrition; Education ; Psychosocial Support; Economic Strengthening; Living Environments; Children's Rights; and Quality Improvement: . http://www.ovcsupport.net

Social Aspects of HIV/AIDS and Health Research Programme: Family and Community Interventions for Children Affected by AIDS. 2004
http://www.ovcsupport.net/graphics/OVC/documents/0000727e00.pdf

UNICEF: Orphans and Other Children Affected by HIV/AIDS 2002
http://www.ovcsupport.net/graphics/OVC/documents/0000177e00.pdf

UNICEF/USAID: Principles to Guide Programming for Orphans and Other Children Affected by HIV/AIDS. 2000
http://www.ovcsupport.net/graphics/OVC/documents/0000077e00.pdf

Cross and Red Crescent Societies: Guiding principles for working with orphans and other children made vulnerable by HIV/AIDS. 2002
http://www.ovcsupport.net/graphics/OVC/documents/0000075e01.pdf
Appendix: http://www.ovcsupport.net/graphics/OVC/documents/0000075e04.pdf

Family Health International:CARE FOR ORPHANS, CHILDREN AFFECTED BY HIV/AIDS AND OTHER VULNERABLE CHILDREN A STRATEGIC FRAMEWORK. 2001
http://www.ovcsupport.net/graphics/OVC/documents/0000127e00.pdf

Paediatric Treatment

UNICEF/WHO: Scale up of HIV-related prevention, diagnosis, care and treatment for infants and children: A Programming Framework, June 2008
http://www.unicef.org/aids/files/UNICEF_WHO_Programming_Framework__June_2008.pdf

WHO: Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults in resource-limited settings: recommendations for a public health approach, 2006
http://www.who.int/hiv/pub/guidelines/ctxguidelines.pdf

WHO: Antiretroviral therapy of HIV infection in infants and children in resource-limited settings, towards Universal Access: Recommendations for a public health approach, 2006
http://www.who.int/hiv/pub/guidelines/pmtctguidelines3.pdf

Cross-cutting Issues

UNICEF:Towards Universal Access: Scaling up priority HIV/AIDS interventions in the health sector: Progress Report, 2008
http://www.unicef.org/aids/files/towards_universal_access_report_2008.pdf

UNICEF, UNAIDS and WHO: Towards Universal Access: Scaling up HIV services for women and children in the health sector: Progress Report, 2008
http://www.unicef.org/aids/files/UNICEF_UA_FINAL_15_July.pdf

WHO:Universal Access: Scaling up Priority HIV/AIDS interventions in the health sector: Progress Report, April 2007
http://www.who.int/hiv/mediacentre/universal_access_progress_report_en.pdf

UNICEF China Office, in collaboration with UNAIDS, ILO, UNFPA, GBC and AusAID**:** Eight Corporate Responses to Children, Young People and AIDS: A win-win guide, April 2007
http://www.unicef.org/aids/files/8_responses_EN.pdf

UNAIDS:Guidelines on Construction of Core Indicators, April 2007
http://data.unaids.org/pub/Manual/2007/20070411_ungass_core_indicators_manual_en.pdf

UNICEF:Sources and prices of selected medicines and diagnostics for people living with HIV/AIDS, June 2005
http://www.unicef.org/supply/files/sourcesandprices2005.pdf

Prevention

WHO, the Inter-Agency Task Team on Young People: Preventing HIV/AIDS in Young People:
http://whqlibdoc.who.int/trs/WHO_TRS_938_eng.pdf

UNAIDS: Intensifying HIV prevention, UNAIDS policy position paper, 2005
http://data.unaids.org/publications/irc-pub06/jc1165-intensif_hiv-newstyle_en.pdf

UNAIDS: At the crossroads: Accelerating youth access to HIV/AIDS interventions, 2004
http://data.unaids.org/publications/irc-pub06/jc1165-intensif_hiv-newstyle_en.pdf

USAID Office of HIV/AIDS, The Synergy Project: A Family is for a Lifetime: Part I – A Discussion of the Need for Family Care for Children Impacted by HIV/AIDS. Part II – An Annotated Bibliography A Family is for a Lifetime: Part I – A Discussion of the Need for Family Care for Children Impacted by HIV/AIDS. Part II – An Annotated Bibliography
http://www.synergyaids.com/documents/AFamilyForALifetimeVersion_1March04.pdf

SECTION 8. MANAGEMENT ISSUES

8.1 RECORDING AND REPORTING OF CHILDREN WITH TB/HIV

Childhood TB is a sentinel epidemiologic event and reflects the effectiveness of TB control programmes including adult case detection, contact tracing, transmission of drug susceptible and resistant TB and BCG vaccination. Accurate recording and reporting of TB and HIV in children is critically important for improved epidemiological surveillance, measuring the impact of interventions and to allow for planning and organization of paediatric TB and HIV services. Other reasons for the necessity for regular reporting and reporting iinclude the need for technical assistance, purchasing of child-friendly drug formulations and determining staff requirements.

How to record and report TB cases and outcomes in children

It is essential to notify the NTP of all identified TB cases in children requiring treatment and recording treatment outcome[1]. All children, in whom TB treatment is initiated, must be entered into the facility-based TB register. All fields in the register should be completed, including the type of TB, HIV status and age of the child. The age of the child is of particular importance as children are required by WHO to be reported in two age groups:

- Children 0-4 years (up to 4 years and 11 months)
- Children 5-14 years

Cohort analysis is the key management tool for evaluating the effectiveness of the NTP. Evaluation of treatment outcome by cohort analysis is a valuable indicator of programme quality. At the end of the treatment, the child's treatment outcome should be recorded in the TB register. The district TB officer compiles and sends the district quarterly reports of all cases registered and their treatment outcomes to the regional TB officer. The regional TB officer verifies veracity of the district reports and submits a regional report to the central NTP. Accurate recording at the facility level will allow for accurate reporting and evaluation of the programme at the district level and beyond.

For children the same outcome definitions apply as for adults (Table 8.1.1)[2] for purposes of consistency of reporting by NTPs. The majority of children with PTB have sputum smear-negative disease and for this reason cure will rarely be recorded. Only four of the standard adult treatment outcomes are applicable to children with smear-negative pulmonary or EPTB: treatment completion, default, death and transfer out. Treatment response in a child with sputum smear-negative TB is assessed through regular monthly assessment and recording of

weight gain and symptom improvement. In children with smear-positive TB, sputum smears should be repeated at 2 and 5 months.

Table 8.1.1. Definitions used by NTPs of standard treatment outcomes[2]

Cured	Patient (sputum smear-positive on diagnosis) who is sputum smear-negative in the last month of treatment and on at least one previous occasion
Completed treatment	Patient who has completed treatment but who does not meet the criteria to be classified as cured or treatment failure
Defaulted	Patient whose treatment was interrupted for 2 consecutive months or more
Died	Patient who dies for any reason during the course of treatment
Treatment failure	Patient who is sputum smear-positive at 5 months or later after strating treatment
Tranferred out	Patient who has been transferred to another recording and reporting unit and for whom the treatment outcome is not known

Recording and reporting of children in the two age bands have become part of the essential data which has to be reported to the WHO. The data required is indicated in the recently published "Revised TB recording and reporting forms and reports: version 2006".[1] These revised forms contain information on the child's HIV status, and use of ART and CPT.

The use of a contact screening registerb as suggested in WHO guidelines[2] should be encouraged. Important screening indicators include the number of children screened, symptoms suggestive of TB, the age and the HIV status of child contacts and the type of treatment the child has received (IPT or anti-TB treatment). The ratio of the number of sputum smear-positive PTB cases to the number of HIV-infected children or children ≤ 5 years of age screened could be used as an indicator of the effectiveness of contact tracing.

Apart from recording in the local TB treatment register, it is important to maintain facility medical records and to include information of TB screening, results and treatment (preventive or curative) on the child's Road to Health Card. This will improve continuity of care and communication between health services. Children should also be included in integrated TB/HIV activities. It is important to establish and maintain linkages between TB and HIV care, recording and reporting in HIV care and treatment settings (ART registers should include recording of TB screening and IPT as well as CPT).

BCG adverse events must also be reported. In most countries this would be to the EPI programme.

Current WHO recommendation [ref 1]

All children treated for TB should be recorded and reported by NTP in one of two age bands.

References

1. Revised TB recording and reporting forms and registers: version 2006.
WHO/HTM/TB/2006.373

2. Guidance for national tuberculosis programmes on the management of tuberculosis in children WHO/HTM/ TB/2006.371 WHO/FCH/CAH/2006.7

8.2 ROLES AND RESPONSIBILITIES IN MANAGING TB AND HIV CONTROL PROGRAMMES FOR CHILDREN

Children who are suspected of having or are diagnosed with TB may be managed by one or more of a range of different care providers with varying levels of expertise and experience, including primary care staff, general clinicians and paediatricians. In order to provide the best care to these children, it is essential to clarify roles and responsibilities of those involved in their management. All providers of TB care should manage TB patients in conjunction with the NTP. Although most adults with TB can be diagnosed with sputum smear microscopy and managed at the primary care level, the situation is different for children, for whom CXR, TST and other tests are recommended, wherever possible.

Levels of care

As the diagnosis of TB in children requires that a minimum of tests be available, service delivery with a structured case management is recommended. The patterns and delivery of services and responsibilities of staff will differ between countries.

Primary care level

Staff

- Medical assistants, nurses and general practitioners.

Minimum requirements

- Recognize the symptoms and signs of childhood TB.
- Recognize the significance of household contact with smear-positive source cases.

Responsibilities

- Identify children with symptoms and signs suggestive of TB as well as contacts of newly diagnosed source cases (usually adults with sputum smear-positive PTB).
- In line with the NTP guidelines, arrange treatment (DOT) for children with TB and ensure referrals and follow-up are carried out.
- HIV counseling and testing (if trained)

Actions

- Refer child to first referral level of care.

First referral level

This level may differ between countries but generally includes community health centres and district hospitals.

Staff

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- Generalists, clinical officers and paediatricians.

Minimum requirements

- Trained to perform TST, lumbar puncture and pleural taps, and read CXRs.
- Have available TSTs, CXRs and HIV tests (in high HIV prevalence areas).

Responsibilities

Diagnose *M. tuberculosis* infection and TB disease by being able to take a history, perform a physical examination and interpret the following tests:

– sputum smear microscopy

– mycobacterial culture

– TST

– CXR

– HIV test (in high HIV prevalence areas)

– lumbar puncture and pleural tap.

Actions

- Refer the child to the NTP officer for registration and appropriate HCW for initiation of treatment.
- Refer the child back to the primary care level for treatment and follow-up.
- Manage common side-effects and more serious cases of disease (e.g. miliary TB).
- Refer child to second referral level of care in cases of severe or complicated TB.

Second referral level

This includes regional or national (tertiary care) hospitals.

Staff

- Person with expertise in managing complicated TB.

Minimum requirements

- These will differ according to national priorities.

Responsibilities

- Diagnose and manage complicated TB, including most cases of disseminated TB, TB meningitis and MDR-TB in children.

Actions

- Advise the NTP on the management of complicated TB cases.
- Refer the child back to the first referral level of care for continued treatment and follow-up.
- Refer the child to and register the child with the NTP.

SECTION 9. RESEARCH GAPS AND PRIORITIES

Although HIV and TB are common in children, especially in HIV-endemic regions of sub-Saharan Africa, there is little research investigating issues related to this field. This guidance was developed to aid health care workers in resource limited countries that manage HIV-infected children with TB, and not as a comprehensive guide to what research is required. Previously there have been other publications giving guidance as to which areas require research in childhood TB. This chapter will only point out the most important areas requiring research in TB-HIV co-infected children.

1. Epidemiology:
    a. Recording and reporting of burden and outcomes of TB/HIV in the two age bands: (0-4 years and 5-14 years)
    b. Investigate barriers to HCT and ART in children with suspected TB

2. Diagnosis of TB in HIV infected children
    a. Determine the feasibility and value of IGRA in the diagnosis of TB, and examine for age and nutritional status.
    b. Determine more effective methods of collecting samples for liquid culture methods.
    c. Feasibility and challenges of implementation of TST at primary clinic level in resource-limited settings
    d. Assess diagnostic algorithms to diagnose and manage childhood TB in communities with a high prevalence of TB/HIV.

3. TB treatment in HIV infected children.
    a. Pharmocokinetic trials to determine the correct TB drug dosages for HIV infected and non-infected children especially in children less than 2 years.
    b. Clinical trials to determine efficacy and safety of higher dose regimens of anti-TB drugs in children
    c. Clinical trials to determine the optimal time for the commencement of ART in children being treated for TB
    d. Clinical trials to determine the optimal ART regimen in children being treated with rifamycin containing anti-TB treatment.
    e. Determine the optimal duration of anti-TB treatment in different forms of TB in HIV infected children.

4. ART during the treatment of tuberculosis.
    a. Pharmocokinetic trials to determine the effect rifamycins have on the drug levels of ART drugs.
    b. Strategies to diminish the drug-drug interactions between anti-tuberculosis and anti-retroviral drugs
    c. Determine the frequency, clinical features and management of IRIS in children dually infected with HIV and TB.

5. Treatment of drug resistant TB in HIV infected children.
    a. Multi-centre randomized control trial to determine the efficacy of preventive therapy in HIV infected children exposed to an index case of MDR TB.
    b. Clinical trial to determine the optimal treatment and duration of treatment of HIV infected children with MDR TB.
    c. Strategies for the rapid diagnosis of MDR TB in children.

6. Preventive therapy for TB in HIV infected children.
    a. Clinical trials to compare dual therapy to isoniazid alone as preventive therapy of TB
    b. Determine the value of IPT after completion of TB treatment
    c. Determine the additional value of IPT to ART to reduce risk of TB while on ART
    d. Feasibility of IGRAs as a method to determine TB infection in child contact screening in resource-limited setting.

7. BCG vaccination in HIV-infected children.
    a. Determine the efficacy of BCG vaccination in HIV exposed children
    b. Determine the feasibility of late vaccination of BCG in HIV infected infants.
    c. Basic research to develop new anti-tuberculosis vaccines with an efficacy and safety profile which allows use in HIV infected children.
    d. Determine safety of BCG in HIV-infected infants after early initiation of ART.

8. Nutritional support
    a. Trials to determine the value of micronutrients as adjuvant therapy in the treatment of TB in HIV infected children.
    b. The effect of regular de-worming in HIV infected children on their morbidity, immunology and mortality.
    c. Strategies to improve the nutrition in HIV infected and affected families.

d. Most effective approaches for treating malnutrition during and after TB treatment—taking into consideration local diets and food availability.

e. Determining caloric requirements for children with TB/HIV and different degrees of malnutrition

f. Successful and varied models for integrating nutritional support into both TB and HIV programmes,

g. Cost-effectiveness of integrated nutritional support

9. Patient and family support in children dually infected with tuberculosis and HIV

a. Investigate the barriers to accessing health care in dually infected children.

b. Financial burden of TB/HIV disease in families.

c. Determine access of families to integrated support.

10. Infection control to prevent HIV infected children being infected with tuberculosis in the HIV era.

a. TB transmission to HIV infected children in health care facilities

b. TB transmission to children in paediatric inpatient facilities.

c. Infection control policies in paediatric health care facilities.

d. Infection control practices to prevent the transmission from HCWs to HIV infected children.

11. Recording and reporting of children with tuberculosis and HIV.

a. Accuracy of reported cases in countries with high burden of TB/HIV.

b. Barriers to the reporting of children with TB/HIV.

c. Global epidemiology of tuberculosis and HIV in children.

d. Reporting of drug resistant TB in HIV infected children.