Module 3: Paediatric HIV-Related Diseases

Session 1: Overview of Opportunistic Infections

Total Session Time: 30 minutes

Learning Objectives

By the end of this session, participants will be able to:
- Define the term opportunistic infection (OI)
- Explain why opportunistic infections are more prevalent in individuals living with HIV
- Outline opportunistic infections in HIV infected children
- Explain strategies to prevent OIs

Definition & Common Features of Opportunistic Infections

Definition: Opportunistic Infections
These are infections that occur more frequently and are more severe in people with weakened immune systems, including children living with HIV.

OIs are infections caused by harmful infectious agents or pathogens that would not cause disease in a child with a well-functioning immune system.

Many people living with human immunodeficiency virus (PLHIV) acquire diseases that also affect otherwise healthy people. In such cases, HIV-infected patients may have a more severe disease course than uninfected people or may develop symptoms that uninfected people do not. However, HIV-infected people are also susceptible to opportunistic infections (OIs), which are infections caused by organisms that in a healthy host would not cause significant disease. Opportunistic infections observed in PLHIVs include a wide range of diseases, from non-severe ailments like chronic skin itching to life threatening conditions like cryptococcal meningitis.

Opportunistic Infections in Children
OIs generally occur with severe immune suppression. Young children have primary infection rather than reactivation. Lack of immunity leads to more severe course than in adults.

In addition to OIs, recurrent bacterial infection account for about 20% of AIDS defining conditions in infants and children. Most recurrent bacterial infections are caused by encapsulated organisms such as S. pnuemoniae and Salmonella, others are Staphylococcus, enterococcus, etc. Most common serious infections are – pneumonia, bacteraemia, sepsis and meningitis (account for more than 50% of infections in HIV infected children).

Common Characteristics of Opportunistic Infections

The most common characteristics of OIs include:

- Often occult, non-localizing: **Occult** means not accompanied by readily detectable signs or symptoms. **Non-localizing** means that the disease is not confined or restricted to a particular locality in the body.
- Unusual organisms
- Unusual presentation
- May be bacterial, viral, fungal, or protozoal

Common Opportunistic Infections

Most common serious of OIs include:

- Pneumocystis jiroveci (formerly Pneumocystis carinii)
- Mycobacterium Avium Complex (MAC)
- Candida Infections
- Common Viral Infections
- CNS Manifestations
- Cardiovascular Manifestations
- Gastrointestinal (GI) Manifestations
- Skin Manifestations
- Hematologic Manifestations
- Malignant Diseases

Skin manifestations can include:

- Bacterial skin infections
- Seborrheic Dermatitis/eczema
- Pruritic Papular eruptions (PPE)
- Scabies

Common viral infections can include:

- Herpes simplex virus
- Chickenpox
- Herpes Zoster
- Measles
- CMV

Common Features of Paediatric HIV in Tanzania

The common presentations of HIV and AIDS in children are similar to adults. These include:

- Lymphadenopathy
- Hepatosplenomegaly
- Growth failure
- Developmental delay or regression such as loss of developmental milestones
- Parotid gland enlargement
- Oral Candidiasis
- Lymphocytic Interstitial Pneumonitis
- Otitis media
- Respiratory illnesses such as bacterial pneumonia and sinusitis, TB, PCP and LIP
- Persistent diarrhoea
- Skin disorders including pruritus, scabies, impetigo

- Kaposi sarcoma
- Peripheral neuropathy

While lymphadenopathy is common along with splenomegaly, one also sees:
- Parotitis
- Growth failure in the form of protein malnutrition
- Protein calorie malnutrition (Kwashiorkor and Marasmus)
- Developmental delay

A child may either not attain milestones or else may lose skills that were previously mastered such as sitting up, crawling, walking or speech.

The infectious disease presentations are similar to what is seen with adults, including oral candidiasis, TB, and other respiratory illnesses such as bacterial pneumonia and PCP (pneumocyctis jiroveci pneumonia), Kaposi sarcoma and diarrhoea. As in adults, peripheral neuropathy is seen both as a manifestation of HIV and as a side effect of some ARV drugs.

Opportunistic Infections and HIV
Prevalence and severity of OIs increase with HIV disease progression. Children with HIV and AIDS are especially susceptible to opportunistic infections due to:
- Suppression of their immune system
- Poor nutritional status
- Psychological stress, which can influence the immune system

OIs are important indicators of HIV infection and may be the trigger for an HIV diagnosis. The natural history of HIV involves a progressive loss of CD4 T lymphocytes. As the CD4 level declines, the risk of contracting OIs increases. However, young HIV-infected infants may catch PCP, even with a normal CD4 levels.

Prevention Strategies of Opportunity Infections

Prevention of Opportunistic Infections
There are three broad strategies for prevention including:
- Avoidance of exposure (safe water, safe food). Currently there are no recommendations for preventing exposure to:
  - P. Jirovecii – no data to support isolation
  - M. avium complex (MAC) – no data
  - S. pneumoniae and H. influenzae – not practical
  - Candidiasis – not practical
  - Cryptococcosis – not practical
- Immunization (antigen, immune globulin)
- Chemoprophylaxis
- Immunization:
  - Give immunizations according to **National guidelines**
  - BCG should not be given to children who present with clear signs and symptoms of HIV-disease or AIDS
  - Avoid missed opportunities for HIV infected children who are sick

BCG is a life attenuated vaccine. Studies have shown that BCG vaccination carries a significantly high risk of disseminated BCG (dBCG) disease in HIV-positive infants, with rates approaching 1%. Other studies have shown that infection with HIV severely impairs the BCG-specific T-cell responses during the first year of life. Thus, BCG may therefore provide little, if any, protection against tuberculosis in HIV-infected infants. Considering the significant risk of dBCG disease, WHO has recommended not to give BCG to children who are known to be infected with HIV. The current WHO recommendation is that for infants born to HIV-infected mothers where early HIV diagnostic testing can be performed, BCG can be deferred until diagnostic testing results are available.

"Missed Opportunity" for immunization (MOI) is defined as missing the benefit of getting immunization by the partially or non-immunized child, during a visit to a health facility for check-up/illness, when there is no absolute contraindication for that particular immunization as per the national policy.

Chemoprophylaxis;
The aim of chemoprophylaxis against opportunistic organisms includes:

- Primary prevention:
  - Prevention of the first episode of OI
- Secondary prevention:
  - Prevention of recurrence after an initial episode of an opportunistic infection

Key Points

- Opportunistic infections are caused by infectious agents, OR pathogens that would not cause disease in a child with a well-functioning immune system
- The risk of contracting OIs increases with decrease in the CD4
- OIs can be prevented through avoidance of exposure, routine immunization and chemoprophylaxis

Sources/Bibliography

- *WHO/EPI/GEN/88-6. GACVS meeting of 3-4 December 2009, published in the WHO Weekly Epidemiological Record on 29 January 2010*

Session 2: Common Childhood Infections

Total Session Time: 1 hour

Learning Objectives

At the end of this session, participants will be able to:
- Describe common childhood infections
- Explain the presentation, diagnosis, treatment and prevention of common opportunistic infections seen in HIV infected children
- Explain the differences of childhood infections between HIV infected and HIV uninfected children

Common Childhood Infections & Management of Common OIs in HIV Infected Children

Common Childhood Infections

Some of the conditions listed below occur in HIV negative children, as well, but in HIV positive children these conditions may be more severe, last longer, recur and be unresponsive to usual treatment. These conditions include:
- Bacterial pneumonia
- Diarrhoeal diseases
- Invasive bacterial infections
- Dermatological conditions
- Malaria
- Measles
- Otitis media

Bacterial Pneumonia

This is the most common pulmonary condition. Presents in the same way as HIV uninfected children with Strep. pneumoniae as the major cause; Other organisms include: *H.influenzae*, *Klebsiella*, *Staph aureus*, non-typhoid Salmonella and enteric gram negatives.

Recurrent bacterial pneumonia suggests severe immune suppression in children (WHO Stage 3). These pathogens are also common causes of bacteraemia and meningitis in children with HIV.

*Refer to **Handout 3.2.1: Classification and Management of Pneumonia** on **page 103** for more information.*

Bacterial Pneumonia Diagnosis

Diagnosis of pneumonia is mainly clinical. Children present with history of fever, cough and fast breathing (tachypnoea) with or without signs of severe pneumonia (chest in-drawing, cyanosis & lethargy). On auscultation of the chest one hears unilateral or bilateral crepitations (crackles), decreased breath sounds or bronchial breathing (lobar pneumonia)

When pulse oximetry is available it might demonstrate hypoxia (0_2 saturation less than 90%). Where complete blood counts can be done a raised WBC with a neutrophilia suggests a bacterial pneumonia, where blood cultures can be done they may assist in identifying the causative agent.

CXR is not necessary but may be useful in ruling out complications or other pulmonary conditions. If the patient is not improving after first line broad spectrum antibiotics, sputum induction and nasopharyngeal aspirate may assist in the diagnosis of PCP or TB.

HIV-infected children often present with a variety of relatively non-specific respiratory symptoms, including cough, dyspnea, sputum production and wheezing. These can result from a variety of causes, some of them non-pulmonary. Respiratory symptoms can be caused by opportunistic infections, lymphoproliferative disorders, immune-mediated conditions and can be caused by conditions seen in children without HIV-infection. These include:

- Upper respiratory infections
- Reactive airway disease
- Bronchitis
- Sinusitis
- Bacterial pneumonia

Differential Diagnosis of Pneumonia

Tuberculosis:

- The shorter history usually differentiates pneumonia from Pulmonary Tuberculosis (PTB).
- Recurrent pneumonia, or pneumonia responding poorly to antibiotics should be investigated further to exclude Tuberculosis. Remember that severe recurrent bacterial pneumonia is a stage 3 condition.

HIV-infected children with TB are also more susceptible to other respiratory diseases. Both bacterial pneumonia and Lymphoid Interstitial Pneumonitis (LIP) may be confused with pulmonary TB.

Other differential diagnoses may include:

- Foreign body
- Bronchiectasis
- Lymphoid Interstitial Pneumonitis (LIP)
- Fungal pneumonias
- Cardiac diseases (CHD, HIV cardiomyopathy)
- Bronchial asthma

Outpatient Management of Pneumonia

Pneumonia is treated at outpatient. If PCP is suspected then high dose CTX should be started (especially if child is less than one year old). Clinician should inform the mother or care taker to bring the child back IF the child develops any of the general danger signs, or becomes worse.

Treatment is the same as in HIV negative children, but duration may need to be longer:

- Oral amoxycillin, or penicillin is adequate
- Where the child is already on Cotrimoxazole prophylaxis, CTX should not be used to treat pneumonia unless PCP is suspected

- If the child is under one year of age the risk of PCP is very high and should be considered
- Give paracetamol for fever

There is a strong evidence based association with the likelihood of developing Infantile Botulism when honey is administered under the age of 1 year (maximum incidence of Botulinism is among infants aged > 6 month old). Therefore honey must be avoided in young children.

Severe pneumonia should be managed in hospital, for management of severe pneumonia or very severe disease, you want to give the first dose of antibiotic IM and refer urgently.

For supportive Care:
- Assess need for supplemental oxygen
- Check oxygen saturation (clinically, pulse oximeter)

Monitor and ensure adequate hydration give IV or oral rehydration solution depending on the severity. Remember: give paracetamol for fever & pain.

The management for each of the different grades of pneumonia
- Severe pneumonia should be managed in hospital and involves use of parenteral antibiotics.
- Start an antibiotic and refer urgently.
- If the child is under one year, PCP must be considered as a differential diagnosis and treatment with high dose Cotrimoxazole and steroids should be started.

Hospital Management of Severe Pneumonia
1st line:
- IV Ampicillin 50mg/kg/6hrly or Benzyl Peniccilin 0.1MU/kg/6hrly + Gentamicin 7.5mg/od (When the child improves on IV antibiotics, switch to oral antibiotics e.g. Amoxicillin (25 mg/kg 2 times a day)).
- If not improving after 48 hours consider staphylococcus infection and add Cloxacillin 50mg/kg 6hrly (If the child does not improve within 48 hours on the first line antibiotics, or deteriorates, look for complications and treat accordingly. If there are no apparent complications, switch to second line antibiotics).

2nd line:
- Ceftriaxone or Cefotaxime if available

Remember antibiotic therapy for HIV infected children needs to be prolonged (10-14 days)

A child with severe pneumonia should be monitored at least every 6 hours. In monitoring, record the respiratory rate and temperature, and note the child's level of consciousness and ability to drink or breastfeed. In the absence of complications, within two days there should be signs of improvement.

Infants < 12 months: PCP must be considered; treatment with high dose Cotrimoxazole & Steriods prescribed.

Investigate for possible HIV infection. Children treated for PCP should continue on PCP prophylaxis until the diagnosis of HIV exposure or infection has been excluded. If *Staph* pneumonia is suspected (e.g. skin lesions, CXR with pneumatoceles, positive blood culture, poor response to 1st line drugs or post measles child) add Cloxacillin 50mg/kg 6hrly or Vancomycin.

Prevention of Bacterial Pneumonia

- Give all vaccines according to Tanzania IVD schedule
- Cotrimoxazole: Given for PCP prophylaxis also protects against bacterial infections.

Invasive Bacterial Infections

HIV-infected children experience more frequent and more severe episodes of invasive bacterial infections (bacteraemia, septicaemia, meningitis). Invasive bacterial infections are indicative of early manifestations of HIV disease. Response to treatment may be slower.

Diarrhoeal Disease

Aetiologies include organisms commonly seen in HIV negative children as well as opportunistic pathogens:

- Rotavirus: Rotavirus is the leading cause of diarrhoea accounting for 60-70% of acute diarrhoea cases in children under 1 year of age.
- Escherichia coli
- Salmonella
- Candida
- Cryptosporidium
- Microsporidium
- Isospora belli
- Cytomegalovirus (CMV)
- Herpes simplex virus (HSV)

Other common causes of diarrhoea include:

- Enterobacter
- Shigella
- Camphylobacter
- Giardia lamblia

In HIV-infected children, other causes of diarrhoea may include atypical mycobacteria and HIV enteropathy. Remember that acute **and** persistent diarrhoea are frequent causes of morbidity in children with HIV.

Acute Watery Diarrhea: 3 times or more liquid or watery stools in 24 h;

- Recurrent
- Complicated by dehydration & malnutrition

Dysentery: Presence of visible blood in stools

Persistent Diarrhoea: Diarrhoea lasting for 14 days or more

- HIV infected children experience more frequent episodes of persistent diarrhoea
- Increased (11-fold) risk for death

Fluid Management:

- Give Low Osmolarity ORS to children with no/some dehydration to replace fluid loss (ORS stands for Oral Rehydration Salts, and ReSoMal stands for Rehydration Solution for Malnutrition)
  - If not dehydrated, give 10ml/kg for every motion of diarrhoea
  - If has some dehydration, give ORS 75ml/kg in the first 4 hrs
- If the child is severely malnourished give ReSoMal for each watery stool
- For severe dehydration give IV fluids (Ringers lactate or normal saline with 5% dextrose)

A child with diarrhoea needs to be assessed for dehydration since this determines how they should be managed. Intra-venous infusions are very dangerous and not recommended in children with severe malnutrition unless the child is in shock.

For severely malnourished with dehydration, start with 5ml/kg every 30 minutes for the first two hours orally or by naso-gastric tube and then adjust according the weight changes observed. If there is continued weight loss then increase the rate of administration of ReSoMal by 10ml/kg/hour. Weigh the child each hour and assess his/her liver size, respiration rate and pulse.

Micronutrient supplementation:

- All children with persistent diarrhoea should receive daily multivitamin and mineral supplementation for 2 weeks
- Zinc: All children with diarrhoea should be given zinc for 10-14 days;
  - 10mg daily for children <6 months
  - 20 mg daily for children $\geq$6 months
- Vitamin A; Dose according to age

Zinc deficiency is common in developing countries and zinc is lost during diarrhoea. Zinc deficiency is associated with impaired electrolyte and water absorption, decreased brush border enzyme activity and impaired cellular and humoral immunity. Treatment with zinc reduces the duration and severity of acute diarrhoea and also reduces the frequency of further episodes during the subsequent 2-3 months.

NOTE: The WHO recommended dose of Vitamin A :

- <6 months 50,000 IU
- 6-12 months 100,000 IU
- 12-60 months 200,000 IU

Nutritional management:

- Advise the mother to reduce the amount of animal milk in the child's diet temporarily
- Continue breastfeeding and give appropriate complementary foods
- Give frequent small meals, at least six times a day

Antibiotic therapy for Dysentery:

- First line: Ciprofloxacin at 15 mg/kg twice a day for 2 days
- Second line: Ceftriaxone IV or IM at 50–80 mg/kg per day for 3 days

Prevention of Diarrhoeal Disease
Proper treatment of diarrhoeal diseases is highly effective in preventing death, but has no impact on the incidence of diarrhoea. Therefore preventive measures should be discussed including:

- Breastfeeding
- Improved feeding practices
- Use of safe water
- Hand washing
- Food safety
- Use of latrines and safe disposal of stools
- Measles immunization

Good and consistent hand-washing (child and family members) with water and soap, where by, each time after using the toilet, before preparing and serving food or eating. Use clean, safe water for drinking, and for washing fruits and vegetables, serve clean, safe food and breastfeeding.

Dermatological Conditions

- Infectious such as: viral, bacterial, fungal, scabies: Scabies is caused by a mite (like a tiny insect) called Sarcoptes scabiei presenting with itching, rash and scratching.
- Non-infectious including:
  - Papular Pruritic Eruption (PPE)
  - Atopic dermatitis
  - Drug reactions

Malaria
HIV infection increases the incidence and severity of clinical malaria;

- Frequent episodes
- Higher levels of parasitaemia
- More prone to malarial anaemia

In areas of stable malaria, HIV infection leads to increased rates of malaria fever. Malaria and parasite density are higher in children with advanced immunosuppression. But in areas of unstable/epidemic malaria, HIV-infected children are more likely to experience severe disease and coma.

Treatment is according to national guidelines. The recommended first line drug for non severe malaria is ALU (Artemether-Lumefantrin) and for severe malaria is Artemether. Better to prevent by using insecticide-treated mosquito nets (ITNs).

Measles
Common features include:

- Causes severe illness in children with HIV infection, particularly those with advanced immunodeficiency
- May occur in early infancy in HIV-infected children
- Severe cases can occur without the typical rash and may be complicated by pneumonia or encephalitis
- Should be treated in hospital
- Has a high case fatality

Prevention of Measles
Prevention: Immunization with MR vaccine. MR is given in 2 doses, first dose at 9 months and a repeat dose at 18 months.

Live attenuated MR vaccine has been recommended for children, adolescents, and young adults with known HIV infection to prevent morbidity and mortality attributable to measles. Although live virus vaccines can pose a risk to those who have immune system problems, like children with HIV, measles vaccination is still recommended because HIV infected children are at greater risk for severe complications if they get measles.

REMEMBER: ALL children should be immunized against **measles.**

Otitis Media
Otitis media is an inflammatory disease of the middle ear which can be:
- Acute (< 14 days duration)
- Chronic (≥ 14 days duration)

Ear infections are common in both HIV infected and uninfected children. If pus is seen draining from the ear and discharge is reported for 14 days or more, it indicates chronic ear infection.
Children with **chronic ear infections**, they need to:
- Check that the mother is wicking the ear correctly, and show her how to do it if not
- Ask the mother if she is still instilling antibiotic ear drops, and explain the need to continue
- Refer the child for further evaluation if the pus is draining after 2 weeks of proper wicking and topical antibiotic

Treatment includes:
- Acute otitis media such as ear wicking and oral antibiotics e.g. amoxycillin
- Chronic otitis media include:
  - Use of oral antibiotics as in acute otitis media OR according to sensitivity pattern if available
  - Ciprofloxacin Ear drops (Refer to IMCI Guidelines)

Clearing of the ear by dry wicking requires the caregiver to do the following 3 times daily:
- Roll clean absorbent cloth or soft, strong tissue paper into a wick
- Place the wick in the child's ear
- Remove the wick when wet
- Replace the wick with a clean one and repeat these steps until the ear is dry
- Instill Ciprofloxacin eardrops for two weeks

Complicated cases of chronic otitis media should be referred. Referral criteria include:
- Children with high fever who are toxic or children with severe ear pain, headache, altered state of consciousness
- Foul smelling ear discharge or a painful chronically discharging ear
- Mastoid abscess (after incision and drainage)
- Otitis in the normal (or better hearing) ear combined with permanent hearing loss in the other ear.
- Secretory otitis with hearing loss that does not improve.

Key Points

- Causative pathogens of common childhood diseases are the same as in non HIV-infected children
- HIV-infected children may experience:
  - More severe disease
  - High disease recurrence rate
  - Higher case fatality rate
- Common infections need aggressive treatment
- Prevention of infections is a crucial component of care

Handout 3.2.1: Classification and Management of Pneumonia

Pneumonia is the most common pulmonary condition and presents in the same way as uninfected children with *Strep. pneumoniae*as the major cause, other organisms include: *H.influenzae, Klebsiella, Staph aureus,* non-typhoid *Salmonella* and enteric gram negatives. Recurrent bacterial pneumonia suggests severe immune suppression in these children (WHO Stage 3). These pathogens are also the common causes of bacteraemia and meningitis in children with HIV.

TheDiagnosis of pneumonia is mainly clinical. Children present with history of fever, cough and fast breathing (tachypnoea) with or without signs of severe pneumonia (chest in-drawing, cyanosis & lethargy). On auscultation of the chest one hears unilateral or bilateral crepitations (crackles), decreased breath sounds or bronchial breathing (lobar pneumonia). When pulse oximetry is available it might demonstrate hypoxia (0_2 saturation less than 90%). Where complete blood counts can be done a raised WBC with a neutrophilia suggests a bacterial pneumonia. Where blood cultures can be done they may assist in identifying the causative agent. CXR is not necessary but may be useful in ruling out complications or other pulmonary conditions. If the patient is not improving after 1st line broad spectrum antibiotics, where possible, sputum induction and nasopharyngeal aspirate may be done to assist in the diagnosis of PCP or TB.

Differential Diagnosis of Bacterial Pneumonia includes: Tuberculosis, Foreign body, Bronchiectasis, Lymphoid Interstitial Pneumonitis (LIP), fungal pneumonias, Cardiac diseases (CHD, HIV cardiomyopathy,) and Bronchial asthma.

Management of Bacterial pneumonia can be outpatient or inpatient depending on the severity. Outpatient- Treatment is the same as in HIV negative children but duration may need to be longer. Oral Amoxycillin or Penicillin is adequate. If the child is already on Cotrimoxazole prophylaxis, CTZ should not be used to treat pneumonia unless PCP is suspected. In children under one year of age the risk of PCP is very high and should be considered. Give Paracetamol for fever.

Severe pneumonia should be managed in hospital. Specific treatment is as follows:

- First line treatment: IV Ampicillin 50mg/kg/6hrly + Gentamycin 7.5mg/od. Alternatives include Ampicillin/Cloxacillin 50mg/kg 6hrly and Gentamycin
- Second line treatment Ceftriaxone or Cefotaxime 50mg/kg/ 12hrly (3^{rd} generation cephalosporin) if available. Remember antibiotic therapy for HIV infected children needs to be longer (10-14 days)

Supportive Care such as supplemental oxygen should be given whenever necessary after assessment and determining oxygen saturation (clinically, pulse oximeter). Monitor and ensure adequate hydration. Give IV or oral rehydration solution depending on the severity. Remember to give Paracetamol for fever and pain.

For Infants < 12 months, PCP must be considered and treatment with high dose Cotrimoxazole and Steroids prescribed. Investigate for possible HIV infection. Children treated for PCP should continue on PCP prophylaxis until the diagnosis of HIV exposure or infection has been excluded. If *Staphylococcal* pneumonia is suspected (e.g. skin lesions,

CXR with pneumatoceles, positive blood culture, poor response to 1st line drugs or post measles child) add Cloxacillin 50mg/kg 6hrly or Vancomycin 5mg/kg.

Bacterial pneumonia can be prevented by giving immunization (pentavalent vaccine [DPT/HB/Hib]), according to EPI schedule. Where available conjugated pneumococcal vaccine can be given, but this is not routine in Tanzania. Cotrimoxazole which is given for PCP prophylaxis also protects against bacterial infections.

Session 3: Diagnosis of Tuberculosis in Children

Total Session Time: 1 hour

Learning Objectives

By the end of the session participants will be able to:
- Describe the epidemiology of Tuberculosis in children
- Explain risk factors for TB in children
- Describe recommended approaches used for diagnosis of tuberculosis in HIV infected children
- Outline the differential diagnoses of TB in children

Epidemiology & Risk Factors for Tuberculosis in Children

Epidemiology: Tuberculosis
TB is a chronic infectious disease caused by Mycobacterium tuberculosis which is also called Acid Fast Bacilli (AFB) as they resist decolourisation with acid or alcohol. TB transmission occurs from persons with active pulmonary TB. TB droplets remain suspended in the air for hours, making TB more infectious than many other respiratory pathogens.

TB is the major cause of morbidity and mortality in HIV-infected children. Children with HIV infection are 5-10 times more likely to develop TB. Children with dual infection of TB and HIV are 4 times more likely to die than those with TB alone.

The World Health Organization estimated in 2011 that HIV prevalence in children infected with TB, in countries with moderate to high prevalence, is 10-60%.

In a Zambia study for instance;
1) Children with TB/HIV had a 6-fold increase in mortality compared to children with HIV alone
2) TB responsible for 32% of deaths in HIV-infected children

Childhood TB:
- Is most common between the ages of 1 and 4 years
- Is less common between 5 and 12 years
- Increases in adolescence

Most children with TB are smear negative hence are not infectious.

Infants and young children < 5 yrs of age have immature immune systems and are at risk of TB infection and progression to disease;
- The time-span between infection and disease may be quite short
- Risk of dissemination is high

NOTE the following points:

- Children are often exposed to TB early in life and so immunization needs to be given as early as possible
- Early immunization on the other hand may not be useful since the immune system of a newborn may not be mature enough to produce an effective immune reaction to the BCG
- When given later, probably those children have already been infected especially in high burden countries
- BCG may not be effective if children are malnourished or have other severe illnesses.

BCG protects against the more severe forms of Tb (Milliary TB and TB Meningitis).

Children usually develop TB disease earlier than adults. Multiple and varied clinical manifestations overlap with other disease manifestations. Commonly present with primary infection rather than the reactivation seen in adults.

Primary pulmonary TB is characterized by the Ghon Complex which consists of a subpleural focus of inflammation, and infected (inflamed) lymph nodes draining the primary, subpleural lesion.

Secondary pulmonary TB (reactivation) is characterized by a focus of infection and granuloma formation usually in the apex of the lung. The granulomas coalesce to form larger areas of consolidation with central caseating necrosis that forms cavities. Regional lymph nodes also contain caseating granulomas.

Post primary TB occurs in adults: Progression to disease is less frequent in young children than in adults, but when young children get TB they are more likely to develop severe forms.

Forms of Paediatric Tuberculosis

Paediatric Tuberculosis categorises into:

- Pulmonary (usually primary):
  - Smear negative in majority, especially in children < 6yrs
  - Smear positive (mostly in children >6 years)
- Extra pulmonary:
  - Miliary TB and TB meningitis (usually in children less than 3 years of age)
  - TB lymphadenopathy (all ages)
  - TB effusions (pleural, pericardial & peritoneal)
  - Spinal TB (often school-aged children)

Clinical presentation of TB meningitis depends on age of the child and stage of the disease. The signs and symptoms of TB Meningitis present over a course of 3 weeks, although onset can be abrupt. In the first stage, child has personality and behavior change, has anorexia, fever, more irritable and/or restlessness. Second stage looks more like a meningitis infection including headache, neck pain, neck stiffness and continued fever. Due to increased intracranial pressure, children can have convulsions and brain damage. When symptoms progress to the third stage, the child may experience a loss of consciousness, irregular pulse and respirations, increasing fever, and death.

Compared to adults (excluding those who are HIV infected), EPTB is more common in children.

TB Transmission

TB transmission occurs from persons with active pulmonary TB. In settings with poor airflow, TB droplets can remain suspended in the air for hours, making TB more infectious than many other respiratory pathogens.

- Person-to-person: Through the air by a person with pulmonary TB disease of the lungs when he or she coughs, sneezes, or speaks.
- Less frequently transmitted by ingestion of Mycobacterium bovis: Found in unpasteurised milk products.

For example of TB droplets suspended in the air

NOTE that, TB lymph-node draining pus is also infectious.

Background Information

- *A person must inhale the air containing the droplet nuclei in order for transmission to occur.*
- *Each untreated patient with pulmonary TB disease infects on average 20 other people in a year.*
- *Although the bacteria can survive in the air for many hours, the bacteria can be killed fast by direct sunlight or cleared out of a room by opening the windows to let fresh air in.*

Risk factors for TB in Children

The risk factors for children to develop TB infection and for the TB to progress include:

Infection

- Contact with an adult or older child with smear-positive PTB
- Extent of exposure to the infectious person

Progression to TB Disease

- Level of immune system maturity
- Weakened immune system
- HIV, Measles, Whooping Cough, Malnutrition

The risk of acquiring TB is higher if the infectious person is the mother/caregiver since the child spends more times with the mother/caregiver. The degree of infectiousness depends on

the amount of bacteria expelled out by a source person. Extent- explain it as duration of exposure

Immune system maturity depends on age. The younger the child the higher risk of progression from infection to TB disease. Also, a child's immune system may be weakened from various diseases including HIV, measles, or malnutrition.

Recommended Approaches to Tuberculosis Diagnosis in HIV Infected Children & Differential Diagnoses of TB in Children

General Approach to TB Diagnostic in Children

Diagnosing TB disease in children can be challenging. Bacteriologic confirmation is achieved in a minority of pediatric TB patients. Achieving accurate TB diagnosis in children is based on the presence of the "classic tetrad" or four characteristics listed.

Bacteriologic confirmation is achieved in only about 30-40% of cases. Therefore, diagnosis often based on presence of a combination of the following four characteristics:

- History of close contact with adult with TB (especially if smear positive)
- Signs and symptoms compatible with TB disease
- A positive tuberculin skin test (TST)
- Suggestive lab results or radiographic findings

NOTE that:

The majority of children with PTB are too young to provide a sputum specimen for smear microscopy. Hence, getting samples for examination is difficult such as gastric aspirate. So may be misclassified as negative.

Background Information:

- *TB risk is increased when there is an active case of TB in the same house, or when child is malnourished, HIV-infected or has had measles in the past few months.*

Approach to Diagnosing TB in Children

Diagnosing TB in children can be made under the following approaches:

- Complete history, including history of TB contact and symptoms of TB disease
- Clinical examination and use of scoring system
- Tuberculin Skin Testing (TST): TST should be made available.
- Bacteriologic confirmation when possible
- Laboratory and radiologic investigations for TB
- HIV testing

TB should be suspected when the child is in contact with people with active TB and is displaying symptoms consistent with a diagnosis of TB.

Consider TB in any child with:

- History of contact with an adult or older child with smear-positive PTB in the last 6 months to 2 years
- History of unexplained weight loss or failure to grow normally or weight faltering
- Unexpected fever, especially lasting longer than 2 weeks, night sweats
- Cough of any duration (not responding to antibiotics)

- Loss of appetite
- Fatigue, reduced playfulness, less active, irritability
- Difficult breathing
- Children older than 5 years of age coughing with blood stained sputum (haemoptysis)
- Failure of response to appropriate antibiotic treatment of presumed bacterial pneumonia or meningitis
- Appearance: Thin or wasted
- Temperature: Normal or elevated
- Lymph nodes: Enlarged, non-tender (common site cervical), sometimes matted, may have a discharging sinus
- Abdomen: masses or ascites
- Bone/joints: swelling, effusion, angulation of the spine
- Signs of meningitis, especially when developed over several days

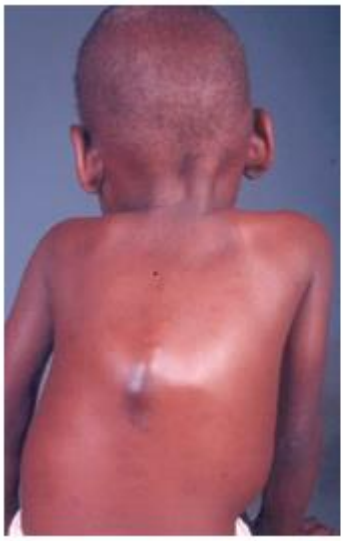
The source of TB in a child is usually an adult with smear positive TB. For this reason a history of TB in an adult family member is one of the criteria for suspecting TB in a child even if the child is asymptomatic. Similarly, children <5 years living with a smear positive TB patient should be evaluated for TB. Ask the mother of a child with suspected TB for the child's RCH card (growth card). If the card is available, look for growth faltering or weight loss.

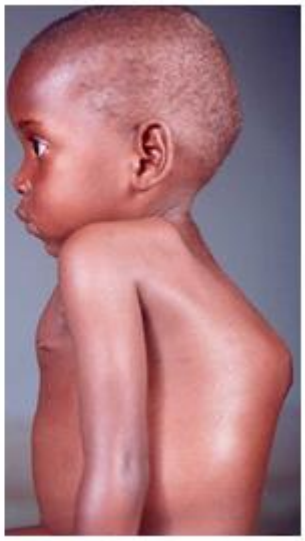
Children with TB may have a low grade fever, stop growing or lose weight. In the case of extrapulmonary TB, symptoms will depend on the site of the disease.

Chest:
- Respiratory rate may be normal or high
- There may be bronchial breathing, crepitations (crackles) and/or wheezing; however, ***breath sounds may be normal (***Breath sounds can be normal, or children can have any type of abnormal lung findings from TB).
- Dullness on percussion (in case of pleural effusions)
- Distant heart sounds if pericardial effusion present

Background Information
- *The signs mentioned in the slide (crepitations or crackles) and wheezing or dullness on percussion are features which are not specific to pulmonary TB. These findings can also occur in other diseases involving the lungs.*
- *Findings indicate the pathologic changes in the lungs rather than the aetiology of lung diseases.*
- *For example, dullness on percussion indicates either fluid or consolidation, tracheal displacement indicates fibrosis or collapse of lung or pleural effusion.*

TB Spine





Evaluation of Suspected Paediatric TB: Laboratory Tests

Two sputum smears are recommended for diagnosis of a new case of TB. Morning specimen usually has the highest yield.

- Microscopic examination of sputum or gastric aspirate for acid-fast bacilli (Ziehl-Nielsen stain).
- Mycobacterial Culture:
  - Expensive
  - Sensitive technique, detects as low as 10 bacilli/mil
  - Higher yield than smear microscopy
  - Requires 2-8 weeks for growth
  - Requires higher level facilities and laboratory staff with advanced training
- GeneXpert (if available): GeneXpert® MTB/RIF is now available in a few sites in Tanzania for and is used for rapid TB diagnosis and detection of rifampicin resistance. It is an automated diagnostic test that can identify *Mycobacterium tuberculosis.*

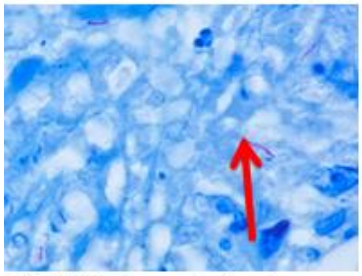
For young children and infants who cannot expectorate, gastric aspirate is used for TB diagnosis. This should be performed by trained personnel by using a nasogastric feeding tube to collect sputum swallowed overnight. This requires two early morning specimens collected on consecutive days *before* child eats or drinks.

Most chest x-rays of children with TB will show enlargement of the hilar or mediastinal lymph nodes rather than parenchymal involvement as in adult TB.

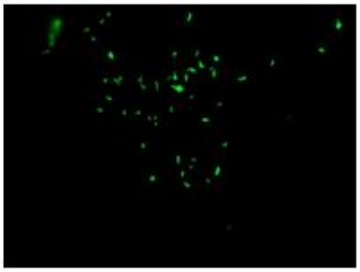
Smear microscopy will continue to be used as the primary screening test for all TB suspects. GeneXpert® will be used as a follow-up test for smear-negative HIV-positive TB suspects and in children as an initial test. It will also be performed on contacts of MDR TB and previously treated patients who are likely to have drug-resistant TB.

Laboratory Tests

Smear Microscopy



Ziehl-Nelsen stained smears with AFBs as seen under microscopy



AFBs as seen under Light Emitting Diode (LED) fluorescence microscopy.

Smear microscopy using Ziehl-Nelsen stained smears and Light Emitting Diode (LED) fluorescence microscopy are main diagnostic tests widely available in Tanzania.

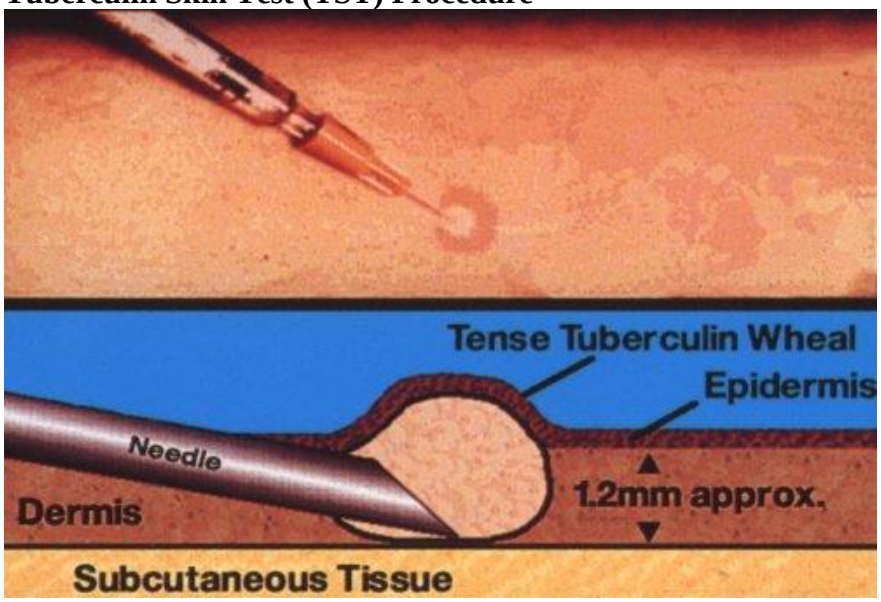
Evaluation of Suspected Paediatric TB: Tuberculin Skin Test (TST)
Also called the Mantoux or PPD (Purified Protein Derivative) test:

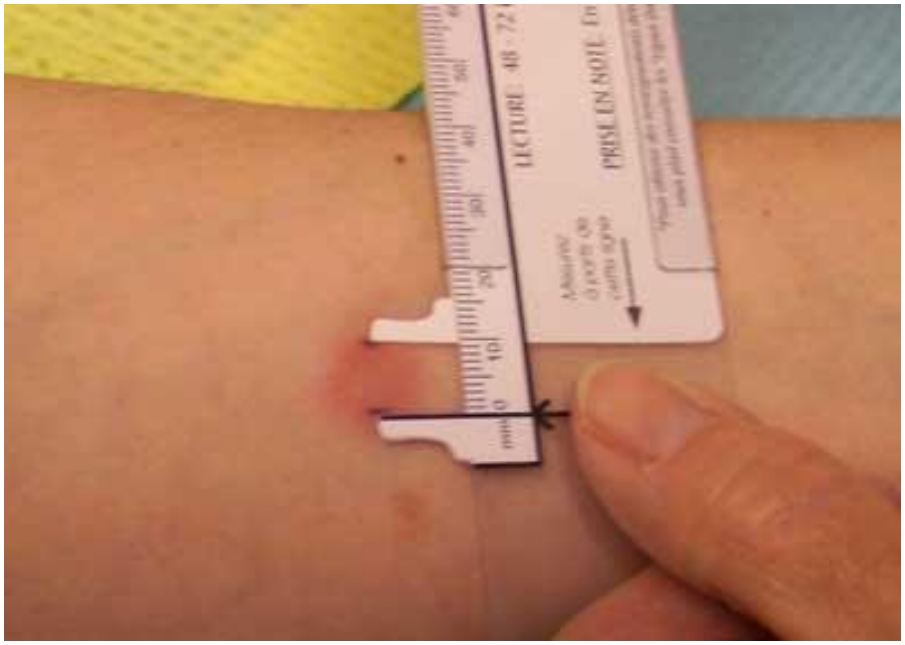
- Indicates mycobacterial infection but NOT necessarily the presence of TB disease
- Should be performed by trained personnel
- Read TST result 48 – 72 hours later by measuring the size of induration

Tuberculin skin tests identify children infected with TB, but not necessarily those with active disease. The test can be positive in children who are asymptomatic (TB infection), as well as those with disease (TB disease).

NOTE: TST must be done to all children suspected to have Tuberculosis.

Tuberculin Skin Test (TST) Procedure





How to insert the needle to place TST:

- The needle should be placed in the subcutaneous tissue and 0.1ml of fluid should be placed. Follow-up in 48-72 hours.

Once injected into the skin (intradermal) of an infected person, it produces a delayed local reaction. After 48 to 72 hours, the skin is examined for induration at the injection site. The diameter of the induration is measured with a soft, flexible ruler, calibrated in millimeters and the site is carefully palpated and if an induration is present, its limits are determined and its largest transverse diameter is measured in millimeters.

A positive test is indicated by the firm swelling, or palpable induration, at the site. Redness or erythema is **NOT** an indication of a positive test.

Interpretation of TST Results

TST results chart

Patient Characteristic	**Positive TST Result**
HIV-infected	≥ 5 mm diameter induration
Severely malnourished (marasmus or kwashiorkor)	≥ 5 mm diameter induration
Contact to a case of infectious TB (smear positive)	≥ 5 mm diameter induration
All other children (regardless of whether they have received a BCG vaccination or not)	≥ 10 mm diameter induration

A **positive TST result** can be used as an adjunct tool for diagnosis of TB disease in children. A positive TST result alone is NEVER diagnostic of TB disease as it indicates infection. The test can be positive in children who are asymptomatic (TB infection), as well as those with disease (TB disease).

Negative Result shows that there is no infection with MTB or anergy (failure of the body to respond to an allergen). This cannot exclude active TB disease as 20-25% of HIV patients

with active TB will have a negative TST. False-negative tests can occur in children with severe malnutrition, after measles and other severe infections.

NOTE: A negative TST does not rule out TB.

False positives can occur from:
- BCG (Bacille Calmette-Guérin) vaccination
- Infection with non-tuberculosis mycobacterium
- Improper administration or interpretation

It is very important to carefully interpret TST results because there can be **false positives** and **false negatives.** False positive results mean that the test is falsely positive when there is in fact no TB. False negative results mean that the test is falsely negative when in fact there is TB present. Therefore it is important to consider clinical signs and symptoms, if patient had contact with someone with TB infection, and laboratory and radiologic testing.

False negatives can occur from:
- Incorrect administration or interpretation of the TST
- Age less than 6 months
- Severe malnutrition
- Advanced HIV disease
- Immune suppression by other diseases or medication
- Viral illness or recent live virus immunizations
- Overwhelming TB disease

Other Investigations
Other investigations of paediatric TB include:
- Histological diagnosis (for TB Adenitis)
- Lumbar puncture (for TB meningitis)
- Pleural/Ascitic tap for microscopy, biochemical analysis (protein and glucose concentrations), cytology and culture
- Molecular techniques (PCR, Serology)
- Haematological tests such as ESR and FBP

Serological tests are not currently recommended for routine diagnosis of childhood TB, as they have been inadequately studied in children and have performed poorly in the few studies which have been done. Other specialized tests, such as computerized chest tomography and bronchoscopy, are not recommended for the routine diagnosis of TB in children.

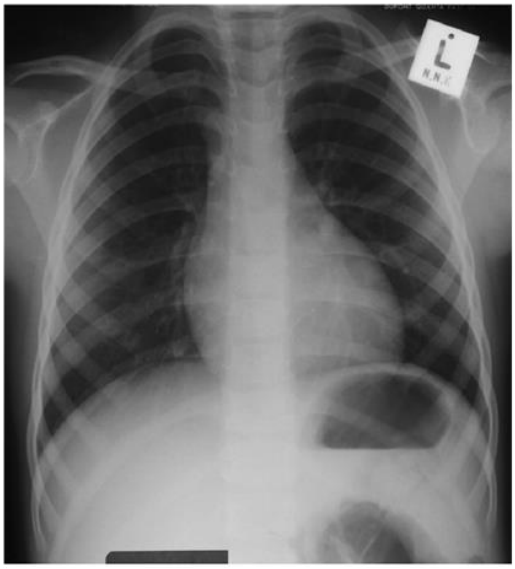
Chest X-Ray
Chest radiography including anterioposterior/posteroanterior and lateral views is required for all children suspected to have pulmonary TB.

Chest x-ray is not a specific diagnostic investigation since there is no typical appearance. All children with suspected pulmonary TB should have a chest x-ray. Chest X-Ray may show features such as lobar opacity, pleural effusion, miliary pattern, lung collapse or hilar enlargement.

Normal Chest Radiograph:

- Note that there is good inspiration, lack of rotation, and good penetration
- The rib ends are marked to aid in evaluating absence of rotation

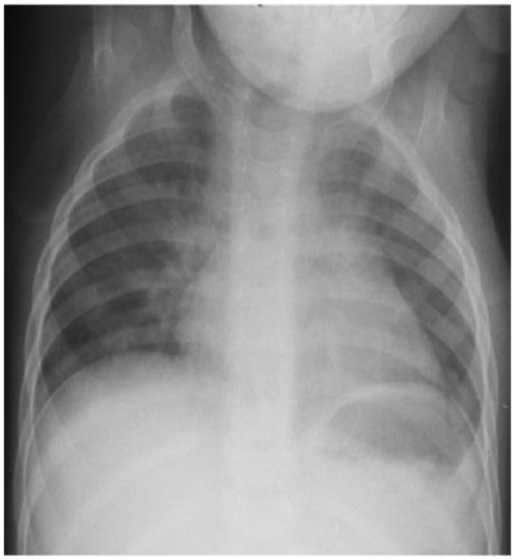
Chest radiographs are difficult to interpret, with great intra-and inter-observer variability reported.



*Refer to **Handout 3.3.1: Steps to Read a Chest X-Ray** on page **121** for more information on how to read a chest x-ray.*

Poor Quality Chest X-Ray;

- What makes this chest X-Ray poor quality?

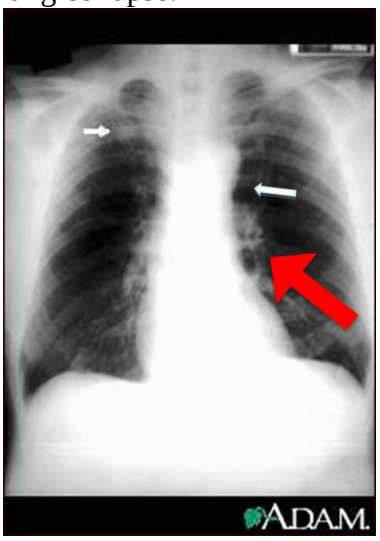


Most common chest radiograph findings in **adolescents** with TB disease include:

- Alveolar opacity/pneumonia;
  - Upper lobe common
- Perihilar lymphadenopathy
- Interstitial opacity/pneumonia

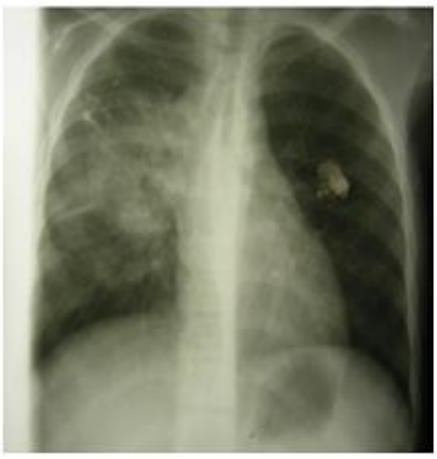
- Expansile pneumonia
- Cavitary lesions

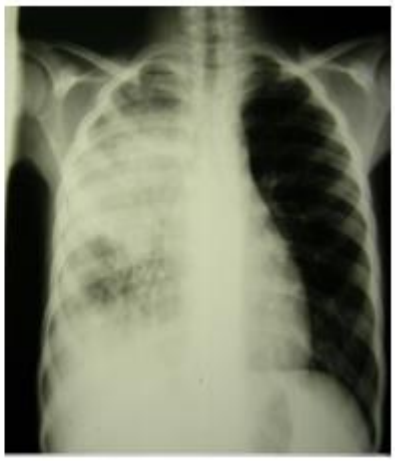
The Chest X-Ray shows a nodule consistent with TB could be lymphadenopathy. Lymph nodes can be as large as to cause compression of bronchials and causing secondary infection or lung collapse.



Adolescents with TB present with typical adult disease findings including upper lobe infiltrates, pleural effusions, and cavitations on chest radiograph.

The x-ray shows lobar consolidation on the Right X-Ray which has involved the whole lung on the Left X-Ray.

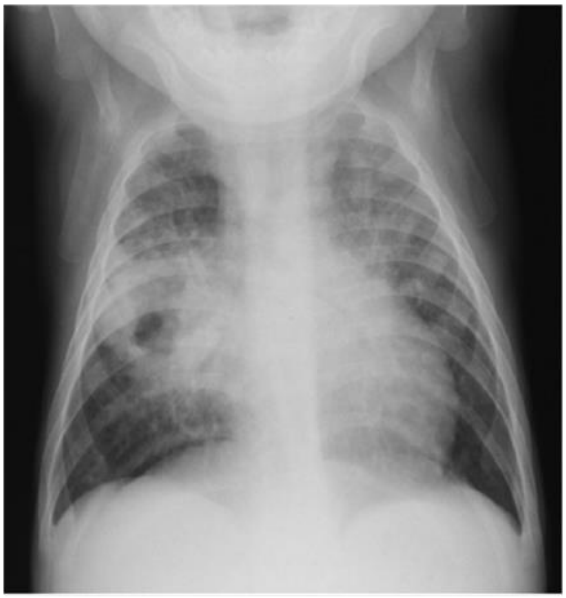




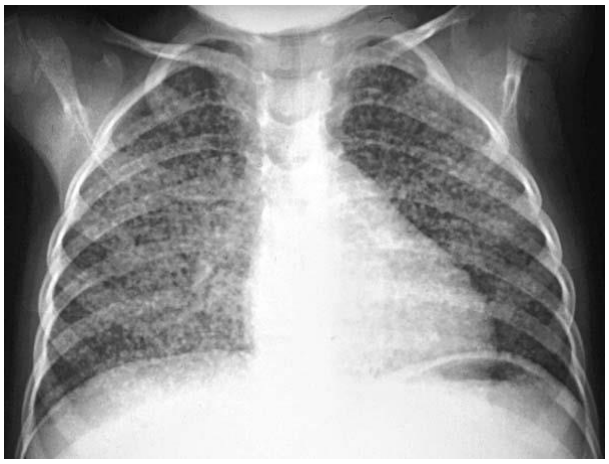
X-rays may be difficult to interpret in HIV infected children but in general they show enlargement of hilar, mediastinal, or subcarinal lymph nodes and lung parenchymal changes.

These two X-Rays are of the same patient. Initially the patient was thought to have lobar pneumonia (X-Ray on the Left side), and was treated with antibiotics. However there was no response after 2 weeks of treatment and therefore TB was diagnosed and the patient responded well to Anti TB and improved clinically. (Control X-Ray could not be available).

Cavity in the right middle lobe resulting in the spread of the TB to the rest of the lung, giving a bronchopneumonic radiological picture.



Miliary Tuberculosis:
The chest x-ray may have a miliary pattern as shown in this x-ray, described as fine, rounded opacities.



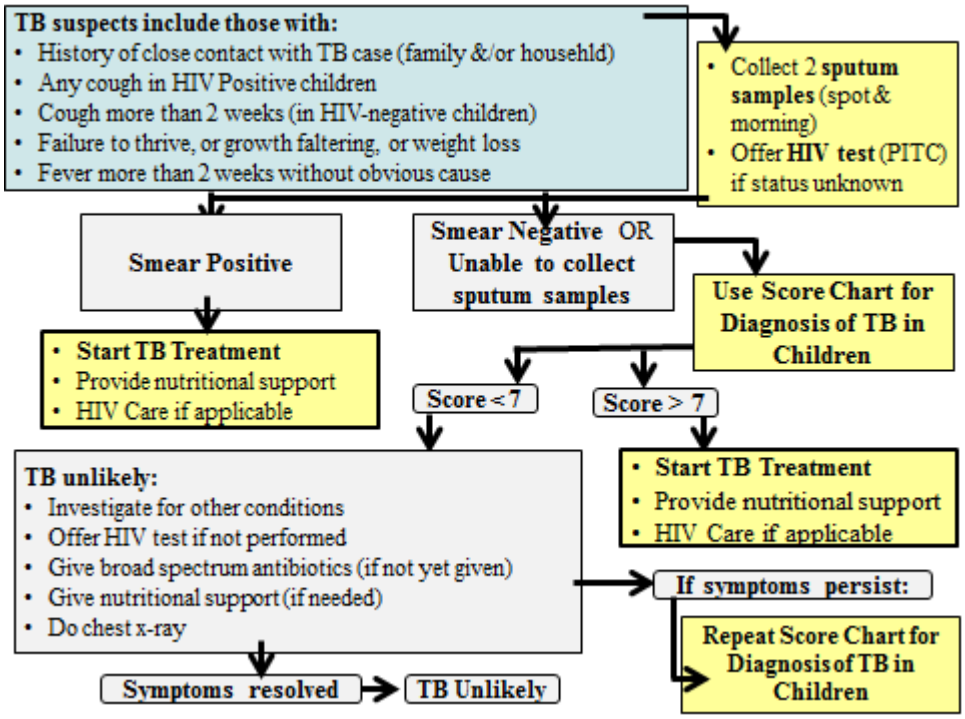
Score Chart for Diagnosis of TB in Children
Due to difficulties in diagnosing TB in children, a score chart which contains signs, symptoms and investigation findings has been developed to aid the diagnosis of TB in children. However, no pediatric scoring system has been well validated in children (especially in HIV-infected children). The scoring system result is suggestive of TB disease in children but is NOT diagnostic.

In the absence of bacteriologic confirmation, use the "Score Chart for Diagnosis of TB in Children". Score of 7 or higher is highly suggestive of TB.

It is difficult to confirm a diagnosis of TB in children owing to:
- A wide range of clinical features which overlap with other common diagnoses in children
- Difficulty in obtaining a sputum sample for bacteriologic confirmation
- Poor yield of sputum samples (results may be negative even on culture)

*Refer to **Handout 3.3.2: Score Chart for the Diagnosis of TB in Children** on page **123** for more information.*

This diagram is the **Algorithm for Diagnosing Pulmonary TB in Children**



*Refer to **Handout 3.3.3: Diagnosing Pulmonary TB in Children Algorithm** on page **125**.*

Symptoms of Extrapulmonary TB

Anatomical Site	Signs & Symptoms
Pleural TB (pleural effusion)	Cough, fast breathing, decreased breath sounds, decreased tactile and vocal fremitus, displaced trachea and cardiac apex, homogeneous opacification of whole hemithorax or obliteration of costophrenic angle
Pericardial TB	Shortness of breath, cough, chest pain, fainting/dizziness, increased heart rate
Abdominal TB	Increased size of abdomen, abdominal discomfort, shortness of breath
TB of spine, bones, joints	Acute angulation of spine, weakness in limbs, joint effusions, joint destruction, retropharyngeal mass, psoas abscess

With pleural TB, excess fluid accumulates in pleural space and can impair breathing, which will cause cough, increased respiratory rate, decreased breath sounds, decreased tactile and vocal fremitus. The fluid volume can be large enough to displace the trachea and cardiac apex. Pericardial TB causes excess fluid accumulation in pericardium impairing cardiac function. Patients may have shortness of breath, cough, chest pain. Abdominal TB presents with ascites which is excess fluid in the abdominal cavity which can cause increase of the abdominal size, causing abdominal pain and shortness of breath. TB of the spine, bones, and

joints commonly occurs 6-36 months after primary infection and will present as angulation of the spine, weakness in limbs, joint effusions and can progress to joint destruction, retropharyngeal mass due to abscess from infected cervical vertebra and psoas abscess.

*Refer to **Handout 3.3.4: Summary of Investigations for Extrapulmonary TB in Children** on page **127***

Differential Diagnosis of PTB
Bacterial pneumonia: Acute bacterial pneumonia usually responds well to standard treatment with penicillin or other broad spectrum antibiotic. Poor response to anti TB may be an indication of a wrong TB diagnosis or co-infection with another organism.

Lymphocytic Interstitial Pneumonitis (LIP);
This presents with symmetrical, generalized lymphadenopathy with chronic parotitis and finger clubbing.

Pneumocystis pneumonia; usually presents as an acute, severe pneumonia in infants < 6 months of age (Severe recurrent bacterial pneumonia is a stage 3 condition).

NOTE that: Both bacterial pneumonia and LIP may be confused with pulmonary TB.

Background information
- *These are other classic lung disorders that may produce chronic cough in immunologically normal persons.*

Differences between LIP and TB

Features	**Miliary TB**	**LIP**
Respiratory distress	+/−	+++
Persistent Fever	++	++
Wasting	+++	+/−
Generalized lymphadenopathy	+/−	+++
Parotid enlargement	−	++
Digital clubbing	−	++
Hepatomegaly	++	++
CXR		
Diffuse micronodular	++	+
Diffuse retinonodular	−	++
Mediastinal lymphadenopathy	+/−	++

Key Points

- TB is the major cause of morbidity and mortality in HIV-infected children
- Recommended approach to diagnose TB in children includes:
  - A careful history (including history of TB contact and symptoms consistent with TB)
  - Clinical examination (including growth assessment)
  - Tuberculin skin testing or Bacteriological confirmation
  - Relevant investigations

Sources/Bibliography

- *Venturini, et al. 2014. "Tuberculosis and HIV Co-Infection in Children," BMC Infectious Diseases, 2014,* ***14****(Suppl 1): S5)*
  http://www.biomedcentral.com/1471-2334/14/S1/S5

Handout 3.3.1: Steps to Read a Chest X-Ray

When looking at the lung on a chest X-Ray, always follow these *three* steps:

1. Compare the sizes of the two lungs
2. Compare the vascularity of the two lungs
3. Compare the two hilar shadows for:
   - Position
   - Size
   - Shape

THEN, check three aspects of the diaphragm and pleura:

1. The position of the left and right diaphragms
2. The two costophrenic angles
3. The pleura on both sides

Background Information

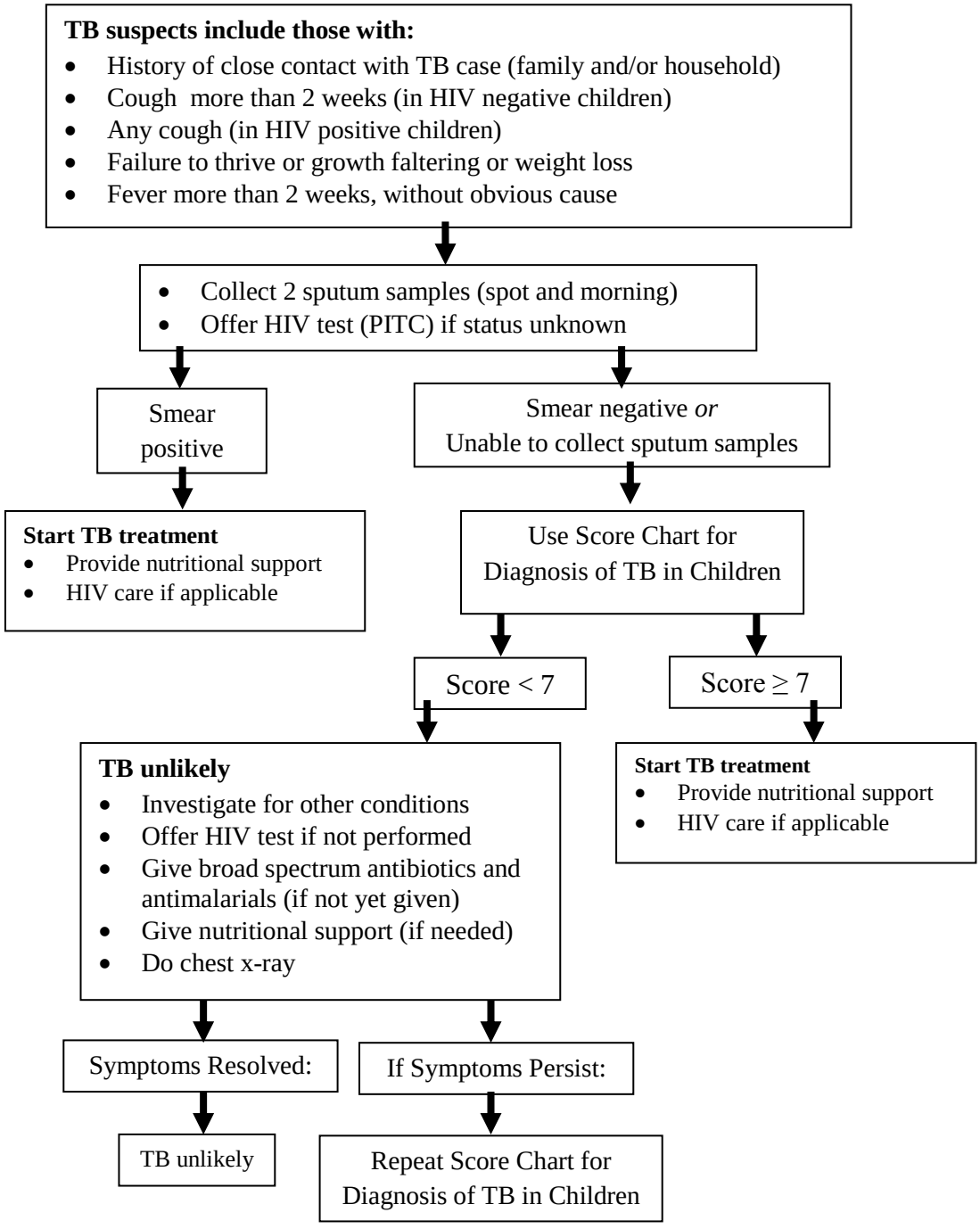
- Abnormalities of the lungs may be due to granulomas or destruction of the lungs. On a chest x-ray, healthy lungs are black while unhealthy lungs appear white or grayish.
- Air in the lung appears black and solid abnormalities including fluid may appear white.
- Other reasons why the lung field may be black:
  - Probability of pneumothorax if the lung field is very black
  - In chronic obstructive lung disease the lung field is also black because of emphysema and the patient presents with chronic cough
- It is important to note that a chest x-ray cannot tell the doctor for sure if a person has TB disease. For example, a person who is HIV+ and has TB disease can still have a normal x-ray.

Handout 3.3.2: Score Chart for Diagnosis of TB in Children

Score if sign or symptom is present.						
	0	**1**	**2**	**3**	**4**	**SCORE**
GENERAL FEATURES						
Duration of illness	Less than 2 weeks	2-4 weeks		More than 4 weeks		
Failure to thrive or weight loss	Weight gain	No weight gain or weight faltering		Weight loss		
TB contact	None	Reported (but no documentation), reported smear negative or EPTB		Smear positive (with documentation)		
TST	Negative, not done			Positive		
Malnutrition not improved after 4 weeks therapy				Present		
Unexplained fever not responding to appropriate therapy			Positive			
LOCAL FEATURES						
Painless, enlarged lymph nodes		Any non-cervical lymph nodes		Positive cervical lymph nodes		
Swelling of bones or joints				Positive		
Unexplained ascites or abdominal mass				Positive		
CNS findings: Meningitis[2], lethargy, irritability and other behaviour changes				Positive		
Angle deformity of the spine					Positive	
TOTAL SCORE[1]						

Notes: (1) A score of 7 or higher indicates a high likelihood of TB; (2) Meningitis not responding to conventional antibiotics. Other causes of meningitis (e.g. bacterial) must be excluded.

Handout 3.3.3: Diagnosing Pulmonary TB in Children Algorithm



Handout 3.3.4: Summary of Investigations for Extrapulmonary TB in Children

Anatomical Site	Recommended Investigations
TB adenitis	Lymph node biopsy or fine needle aspiration; sputum if coughing.
Miliary TB	Sputum and chest x-ray. Perform additional diagnostic tests as appropriate for associated symptoms and signs (e.g., lumbar puncture to test for meningitis).
TB meningitis	Lumbar puncture (CSF for white blood cell count with differential); biochemical analysis for protein and glucose concentration, AFB smear, and mycobacterial culture; chest x-ray; and sputum.
Pleural effusion	Chest x-ray; pleural tap for biochemical analysis (protein and glucose concentration, white blood cell count, AFB smear and mycobacterial culture); sputum.
Abdominal TB	Abdominal ultrasound and ascitic tap for white blood cell count total and differential; biochemical analysis for protein and glucose concentration, AFB smear, and mycobacterial culture; sputum; and chest x-ray if coughing.
TB of the spine/bones/joints(osteoarticular TB)	x-ray; joint tap for white blood cell count total and differential; biochemical analysis for protein and glucose concentration, AFB smear, and mycobacterial culture; synovial biopsy; sputum if coughing.
Pericardial TB	Chest x-ray; chest ultrasound; pericardial tap for white blood cell count total and differential; biochemical analysis for protein and glucose concentration, AFB smear, and mycobacterial culture; sputum if coughing.
Neonatal TB	Chest x-ray; lumbar puncture; CSF and gastric aspirates for AFB smear and mycobacterial cultures; histopathology examination of the placenta for AFB and granulomata; evaluation of the mother for TB.
Drug-resistant TB: any anatomical site	Mycobacterial culture and drug susceptibility testing of relevant specimens.

Session 4: Management of Tuberculosis in Children

Total Session Time: 1 hour 15 minutes

Learning Objectives

By the end of the session participants shall be able to:
- Explain challenges of managing TB in children
- Explain the treatment regimens and dosing approach used for children co-infected with TB and HIV
- Describe clinical and laboratory approaches to monitor treatment of tuberculosis in HIV infected children
- Identify HIV infected children considered for Isoniazid Preventive Therapy (IPT)

Challenges of Managing TB in Children & Principles of TB Treatment and Dosing Approach

Challenges of Managing TB in Children

The challenges in managing TB in children include:
- Drug interaction
- Children with HIV have immune suppression resulting from:
  - Immature immunity due to young age
  - HIV related immune suppression
- Extrapulmonary TB is seen more commonly in HIV-infected children
- Children with TB/HIV have a higher case fatality rate

Principles of TB Treatment

In general, treatment regimens for children are similar to those used for adults. In order to achieve effective treatment, adequate anti-TB drugs should be prescribed:
- In appropriate combination
- With the right dosage
- In an appropriate formulation
- For the right duration of treatment

The main objectives of anti-TB treatment are to:
1. Cure the patient of TB (by rapidly eliminating most of the bacilli);
2. Prevent death from active TB or its late effects;
3. Prevent relapse of TB (by eliminating the dormant bacilli);
4. Prevent the development of drug resistance (by using a combination of drugs);
5. Decrease TB transmission to others.

Directly Observed Treatment (DOT) is the cornerstone of TB treatment.
The importance of DOTs:
- If children do not take the drugs as directed, or stop before completing the full treatment:
  - They will not get cured, and may even die of TB
  - The disease will be prolonged and more difficult to treat in the future.

- Children may miss doses or parents/caregivers may stop giving the medicines when the child starts to feel better or if they develop side effects
- With DOT, a parent/caregiver or trained supervisor watches children taking their medicine.

TB treatment in children
Recommended drugs include:
- Isoniazid (H)
- Rifampicin (R)
- Pyrazinamide (Z)
- Ethambutol (E)

These are the first line drugs used to treat new cases presumed to have drug susceptible (non-resistant) TB disease.

Background information
- *First-line therapy includes two treatment regimens: category I for new patients and category II for re-treatment patients who may have TB resistant to one medication.*
- *Second-line therapy is treatment for patients with TB resistant to more than one drug.*

Mode of Action and Potency of Anti- TB Drugs

Anti-TB treatment	Mode of Action, most important target	Potency/ Strength
Isoniazid (H)	**Bactericidal, kills rapidly growing and dormant bacilli**	++++
Rifampicin (R)	**Bactericidal, kills slow growing bacilli**	++++
Pyrazinamide (Z)	**Bactericidal, kills bacilli inside the macrophage and cavities and slow growing bacilli**	+++
Ethambutol (E)	**Bacteriostatic**	++

Isoniazid (H) and rifampicin (R) are the two most important and powerful first line drugs.

Bactericidal medications kill and bacteriostatic medications prevent growth but do not kill the bacteria.

There were originally fears of using Ethambutol in children younger than 12 years because of the fears of retrobulbar neuritis (inflammation of the optic nerve) compounded by inability of especially younger children not being able to identify visual side-effects and report them. However little evidence of ocular toxicity has been documented in children receiving EMB at doses of from 15-30 mg/kg according to a WHO review. The side effect may occur however with long-term use.

Recommended Regimens for Children with TB in Tanzania

TB Disease Category	Recommended Regimen	
	Intensive Phase	**Continuation Phase**
All forms of pulmonary TB and extra pulmonary TB except TB meningitis, milliary TB and TB of the spine/bone/joints	2RHZE	4RH
TB meningitis, milliary TB, TB of the spine/bone/joints	2RHZE	10RH
Previously treated smear positive pulmonary TB (Relapse, Return after default, Treatment failure)	3RHZE*	5RHE

NOTE : H=Isoniazid, R=Rifampicin, Z=Pyrazinamide, E=Ethambutol

WHO recommends 4-drug therapy during intensive phase for all patients.

Asterisk in the last row of the table: *You may use streptomycin in special considerations e.g., drug re-challenging or when susceptibility is confirmed.

The number preceding the Regimen refers to the number of months of the regimen e.g. 2 RHZE refers to two months of daily Rifampicin, Isoniazid, Pyrazinamide and Ethambutol.

RHE in the continuation phase is indicated in treatment of previously treated TB patients to prevent development of resistance. This regimen cures patients who may still be excreting bacilli resistant to isoniazid and/or streptomycin. These patients (retreatment) are those most likely to develop MDR-TB.

All retreatment cases should be evaluated for MDR and even in some of new cases. Relapse cases are those who received Anti-TB in the past and were declared cured or treatment completed but now present with another episode of bacteriologically confirmed TB disease.

Relapse patient: Patient has been previously treated for TB, was declared cured or treatment completed at the end of the most recent treatment episode, and is now diagnosed with a recurrent episode of TB. Treatment failure: A patient who was previously treated for TB and whose treatment failed at the end of the most recent treatment episode. Default: A patient previously treated for TB who was declared lost to follow-up at the end of the most recent treatment episode.

Drug dosing for the treatment of TB in children

Drugs	Drug formulations	Daily dose & range mg/kg	Maximum Dose	Adverse Reactions
Isoniazid	***Scored tablets:*** 100 mg 300 mg ***Syrup:*** 10 mg/ml	10 (10-15)	Daily 300 mg	Mild hepatic enzyme elevation, hepatitis*, peripheral neuritis, hypersensitivity
Rifampicin	***Capsules:*** 150 mg 300 mg	15 (10-20)	600 mg	Orange discoloration of secretions or urine, vomiting, hepatitis, influenza-like reaction, thrombocytopenia, pruritus
Pyrazinamide	***Scored tablets:*** 500 mg	35 (30-40)	2 gm	Hepatoxic effects, hyperuricemia, arthralgias, GI tract upset
Ethambutol	***Scored tablets:*** 100 mg 400 mg	20 (15-25)	1200 mg	Optic neuritis (generally reversible),decreased red-green color discrimination, GI tract disturbances, hypersensitivity
Streptomycin	**Vials** 1g	15 (12-18)	1500 mg	Irreversible auditory nerve damage

*Refer to **Handout 3.4.1: Drug Dosing for Treatment of TB in Children** on page **137** for more information.*

The anti-TB medicines should be prescribed based on weight, shown here are the recommended milligrams per killogram doses and the acceptable range, along with the maximum dose. Because doses are weight-based, it is essential that a child be weighed on a reliable and appropriate scale at every visit (e.g. infants should weigh on infant scales, not bathroom style scales). Each drug may cause an adverse reaction as summarized in the last column.

Fixed Dose Combination (FDC)

Fixed Dose Combinations (FDCs) for both adults and children are available and in use in the country. FDCs have been used in the NTLP as 2-drug combinations (Rifampicin-Isoniazid and Ethambutol-Isoniazid) for many years.

Use of FDCs facilitates adherence and simplifies regimens. Three different FDCs are available for use in children:

- RH: 60/30 mg or 150/75 mg
- RHZ: 60/30/150 mg
- RHZE: 150/75/400/275 mg

*Refer to **Handout 3.4.1: Drug Dosing for Treatment of TB in Children** on page **137***

Weight-based dosing of Anti-TB Medicines using Pediatric Formulations (2-20kg)

	Intensive Phase (2 months)		Continuation Phase (4 months)
Weight (kg)	**RHZ (pediatric) 60/30/150**	**Ethambutol 100 mg**	**RH (pediatric) 60/30**
2 - 2.9 kg	1/2 tablet	1/2 tablet	1/2 tablet
3 - 3.9 kg	1 tablet	1/2 tablet	1 tablet
4 - 5.9 kg	1 tablet	1 tablet	1 tablet
6 - 7.9 kg	1.5 tablets	1.5 tablets	1.5 tablets
8 - 10.9 kg	2 tablets	2 tablets	2 tablets
11 - 13.9 kg	3 tablets	2 tablets	3 tablets
14 - 19.9kg	4 tablets	3 tablets	4 tablets

WHO recommends 4 drug therapy during intensive phase for all patients with HIV infection or living in areas with a generalized HIV epidemic.

Weight-based dosing of Anti-TB Medicines using Adult FDC formulations (> 5 kg)

	Intensive Phase (2 months)	Continuation Phase (4 months)
Weight (kg)	**RHZE (adult) 150/75/400/275**	**RH (adult) 150/75**
5-9.9 kg	1/2 tablet	**Use pediatric formulation if available**, or 1/2 tablet
10-14.9 kg	1 tablet	**Use pediatric formulation if available**, or 1 tablet
15-19.9 kg	1.5 tablets	**Use pediatric formulation if available**, or 1.5 tablets
20-24.9 kg	2 tablets	2 tablets
25-29.9 kg	2.5 tablets	2.5 tablets
30-40 kg	3 tablets	3 tablets
>40 kg	4 tablets	4 tablets

Adult FDC formulations can be used in case of medication shortages, but for children less than 20kg, it is preferred to use pediatric formulations.

*Refer to **Handout 3.4.1: Drug Dosing for Treatment of TB in Children** on page **137***

Steroid Use in Pediatric TB

Corticosteroids are generally indicated when treating children with:

- TB meningitis
- Severe miliary / disseminated TB
- Pericardial effusion
- Pleural TB with massive effusions
- Pulmonary TB with mediastinal lymph nodes obstructing airways

Prescribe: Prednisolone 1-2mg/kg/day up to 4mg/kg (max dose 60mg/day) for 4-6 weeks, followed by 2 week tapering.

Children with serious forms of TB may benefit from adding steroids to their treatment as it reduces inflammation and in life threatening conditions mentioned above. This is done when children are very ill and require hospitalization.

Clinical and Laboratory Approaches to monitor treatment of TB & Isoniazid Preventive Therapy (IPT)

Monitoring Treatment Schedule

Monitoring is done at several points during the course of anti-TB treatment. Here is a summary of the frequency of evaluations and what should be done at each evaluation.

- Evaluate at 1-week intervals during the intensive phase
- Evaluate at 2-week intervals during the continuation phase: During intensive phase children should come for follow up every 1 week. During the continuation phase (if the children are doing well) they should come for follow up every 2 weeks.
- Evaluations should include:
  - Weight measurement, to see whether they are gaining weight and return to their growth curve in the RCH Card No. 1
  - Assessment of response to treatment (checking for signs and symptoms which the child had before starting TB therapy)
  - Adherence
  - Any adverse drug reactions or events
  - Screen for new cases in the home (or close contacts)
- Adjust doses as needed as children gain weight

At each visit patients should be evaluated for clinical improvement (or new problems), weight gain/loss, response to treatment, adherence, adverse drug reactions and screening for new case findings. The medication doses need to be adjusted as the child gains weight.

Continuation phase of treatment will be started according to the following guidelines:

- For sputum smear negative and EPTB cases (most children): start after child has taken all of the required 56 doses (2 months) of the intensive phase of treatment.
- For sputum smear positive cases: start if follow-up sputum result at the end of 2nd month (3^{rd} month for retreatment cases) is negative.

Throughout treatment monitor for clinical improvement; If not improving clinically, confirm adherence and refer for MDR TB evaluation if adherent.

For smear negative and EPTB cases: Complete full course of treatment (6 or 12 months depending on site of disease).

For smear positive cases: Obtain sputum during 5th month of treatment; if result is negative, complete remaining therapy and declared patient cured. If result is positive, refer for MDR TB evaluation.

End of treatment evaluation is necessary to ensure the patient is successfully treated and medicines can be stopped. In addition, this is when a patient is assigned a treatment outcome.

*Refer to **Handout 3.4.2: Definitions of Treatment Outcomes** on **page 139** for more information.*

Initiating ART in a Child with TB/HIV Co-infection
If a patient is co-infected with TB and HIV, ART is initiated regardless of the patient's CD4 count or CD4% and the clinical stage of the disease.

Start ART in all children with TB/HIV regardless of CD4 levels once TB treatment is tolerated (within 2-8 weeks). Treatment for TB should ideally be initiated some weeks before ARV treatment, allowing the child to stabilise before starting ART.

Special considerations to TB/HIV co-treatment:
- Pill burden
- Adherence concerns
- Increased likelihood of drug toxicity
- Drug interactions between Rifampicin & ARVs

ART regimen for children with TB-HIV who have not yet started ART, use **default regimen** such as:
- For children < 3 years of age and < 10Kg BWT;
  - ABC + 3TC + AZT is recommended
- For children >3 years of age and > 10Kg BWT;
  - ABC + 3TC + EFV is recommended

Children < 3yrs and/or <10kg BWTwho develop TB while on an ART regimen containing NVP or LPV/r:
- ABC + 3TC + AZT is recommended
- Once TB therapy has been completed, this regimen should be stopped and the initial (default) regimen should be restarted

For children >3 years of age and > 10Kg BWT continue with default regimen.

Where LPV/r (lopinavir boosted with ritonavir) cannot be avoided as in anaemia, consider adding RTV in a 1:1 ratio to achieve a fully therapeutic dose of LPV. In situations where NVP cannot be avoided, NVP should be used at maximum dose (i.e. 200mg/m^2) twice daily.

*Refer to **Handout 3.4.3: Recommended ART Regimens for Children receiving standard TB Treatment** on **page 141** for more information.*

Drug Interactions
Rifampicin reduces levels of both non-nucleoside reverse transcriptase inhibitors and HIV protease inhibitor.

Rifampicin is a potent inducer of the cytochrome P450 liver enzyme system:
- Decreases serum levels of lopinavir; thus Lopinavir/Ritonavir based regimens require addition of additional Ritonavir.
- Decreases serum levels of nevirapine, necessitating an increased dose of neverapine.

Shared drug toxicity
Both ART and TB treatment can be hepatotoxic:
- Clinically monitor for development of jaundice
- Monitor liver enzymes (ALT)
- Pyridoxine (vitamin B6) is protective for INH-induced peripheral neuropathy but not for hepatotoxicity

Isoniazid (INH) Preventive Therapy (IPT)
Prior to initiation of INH preventive therapy, patients should be screened for signs and symptoms of active TB disease. Children who should be considered for IPT:
- All newborns with no symptoms of active TB disease born to mothers with active TB disease.
- All HIV-infected children <12 months with no symptoms of active TB disease and with a known TB contact.
- All HIV-infected children ≥12 months with no symptoms of active TB disease.

Prophylactic dose: INH 10mg/kg/day for 6 mo. Close collaboration with TB/DOTS clinic to exclude active TB (history, X-ray, sputum exam).

Activity: Case Studies

*Refer to **Worksheet 3.4.1: Case Studies** on **page 143** for more information.*

Key Points

- Treatment of TB in children with HIV should follow the National Guidelines
- Since most children are smear negative, treatment outcome is based on response to therapy (clinical improvement) and treatment completion
- Chemoprophylaxis for all children in household members with open TB contact should be considered

Sources/Bibliography

- *http://whqlibdoc.who.int/hq/2006/WHO_HTM_TB_2006.365_eng.pdf*

Handout 3.4.1: Drug Dosing for Treatment of TB in Children

Drugs	Drug Formulations	Daily Dose and range mg/kg	Maximum Dose	Adverse Reactions
Isoniazid	***Scored tablets:*** 100 mg 300 mg ***Syrup:*** 10 mg/ml	10 (10-15)	***Daily:*** 300 mg	Mild hepatic enzyme elevation, hepatitis*, peripheral neuritis, hypersensitivity
Rifampicin	***Capsules:*** 150mg 300 mg	15mg (10-20)	600 mg	Orange discolouration of secretions or urine, vomiting, hepatitis, influenza-like reaction, thrombocytopenia, pruritus
Pyrazinamide	***Scored tablet:*** 500mg	35 (30-40)	2 gm	Hepatotoxic effects, hyperuricemia, arthralgias, gastrointestinal tract upset
Ethambutol*	***Tablets:*** 100 mg 400 mg (scored)	20 (15-25)	1200 mg	Optic neuritis (usually reversible), decreased red-green colour discrimination, gastrointestinal tract disturbances, hypersensitivity
Streptomycin	***Vials:*** 1 g	15 (12-18)	1500 mg	Irreversible auditory nerve damage

*Ethambutol was previously omitted from treatment regimens for children due to concerns about optic toxicity, but a review of the literature indicates it is safe and should be used to treat TB in children of all ages at recommended dosages.

Continued on next page

Weight-based dosing of Anti-TB Medicines using Pediatric Formulations (2-20kg):

	Intensive Phase (2 months)		Continuation Phase (4 months)
Weight (kg)	**RHZ (pediatric) 60/30/150**	**Ethambutol 100 mg**	**RH (pediatric) 60/30**
2 - 2.9 kg	½ tablet	½ tablet	½ tablet
3 - 3.9 kg	1 tablet	½ tablet	1 tablet
4 - 5.9 kg	1 tablet	1 tablet	1 tablet
6 - 7.9 kg	1.5 tablets	1.5 tablets	1.5 tablets
8 - 10.9 kg	2 tablets	2 tablets	2 tablets
11 - 13.9 kg	3 tablets	2 tablets	3 tablets
14 - 19.9kg	4 tablets	3 tablets	4 tablets

Weight-based dosing of Anti-TB Medicines using Adult FDC Formulations (> 5 kg)

	Intensive Phase (2 months)	Continuation Phase (4 months)
Weight (kg)	**RHZE (adult) 150/75/400/275**	**RH (adult) 150/75**
5 - 9.9 kg	½ tablet	**Use pediatric formulation if available**, or ½ tablet adult
10 - 14.9 kg	1 tablet	**Use pediatric formulation if available**, or 1 tablet adult
15 - 19.9 kg	1.5 tablets	**Use pediatric formulation available**, or 1.5 tablets
20 - 24.9 kg	2 tablets	2 tablets
25 - 29.9 kg	2.5 tablets	2.5 tablets
30 - 40 kg	3 tablets	3 tablets
> 40 kg	4 tablets	4 tablets

Handout 3.4.2: Definitions of Treatment Outcomes

Treatment Outcome	Definition
Cured	A patient whose sputum smear or culture was positive at the beginning of treatment but who was smear or culture negative in the last month of treatment and on at least one previous occasion.
Treatment Completed	A patient who completed a treatment course but who does not have a negative sputum smear or culture result in the last month of treatment and on at least one previous occasion. *Note: The sputum examination may not have been done or the results may not be available.*
Failure	A patient whose sputum smear or culture is positive at 5 months or later during treatment. Also included in this definition are patients found to harbor a multi-drug resistant strain at any point of time during the treatment, whether they are smear negative or positive.
Died	A patient who dies for any reason during the course of TB treatment.
Default	A patient whose treatment was interrupted for 2 consecutive months or more.
Transferred Out	A patient who has been transferred to another recording and reporting unit and whose treatment outcome is unknown.

Source: Tanzania National Tuberculosis and Leprosy Program (NTLP). 2012. National Guidelines for the Management of Tuberculosis in Children. Dar es Salaam: NTLP/MOHSW.

Handout 3.4.3: Recommended ART Regimens for Children Receiving Standard TB Treatment

Status	Regimen
Children on anti-TB treatment but not yet initiated on ART	For children <3 years of age and/or weighing <10 kg: Initiate ABC + 3TC + AZT Alternative regimen ABC+3TC+NVP (if anaemic) For children >3 years of age and weighing >10 kg: Initiate AZT/3TC/EFV
Children who develop TB while on an ART regimen containing NVP or LPV/r.	Continue ART regimen For children <3 years of age and/or weighing <10 kg: ABC + 3TC + AZT is recommended regimen as an option for children who develop TB while on an ART regimen containing NVP or LPV/r. Once TB therapy has been completed, this regimen should be stopped and the initial regimen should be restarted. For children >3 years of age and weighing >10 kg: substitute NVP or LPV/r with EFV

Abbreviations:

- 3TC: lamivudine;
- ABC: abacavir;
- AZT: zidovudine;
- EFV: efavirenz;
- NRTI: nucloside reverse transcriptase inhibitor;
- NVP: nevirapine

Source: Tanzania National Tuberculosis and Leprosy Program (NTLP). 2012. National Guidelines for the Management of Tuberculosis in Children. Dar es Salaam: NTLP/MOHSW.

Worksheet 3.4.1: Case Studies

Instructions:

- In small groups, read the case study below and answer the questions.
- Be prepared to share and discuss your responses in plenary.

Case Study 1: Bahati

Bahati, aged 3 years old, is brought to the hospital because she no longer likes to eat, has lost weight and is malnourished despite of supplemental nutritional therapy over the past month. Her father says she has been ill for 3 weeks, eats poorly, doesn't play, and feels hot mostly in the evenings. Her temperature is 39ºC. She weighs 50% of the expected weight for height. She has enlarged lymph nodes in the neck, axilla, and inguinal areas, swollen parotid glands and an enlarged liver and spleen. There is no history of TB in the family.

1a. What is your provisional diagnosis, and why?

1b. What investigations should be performed to confirm your diagnosis?
What other investigations do you need to support your diagnosis?

1c. Use the TB Score Chart to rate Bahati's signs and symptoms.

1d. Using only what you already know about this child, should she receive treatment for tuberculosis disease? Why or why not?

Case Study 2: Esther

A 5 year old girl named Esther has been diagnosed with TB lymphadenitis of the cervical nodes based on a fine needle biopsy. The child's aunt was diagnosed with drug susceptible PTB last year. The child weighs 16.4 kg.

2a. What regimen do you want to start in this child?

2b. What dose and pill combinations will you prescribe?

2c. The child is started on treatment. What will you assess after one month of treatment?

Session 5: Pneumocystis Pneumonia and Other OIs

Total Session Time: 1 hour

Learning Objectives

At the end of the session participants will be able to:
- Describe the management of PCP
- Describe the management of Candidiasis
- Describe the management of Cryptococcal meningitis
- Describe the management of Toxoplasmosis
- Explain the management of viral diseases (HSV, varicella zoster & CMV)

Management of PCP & Candidiasis

Pneumocystis Pneumonia (PCP)
Pneumocystis pneumonia is an opportunistic infection caused by a yeast-like fungus that is a major cause of death in patients with late-stage AIDS. *P. carinii* has been renamed *P. jirovecii* but the acronym PCP is retained representing **P**neumo**C**ystis **P**neumonia. *Pneumocystis jirovecii*, is commonly found in the environment.

The primary infection occurs in childhood; about 90% are sero-positive with Pneumocysistis antibodies by 4 years of age, usually sub-clinical. The major cause of morbidity and mortality in HIV infected children.

Pneumocystis Pneumonia (PCP) is more common under the age of 1 year and in severely immunosuppressed children. But PCP is relatively rare in people with normal immune systems, but common among people with weakened immune system, such as premature or severely malnourished children, the elderly. PCP can also develop in patients who are taking immunosuppressive medications, in patients who have undergone organ transplant or bone marrow transplantation, and after surgery.

Clinical presentation includes:
- Usually less than 1 year, majority < 6 months
- Tachypnoea
- Dyspnoea
- Low grade fever or afebrile
- Hypoxemia (paO2 < 90%)
- Cough

Common clinical symptoms of PCP in older children and adults may include fever, non-productive cough (because sputum is too viscous to become productive), shortness of breath (especially on exertion), weight loss and night sweats.

The fungus can invade other visceral organs, such as the liver, spleen and kidney, but only in a minority of cases.

Pneumothorax is a well-known complication of PCP presenting typically with an acute history of chest pain with breathlessness and diminished breath sounds.

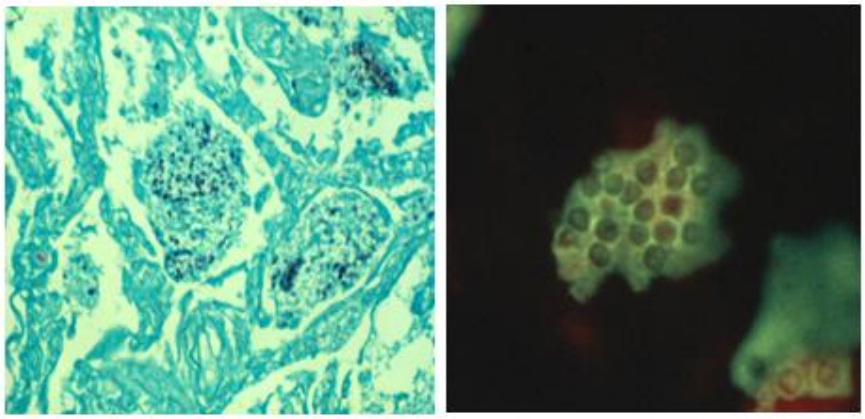
Diagnosis of PCP

The diagnostic procedures for PCP include:

- Clinical presentation including the mainstay of diagnosis
- Chest X-ray shows hyperinflation, diffuse infiltrates or may be normal
- Sputum stained with Silver or Immunofluorescent stain

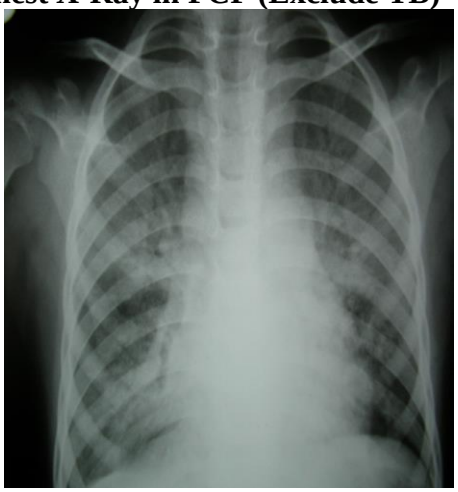
The diagnosis of PCP can be highly suspected by the characteristic appearance of the chest X-ray which shows widespread pulmonary infiltrates, and an arterial oxygen level (pO_2) strikingly lower than would be expected from symptoms. The diagnosis can be definitively confirmed by histological identification of the causative organism in sputum or broncho-alveolar lavage (lung rinse).

Image of *Pneumocystis Jirovecii*



Pneumocystis infection can also be diagnosed by immune-fluorescent or histochemical staining of the specimen, and more recently by molecular analysis of PCR.

Chest X-Ray in PCP (Exclude TB)



The X-ray of *Pneumocystis jirovecii* pneumonia shows increased opacification (whiteness) in the mid and lower zones on both sides, characteristic of *Pneumocystis* pneumonia include:

- Normal in 10-30%

- Majority have diffuse, bilateral infiltrates
- Infrequent nodules, cavities
- Infrequent pleural effusions

Management of PCP
Ideally children with PCP should be referred to a hospital, but treatment can be started before referral. A patient often worsens when therapy is initiated. Some patients go on to respiratory failure and Acute Respiratory Distress Syndrome (ARDS).
Needed supportive care includes:
- Oxygen/ventilatory support
- Maintain and monitor hydration
- Nutritional support
- Continue therapy for bacterial pneumonia

PCP Treatment
The most commonly used medication of PCP includes:
- Cotrimoxazole IV:
  - TMP 15–20 mg + SMX 75–100 mg/kg/day IV given 6 or 8 hrly for 21 days
  - May switch to PO after clinical improvement. **OR** (if IV is not available)
- Cotrimoxazole PO;
  - TMP 20 mg + SMX 100mg /kg/day 6 or 8 hrly for 21 days
- Alternative Therapy;
  - Pentamidine 4 mg/kg IV once daily for 21 days infused over at least 60 minutes; may reduce the dose to 3 mg/kg IV once daily because of toxicities
- Adjunctive corticosteroid:
  - Indicated in some moderate to severe cases
  - Give Prednisone 2mg/kg for 7-14 days
  - Prednisone should be started as early as possible (within 72 hours of PCP therapy)
- Secondary PCP prophylaxis;
  - After completion of therapy, continue with CTX prophylaxis as per National Guidelines

Antipneumocystic medication is used concomitantly with steroids in order to avoid inflammation, which causes an exacerbation of symptoms about four days after treatment begins if steroids are not used.

By far the most commonly used medication is co-trimoxazole, but some patients are unable to tolerate this treatment due to allergies. Other medications that may be used, alone or in combination, include pentamidine, trimetrexate, dapsone, atovaquine, primaquine and clindamycin. However most of these are not available in our country and some have serious side effects e.g pentamidine.

Children with a history of treated PCP should be administered secondary co-trimoxazole prophylaxis with the same regimen recommended for primary prophylaxis.

PCP Prophylaxis
Indications for PCP Prophylaxis:
- All HIV exposed infants should start Cotrimoxazole prophylaxis from 4-6 weeks of age until HIV infection is excluded

- All children < 5 year of age confirmed to be HIV infected regardless of symptoms or CD4%
- All HIV infected children >5 years of age who are symptomatic (WHO clinical stages 2, 3 or 4) or with a CD4 of ≤ 500.

Data from randomized clinical trials and observational studies demonstrate the effectiveness of co-trimoxazole in preventing PCP in infants and reducing morbidity and mortality among infants and children living with or exposed to HIV.

*Refer to **Handout 3.5.1: Cotrimoxazole Prophylaxis in Children and Adults** on page **157***

PCP Prophylactic Regimen
- TMP-SMX (Cotrimoxazole):
  - TMP 5 – 10 mg/kg body weight + SMX 25–50 mg/kg body weight PO once daily.
- Alternative therapy when Co-trimoxazole is contraindicated;
  - Dapsone 2 mg/kg body weight (maximum 100 mg) PO once daily for *Children aged ≥1 months*
- Contraindications to cotrimoxazole include:
  - Sulfa allergy
  - Severe renal insufficiency (creatinine > 3 times normal)
  - Severe hepatic insufficiency (LFTs > 5 times normal)

*Refer to **Handout 3.5.2: Recommended Dosage for PCP** on **page 159** for more information on dosage for PCP.*

Candidiasis
Oral candidiasis/thrush is predictive of HIV infection:
- If seen after the neonatal period without prior antibiotic treatment
- If lasting for more than 30 days
- If it is recurrent

Candidiasis is an infection caused by a species of the yeast *Candida*, usually *Candida albicans*. *Candida* is found on various parts of the body as normal flora. Candidiasis can affect the skin, nails, and mucous membranes throughout the body including the mouth (thrush), oesophagus, vagina intestines and lungs.

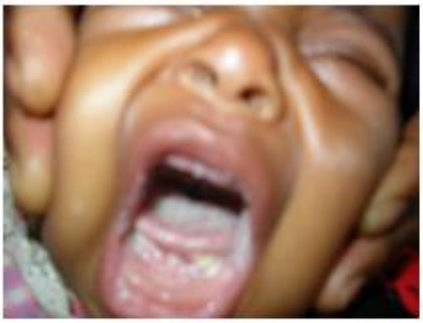
Oropharyngeal/oesophageal candidiasis is associated with difficulty feeding or pain in swallowing; that is commonly diagnosed clinically.

Candida may cause thrush in children with reduced immune function or in children taking certain antibiotics. Antibiotics may upset the balance of microorganisms in the body and allow an overgrowth of *Candida*.

Many infants acquire candidiasis from their mothers during the process of birth, when the baby comes in contact with naturally existing *Candida* found in the mother's vagina.

Candidiasis is not considered harmful to infants unless it lasts more than several weeks after birth. These yeast mouth infections cause creamy white, curd-like patches on the tongue, inside of the mouth, and on the back of the throat. Under the whitish material, there are red lesions that may bleed.

Candidiasis Images



Severe oral candidiasis/ thrush in a 3-month old

Oral candidiasis

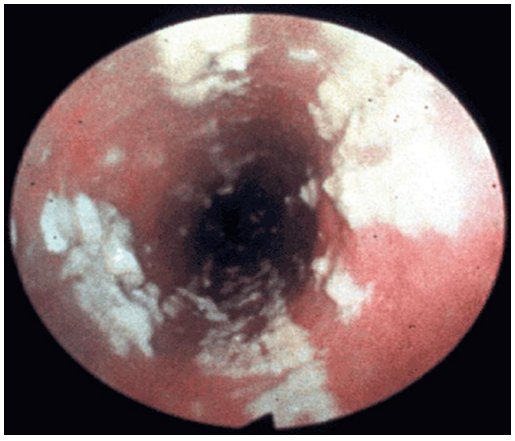
Oesophageal/Oropharyngeal Candidiasis

Oesophageal Candidiasis is the most common type of non-peptic inflammation of the gut. Oesophageal Candidiasis is a thrush infection of the oesophagus and is associated with numerous medical conditions or use of medications.

The most common symptom it causes is difficulty in swallowing or pain on swallowing and sometimes pain behind the breastbone/sternum. It is important to diagnose and treat because of the other associations. This results in inadequate oral intake leading to:

- Dehydration
- Malnutrition
- Death

Image of Oesophageal/Oropharyngeal Candidiasis



Diagnosis and Treatment of Candidiasis

Candidiasis is clinically diagnosed. Treatment is by:

- Oral Candidiasis;
  - Local treatments (Clotrimazole, Miconazole, Nystatin 2-4 million units/day divided every 6 hours until resolution)
- Oesophageal Candidiasis;
  - Fluconazole 3-6 mg/kg once daily IV/orally
  - In case of treatment failure refer to a centre where endoscopy, culture or barium swallow is possible

Cryptococcal Meningitis & Toxoplasmosis

Cryptococcal Meningitis

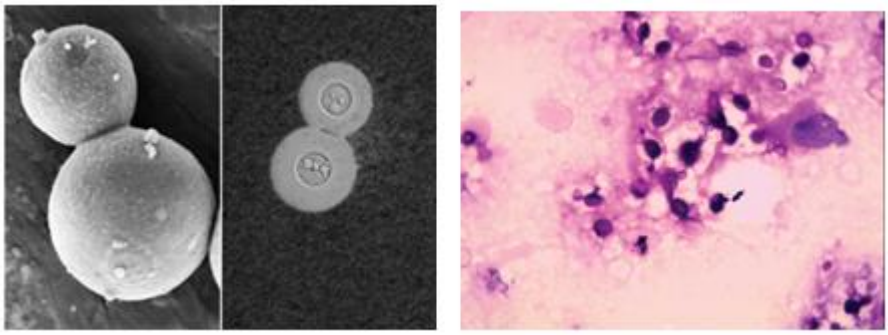
Caused by *Cryptococcus neoformans;* an encapsulated yeast-like fungus.

Its clinical presentation depends on age, however some common features include:

- Headache, unexplained fever
- Nausea and vomiting
- Neck stiffness
- Confusion, seizures, abnormal behaviour
- Altered level of consciousness focal neurological signs or coma

Other clinical signs and symptoms may include nuchal rigidity, Brudzinski's and Kernig's signs, exaggerated deep tendon reflexes, opisthotonos, sinus arrhythmias, irritability, photophobia, deep stupor, coma.

Image of Cryptococcal *neoformans*



Serum/CSF antigen testing is superior to Indian ink stain above (sensitivity of >95% vs 60-80%).

Diagnosis of Cryptococcal Meningitis

The clinical signs and symptoms of Cryptococcal Meningitis include fever, fatigue, nausea, vomiting, headache, confusion, behaviour changes, photophobia, mental status change.

Investigations include:

- Lumbar puncture CSF for Indian Ink
- Cryptococcal Antigen test
- CT scan of brain (where available), if focal neurological signs are present

Treatment of Cryptococcal Meningitis

Relapse episodes should be treated for 4-8 weeks, preferably until CSF fungal culture is negative. Adequate hydration during amphotericin B treatment should be maintained.

Induction phase (2 weeks):

- Amphotericin B 0.7-1 mg/kg/day + flucytosine 100 mg/kg/day OR
- Amphotericin B 0.7-1 mg/kg/day + fluconazole 12 mg/kg/day up to 800 mg/day

Alternative Regimen when Amphotericin B is not available:

- Fluconazole 12 mg/kg/day up to 1200 mg/day ± flucytosine 100 mg/kg/day
- Fluconazole 12 mg/kg/day up to 1200 mg/day alone

Consolidation phase (8 weeks):

- Fluconazole 6-12 mg/kg/ day up to 400-800 mg/day after induction with Amphotericin B regimen **OR**
- Fluconazole 12mg/kg/day up to 800 mg/day after induction with a Fluconazole based regimen if below 19 years

Maintenance (or secondary prophylaxis):

- Fluconazole 6 mg/kg/day up to 200 mg/day

In HIV-infected adults, adolescents and children above two years of age with successfully treated cryptococcal disease, discontinuation of anti-fungal maintenance treatment is recommended when patients are stable and adherent to ART and anti-fungal maintenance therapy for at least one year and show evidence of immune reconstitution.

- **2-6 years old:** CD4 percent > 25%,
- **More than 6 years old:** CD4 count > 350 cells/mm3

In children aged less than two years with successfully treated cryptococcal disease, anti-fungal maintenance treatment should NOT be discontinued.

Toxoplasmosis

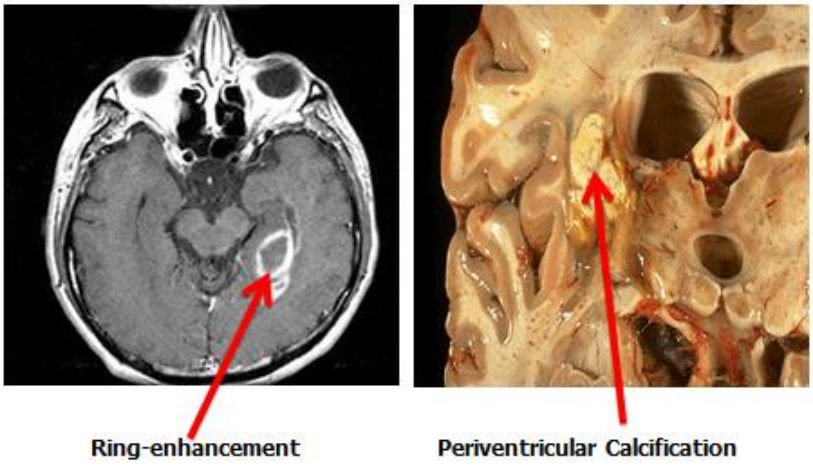
Toxoplasmosis is an infection with worldwide distribution caused by a protozoa *Toxoplasma gondii.*

Clinically is similar to toxoplasmosis in HIV uninfected infants:

- Hepatosplenomegaly
- Fever
- Chorioretinitis
- Seizures
- Periventricular calcifications
- Hypodense lesions with ring enhancement in the brain on CT scan

Immunocompetent persons with primary infection are usually asymptomatic and that latent infection can persist for the life of the host. In immunosuppressed patients, especially with AIDS, the parasite can reactivate and cause disease. Usually occurs when the CD4 count falls below 100. With CD4 <100, there is a 30% probability of developing reactivated toxoplasmosis if effective prophylaxis is not taken. The infection is most commonly acquired from contact with cats and their feces or with raw or undercooked meat.

Images of Toxoplasmosis



The diagram on the left shows MRI with contrast of a patient with new seizures, focal weakness, and HIV infection. Ring-enhancing lesions are seen in the periventricular white matter, consistent with *Toxoplasma* encephalitis. BUT the diagram on the right shows a cross section of brain showing periventricular calcifications.

Most patients with AIDS will have multiple, ring-enhancing brain lesions often associated with edema. There is a predilection for involvement of the basal ganglia and periventricular white matter of the brain.

NOTE: An MRI is more sensitive than CT for identifying lesions.

Diagnosis of Toxoplasmosis

Toxoplasmosis is associated with:

- Clinically it's most common manifestations are encephalitis, mental changes, fever, headache and confusion.
- Toxoplasma antibodies (IgM)
- Response to empiric treatment most practical means of making a diagnosis

Children born with toxoplasmosis can be afflicted with mental retardation, convulsions, spasticity, cerebral palsy, deafness, and severely impaired vision. The infant's head may be abnormally small (microcephaly) or abnormally large due to increased pressure on the brain (hydrocephalus).

The majority of patients are seropositive for anti-toxoplasma IgG antibodies. Anti-toxoplasma IgM antibodies are usually absent.

Differential Diagnosis of Toxoplasmosis

These include:

- Cryptococcosis
- Histoplasmosis
- Aspergillosis
- Tuberculosis
- Trypanosomiasis
- CNS lymphoma

Treatment of Toxoplasmosis
Cotrimoxazole;
- TMP-SMX—TMP 5 mg/kg body weight + SMX 25 mg/kg body weight per dose IV or PO twice daily for 4 weeks

Alternative Therapy:
- Pyrimethamine: loading dose – 2 mg/kg body weight (maximum 50 mg) PO once daily for 3 days; then 1 mg/kg body weight (maximum 25 mg) PO once daily, **plus**
- Sulfadiazine 25–50 mg/kg body weight (maximum 1–1.5 g/dose) PO per dose 4 times daily,

The lack of clinical or radiographic improvement within 10 to 14 days of empiric therapy should raise the possibility of an alternate diagnosis.

NOTE: Cerebral toxoplasmosis usually responds promptly to treatment. Anticonvulsants should be given to patients with a history of seizures.

Toxoplasmosis Prophylaxis
Indications for prophylaxis;
- ALL HIV infected children should be on CTX prophylaxis for PCP which also protects against Toxoplasmosis

Prophylaxis regimen;
- Same as for PCP prophylaxis

Management of Viral Diseases (HSV, Varicella Zoster & CMV)

Herpes Simplex Virus Types 1 & 2
Herpes simplex 1 virus typically causes ulcers and painful blisters and/or itching on lips.

Herpes simplex 2 virus typically causes ulcers and painful blisters and/or itching on anus and/or genitals.

These are:
- Neonatal infections with high case fatality such as;
  - CNS
  - Skin
- Oro-facial infection (gingivostomatitis)
- Encephalitis (>95% type 1);
  - Recurrence common
- Gastrointestinal

Diagnosis of Herpes Simplex Virus Types 1 & 2
Mainstay of diagnosis is clinical. The clinical symptoms include;
- A blister or multiple blisters on or around affected areas, usually the mouth, genitals, or rectum.
- The blisters break, leaving tender sores.

Rising serum HSV titres and increased ratio of CSF-to-serum concentration of HSV antibody is a diagnostic option in a few selected laboratories in the region.

Treatment of Herpes Simplex Virus Types 1 & 2 (1)
Neonatal CNS or disseminated disease:

- Acyclovir 20 mg/kg body weight IV/dose 8hrly for ≥21 days

Neonatal skin, eye, or mouth disease:

- Acyclovir 20 mg/kg body weight IV/dose 8hrly for 14 days

CNS or disseminated disease in children outside the neonatal period:

- Acyclovir 10 mg/kg body weight (up to 20 mg/kg body weight/dose in children <12 years) IV 8hrly for 21 days

Moderate to Severe Symptomatic Gingivostomatitis:

- Acyclovir 5–10 mg/kg body weight/dose IV 8hrly
- Switch to oral therapy after lesions have begun to regress and therapy continued until lesions have completely healed

Mild Symptomatic Gingivostomatitis:

- Acyclovir 20 mg/kg body weight (maximum 400 mg/dose) dose by mouth 6hrly for 7–10 days

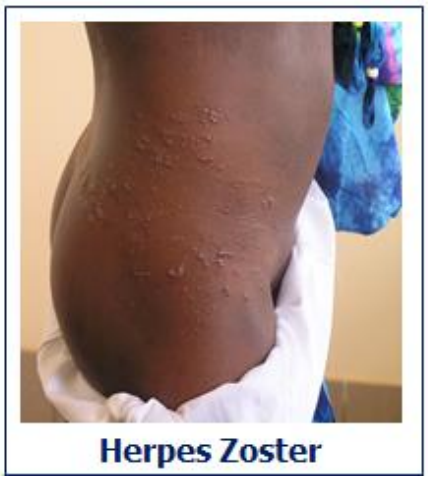
Varicella Zoster Virus
It's a chicken pox; which may be lethal in HIV infected children

Herpes Zoster;

- Typical dermatomal presentation
- Can cause disseminated disease
- Encephalitis as a complication

Diagnosis: mainly clinical

Varicella Zoster Virus Images


Herpes Zoster


Chicken Pox

Varicella Zoster Virus Treatment
All severe cases to be hospitalised and treated, if possible, with IV acyclovir 30mg/kg/day in three divided 3 for a total of 7 days or 2 days after cessation of new lesion formation, whichever is longer.

NOTE that: Oral acyclovir may be used if the IV is not available.

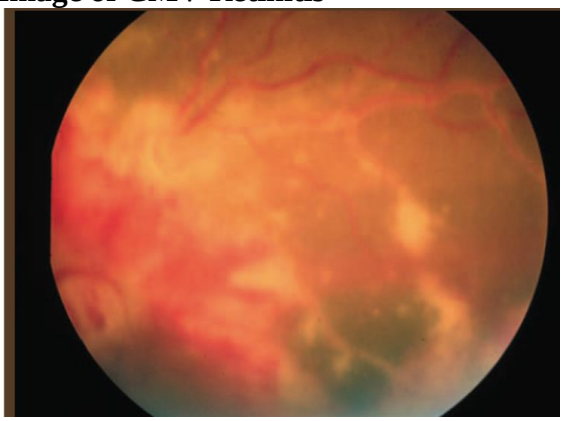
Cytomegalovirus (CMV)
Clinical conditions associated with CMV:
- Pneumonia
- Retinitis presenting with painless visual impairment
- Gastritis
- Colitis
- Meningoencephalitis

Cytomegalovirus Signs & Symptoms
CMV often causes a fever and affects different parts of the body, including:
- Blurred vision in eyes
- Pain and ulcers in oesophagus and difficulty swallowing
- Diarrheal, abdominal pain and colitis
- Pneumonia
- Infections of the CNS which causes encephalitis, dementia, apathy, delirium, confusion, lethargy

Cytomegalovirus Diagnosis and Treatment
Diagnosis includes:
- Fundoscopy
- Serology (IgM)
- CMV Culture
- CMV PCR
- Histopathology

Treatment of cytomegalovirus includes:
- Ganciclovir 7.5-10mg/kg/d in two divided doses for 2-3 weeks. Foscarnet 180 mg/kg/day in 3 divided doses for 14—21 days may be used when there is sight-threatening CMV retinitis.

Image of CMV Retinitis



The picture above shows Fundoscopic exam of a 16-year-old girl with HIV infection and cytomegalovirus retinitis. There are extensive areas of haemorrhage, with white retinal exudates.

Key Points

- PCP is more common under the age of 1 year and in severely immunosuppressed children
- Opportunistic infections in HIV infected children have varied systemic presentation
- Diagnosis and treatment of most OIs has significant challenges because lab tests and therapies are not readily available
- Chemoprophylaxis reduces morbidity and mortality

Sources/Bibliography

- *Chintu C et al. Cotrimoxazole as prophylaxis against opportunistic infections as HIV infected Zambian children (CHAP): a double-blind randomised placebo-controlled trial. Lancet, 2004, 364:1865–1871.*
- *Diagnosis, Prevention and Management of Cryptococcal Disease in HIV-infected Adults, Adolescents and Children. WHO Dec. 2011*
- *Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children: AIDS-Info 2013*

Handout 3.5.1: Cotrimoxazole Prophylaxis in Children and Adults

Indications for Cotrimoxazole Initiation and Discontinuation

	Indication for Primary PCP Prophylaxis with Cotrimoxazole	**Indication for Discontinuation of Primary PCP Prophylaxis with Cotrimoxazole**
HIV-Exposed Infants and Children*	All HIV-Exposed Infants and Children starting at 4 weeks of age	Continue until HIV Infection has definitively been excluded. (Confirmed negative by testing and no longer at risk of acquiring HIV through breastfeeding)
HIV-Infected Infants < 5 year of age	All children < 5 year of age confirmed to be HIV infected regardless of symptoms or CD4%	Continue until 5 years of age regardless of changes in WHO Stage or CD4 count.
HIV-Infected Children> 5 years of age	All HIV infected children >5 years of age who are symptomatic (WHO clinical stages 2, 3 or 4) or with a CD4 of $\leq$ 500.	Stop primary prophylaxis for adults and children $\geq$ 5 years once the patient has a CD4 $\geq$ 500.
Adolescents and Adults	WHO Stage 2, 3, 4, or CD4 <500 cell/mm^3 All Pregnant women	Stop primary prophylaxis for adults and children $\geq$ 5 years once the patient has a CD4 $\geq$ 500.

*Defined as a child born to mother living with HIV or a child breastfeeding from a mother living with HIV until HIV exposure stops (six weeks after complete cessation of breastfeeding) and infection can be excluded.

Handout 3.5.2: Recommended Dosage for PCP Prophylaxis

Recommended Daily Dosage	Suspension (5ml of syrup 200mg/40mg)	Child Tablet (100mg/20mg)	Single Strength Adult Tablet (400mg /80mg)	Double Strength Adult Tablet (800mg/160 mg)
< 6 months (<5 kg) 100mg sulfamethoxazole/ 20mg trimethoprim	2.5 ml	1 tablet	¼ tablet, possibly mixed with feeding	–
6 months –5 years (5-15 kg) 200mg sulfamethoxazole/ 40mg trimethoprim	5 ml	2 tablets	½ tablet	–
6 – 14 years (15-30 kg) 400mg sulfamethoxazole/ 80mg trimethoprim	10 ml	4 tablets	1 tablet	½ tablet
> 14 years (>30 kg) 800mg sulfamethoxazole/ 160mg trimethoprim	–	–	2 tablets	1 tablet
Frequency: Once a day				

Session 6: Other HIV-Related Conditions

Total Session Time: 45 minutes

Learning Objectives

At the end of the session participants will be able to:

- Describe the management of HIV related conditions (Lymphoid Interstitial Pneumoninitis [LIP], Parotitis and Kaposi's Sarcoma)
- Explain the management of HIV related encephalopathy, and skin and haematological conditions

Management of HIV Related Conditions

Lymphoid Interstitial Pneumonitis (LIP)

LIP occurs in at least 40% of children with perinatal HIV, but is rare in adults (LIP develops in about 3% of adults with HIV), and usually occurs in children more than two years of age. Various studies in Africa have documented a 30–40% prevalence of LIP in HIV-infected children, and up to 60% prevalence in those with chronic lung disease.

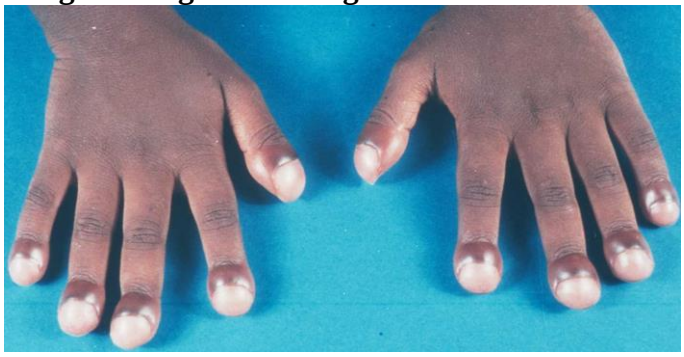
LIP is a chronic inflammatory disease of the lung. It is unique to children, very rare in adults, which usually occur in older children usually over 2 years of age. LIP has a better prognosis than other HIV associated conditions.

Clinical Presentation of LIP

LIP is often mistaken for pulmonary TB (miliary) because of the chronic cough and the miliary-like pattern on chest X-ray. LIP is associated with:

- Chronic cough
- Cyanosis
- Finger clubbing
- Difficulty in breathing and hypoxia
- Associated features such as Parotitis, generalised lymphadenopathy and hepatosplenomegaly.
- Poor response to TB therapy
- Abnormal chest x-ray

Image of Finger Clubbing in LIP

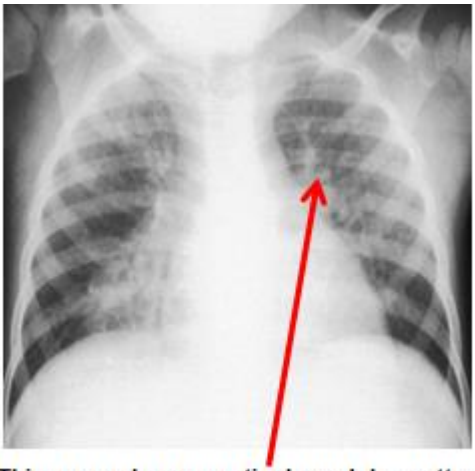


NOTE: Initially there is minimal finger clubbing which may not be very obvious.

Radiological Picture of LIP

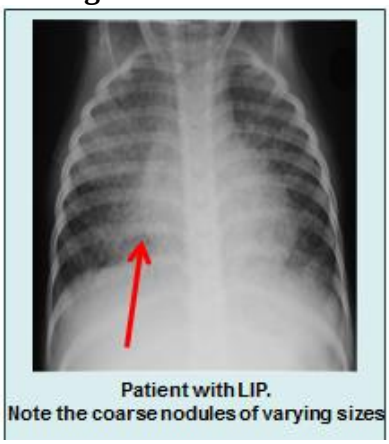
- Diffuse bilateral reticulonodular infiltrates may appear similar to miliary TB
- May develop consolidation, cystic lesions
- Bilateral hilar or mediastinal lymph node enlargement
- Particularly difficult to differentiate from TB

Chest X-Ray Findings in LIP

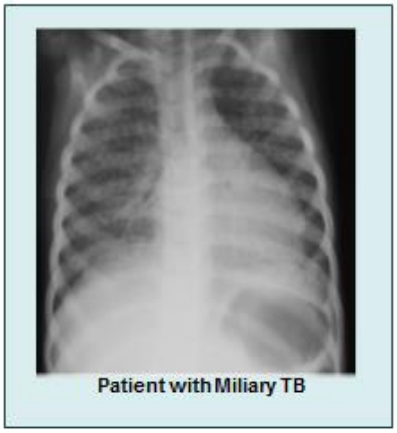


This x-ray shows a reticulo-nodular pattern

LIP Images



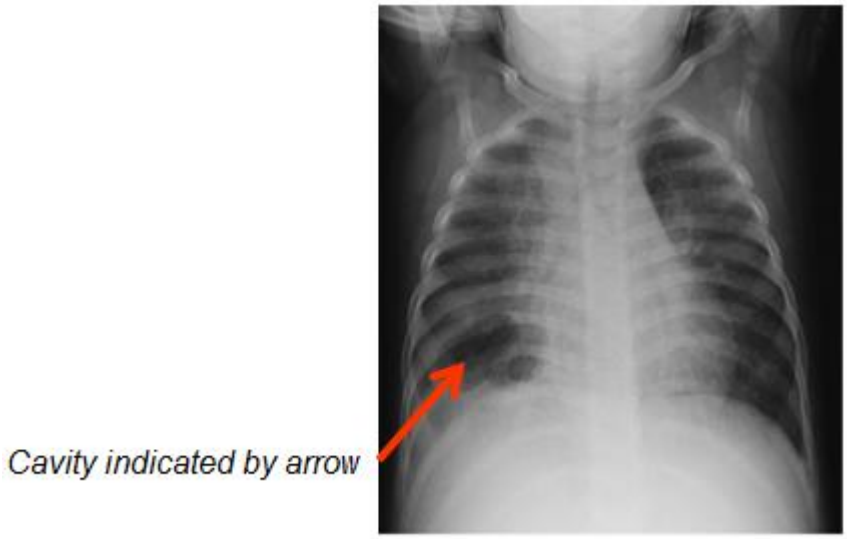
Patient with LIP.
Note the coarse nodules of varying sizes



Patient with Miliary TB

The typical features of LIP are bilateral diffuse reticulonodular infiltration with bilateral peripheral lymphnode enlargement. Miliary TB presents with typical bilateral diffuse micronodular pattern.

Image of LIP and TB



A patient with LIP who has developed a cavity in the right lower lobe due to concomitant infection with TB

Treatment of LIP

Treatment of LIP depends on:

- Steroids if significant respiratory distress: Prednisone 2 mg/kg/day - initially for 4 weeks daily and then an alternate day maintenance for 2-3 months and review.
- Oxygen therapy during episodes of hypoxia
- Bronchodilators like salbutamol if wheezing
- Antibiotics if concurrent superinfection with pneumonia
- Chest physiotherapy and postural drainage if there is secondary bronchiectasis
- Supportive care including correction of anaemia especially iron supplementation
- Refer for specialist care if resistant to therapy

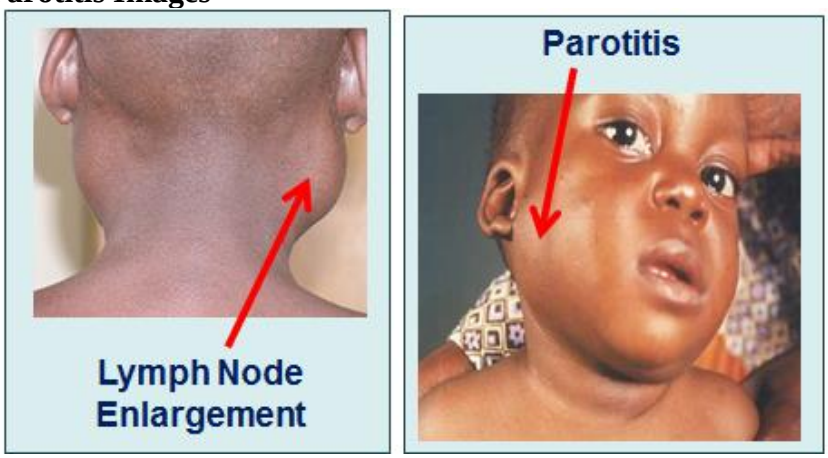
Note: Antiretroviral therapy is the specific therapy.

Parotitis

It is usually common in older children who are slow progressors. Parotitis may be associated with lymphoid interstitial pneumonitis (LIP). Super-infection requires antibiotics and analgesics. Surgery NOT required.

Parotid enlargement is usually not tender, when they become tender, prescribe antibiotics and analgesics.

Parotitis Images



Kaposi's Sarcoma (KS)

Kaposi's Sarcoma is a cancer of skin and organs associated with a herpes virus, HHV-8. Small, purplish lesions are visible on skin.

Before HIV pandemic, KS was rare in children. Present as early as first month of life. May presents as black purple mucocutaneous lesions (skin, eye, and oral cavity).

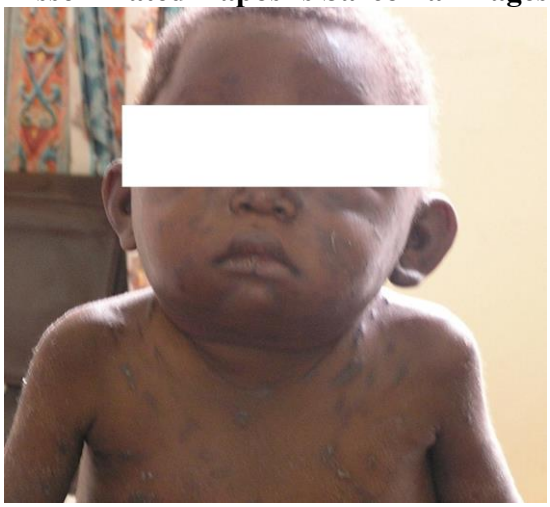
KS generalized lymphadenopathy, which may mimic cutaneous TB and can involve the lungs and other organs. It's clinically diagnosed as biopsy. The treatment: ART ± Chemotherapy.

ART is associated with significant improvement in the survival of patients with KS, and has become an essential component of KS management.

Prior to the availability of effective ART, 90% of patients with pulmonary KS progressed and died of their disease. In contrast, where effective ART is available, the proportion of patients with pulmonary KS experiencing fatal disease progression has been reduced to 47%.

In addition to the indirect effect of ART on KS growth, some of the protease inhibitors have specific antineoplastic effects.

Disseminated Kaposi's Sarcoma Images



Kaposi's sarcoma is the most common malignant tumor associated with HIV infection. Recent investigations have implicated a herpes virus (HHV-8) in the aetiology of Kaposi's Sarcoma. The behaviour of Kaposi's sarcoma is unpredictable. Lesions may interfere with function, may be cosmetically objectionable and may proliferate uncontrollable. Oral lesions of Kaposi's sarcoma appear as reddish-purple, flat or raised lesions. The size of the lesions ranges from small to extensive and oral lesions may be single or multiple. The palate and gingival are the most commonly affected oral sites. The definitive diagnosis is made by biopsy and histologic examination. There is no curative therapy—radiation treatment, systemic and intralesional chemotherapy have been used to control lesions.

Management of HIV Related Encephalopathy, and Skin and Haematological Conditions

HIV Encephalopathy

Occurs in approximately 20% of HIV infected children, may presents as delayed/regression of milestones.

Diagnosis is clinical (at least 2 of the following):

- Failure to attain or loss of milestones
- Impaired brain growth or acquired microcephaly
- Acquired symmetrical motor deficits

Acquired symmetrical motor deficit is manifested by two or more of the following: paresis, pathological reflexes, ataxia, or gait disturbances. Cerebrospinal fluid is normal or has non-specific findings and CT scan shows diffuse brain atrophy.

Treatment is supportive depending on clinical presentation and antiretroviral therapy is the mainstay therapy.

Skin Manifestations

The most common skin conditions among HIV-infected children are infections followed by eczematous dermatitis, unlike HIV-uninfected children where the most frequent condition is eczematous dermatitis followed by infections. But the most common skin manifestation of HIV and AIDS in children is a non-specific generalized dermatitis.

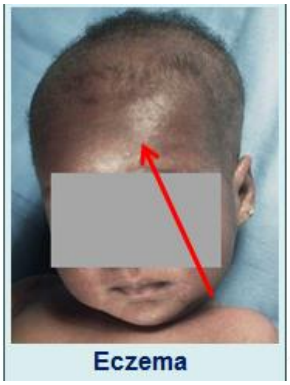
Other skin lesions are secondary infections such as:

- The frequency is related to the severity of immune suppression
- Bacterial, and fungal skin infections are more common, but also more difficult to treat, than in children who are not immunocompromised

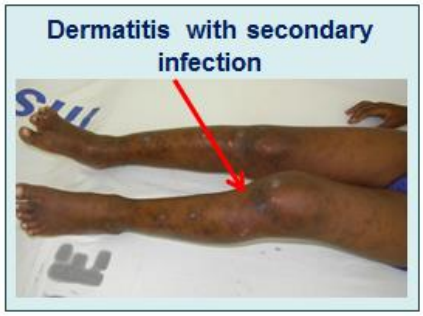
NOTE: Treatment as per national recommendations

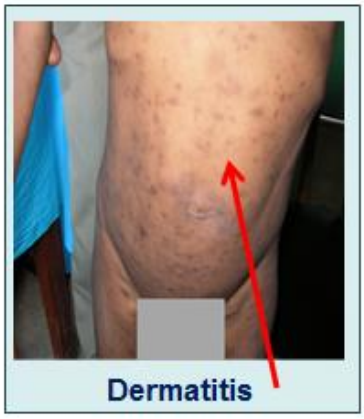
Skin Manifestation Images

Non-Specific Dermatitis



Eczema





Dermatitis

Haematological Conditions-Anaemia

Hematologic abnormalities are among the most common manifestations of HIV/AIDS infection in children. HIV infection alone, without other complicating illness, may also produce anemia in some patients.

This is very common in patients with HIV infection, particularly those with advanced disease that contributes significantly to mortality.

Prevalence is determined by the prevalence of other conditions:

- Malnutrition
- Malaria

- Helminthic infections

Haematological Conditions - Thrombocytopaenia
May occur with bleeding tendencies due to HIV related low platelet count or platelet dysfunction presenting with;
- Nosebleeds,
- Excessive bleeding in cuts
- Easy bruising
- Small and large red spots on skin

Thrombocytopaenia can develop Idiopathic thrombocytopenia purpura (ITP). First line treatment: Prednisolone 1-2mg/kg/day for 7 to 14 days.

Possible aetiologies of thrombocytopaenia in patients with HIV infection include immune-mediated destruction, thrombotic thrombocytopaenic purpura, impaired haematopoiesis, and toxic effects of medications. Therefore thrombocytopenia occurs as a result of:
- Increased peripheral destruction or
- Increased peripheral sequestration or
- Decreased production or
- A combination of the above.

HIV-associated ITP clinically resembles classic ITP but, in spite of very low platelet numbers, bleeding is rarely severe, and moderate splenomegaly and lymphadenopathy are seldom present. Treatment is the same as that given for classic ITP because the pathogenesis is in many ways similar. HIV-related thrombocytopenia (HIV-TP) responds to antiretroviral therapy. Combination therapy (HAART) results in sustained platelet increases.

Treatment of Haematological Conditions
Treatment of haematological conditions includes:
- Nutritional, vitamins, haematinics and blood products as required
- Antiretroviral therapy is the specific therapy in HIV related anaemia

Case Studies on HIV-Related Illnesses

*Refer to **Worksheet 3.6.1: Case Studies on HIV-Related Illnesses** on page **169** for more information.*

Key Points

- LIP is a chronic inflammatory disease of the lung
- LIP is common in children >2yrs
- Chest X ray findings of LIP can mimic those PTB
- Kaposi's Sarcoma is a cancer of skin and organs associated with a human herpes virus type 8
- HIV encephalopathy occurs in approximately 20% of HIV infected children
- Anaemia contributes significantly to mortality in HIV infected children
- Treatment for these conditions is ART and specific treatment

Sources/Bibliography

- *Pati S, et al. Antitumorigenic effects of HIV protease inhibitor ritonavir: inhibition of Kaposi sarcoma. Blood. 2002 May 15;99(10):3771-9.*
- *Sgadari C, et al. HIV protease inhibitors are potent anti-angiogenic molecules and promote regression of Kaposi sarcoma. Nat Med. 2002 Mar;8(3):225-32.)*
- *Tam HK, et al. Effect of highly active antiretroviral therapy on survival among HIV-infected men with Kaposi sarcoma or non-Hodgkin lymphoma. Int J Cancer. 2002 Apr 20;98(6):916-22.*

Worksheet 3.6.1: Case Studies on HIV-Related Illness in Children

Instructions:

- In small groups, read the case studies below and answer the questions. Each case study includes discussion questions and multiple choice questions.
- You will have approximately 20 minutes to complete the case study.
- Be prepared to share and discuss your responses in plenary.

Case Study 1

Rashid is a 4 years old child presented with FTT, chronic cough and night sweats. He has been treated several times for pneumonia with short relief. His father died 3 years ago due to HIV/AIDS (recurrent pneumonia). His auscultation is unremarkable, has a RR of 41b/min. He is severely wasted, has an unspecific skin rash and a mild generalized lymphadenopathy. Serology for HIV is positive, ESR 68 and CD4 is 497/ml. CXR shows micro nodular lesions in both lung fields.

1A. What is the most likely diagnosis?

1B. At what clinical stage is this patient?

1C. What treatment would you recommend for this child?

Case Study 2

A 4 month old child referred to your hospital from dispensary with history of gradual onset of cough, then fever and increasing DIB over the last 5 days. Amoxicillin gave the child only short relief. O/E: the child is restless, slightly cyanosed, chest in drawing, nasal flaring, RR 59/min, on auscultation nothing abnormal detected. Chest X-Ray has no remarkable findings.

2A. What is your provisional diagnosis and treatment?

2B. You start your treatment but after 72 hours there was no significant clinical response. What do you ask the mother?

2C. The mother was PMTCT 1 (HIV infected diagnosed during pregnancy) but she has not been on treatment and the child did not receive any medication. What is your diagnosis and treatment? A 4 months old baby girl with body weight 5.4kg.

Case Study 3

A 4-year-old HIV-infected child presents to your clinic. The caregiver states that the child has a rash that started on the head/face about four days ago. It has continued to spread down the body and the child is scratching a great deal. The lesions start out as vesicles (small fluid-filled lesions), but the earliest ones have crusted over. The caregiver states that her next-door neighbor's child had a similar rash the week before and the two children had been left together. Currently the child has no fever, is eating and drinking well, but is uncomfortable because the rash itches so much.

3A. What is the most likely diagnosis? ***Select one:***

a. Scabies
b. Kaposi's Sarcoma
c. Varicella zoster
d. Impetigo

3B. What treatment would you recommend for this child? ***Select one:***

a. Symptomatic treatment only
b. Varicella zoster immune globulin
c. Acyclovir
d. All of the above
e. A and C only

3C. What would you advice the caregiver to watch for in the next several days? ***Select one:***

a. Fever
b. Change in the rash, especially a new redder appearance
c. Difficulty breathing
d. Abdominal pain
e. All of the above