PART II: SYSTEMIC MANIFESTATIONS AND OPPORTUNISTIC INFECTIONS IN PAEDIATRIC HIV

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Introduction

Symptoms and signs of HIV infection in childhood similar to those of other diseases seen in the tropics; but may be more severe and occur more frequently and more commonly infectious in nature.

Early features are usually non-specific:

- Fever
- Diarrhoea
- Failure to thrive
- Cough
- Generalized lymphadenopathy

Later the child presents with features indicative of severe immune suppression:

- Signs of opportunistic infections e.g. tuberculosis
- Recurrent and more severe forms of common illnesses e.g. bacterial pneumonia
- Malignancies e.g. Kaposi sarcoma

HIV is also systemic and all parts of the body can be affected by the virus itself. Systemic manifestations of HIV infection include:

- Skin and oral mucosa (Part 1 of the atlas)
- Malnutrition
- Reticuloendothelial system- generalized lymphadenopathy, hepatomegaly, splenomegaly
- Blood - anaemia, thrombocytopaenia and leukopenia
- Lung - lymphoid interstitial pneumonitis
- Central nervous system – encephalopathy
- Renal – nephropathy
- Cardiovascular - cardiomyopathy.

This second part of the atlas deals with non-dermatological manifestations of paediatric HIV infection including opportunistic infections, malignancies, systemic manifestations of the disease and immune reconstitution inflammatory syndrome that may complicate antiretroviral therapy.

CHAPTER 9: PAROTID ENLARGEMENT

Parotid enlargement is estimated to occur in about 3 to 6% of HIV positive adults and 1 to 10% of children and is so unusual in the HIV negative population that cystic enlargement of the parotid gland is an indication for HIV testing. It is secondary to benign lymphoepithelial cysts and is categorised under stage 2 HIV disease.

Diagnosis: Differential causes of swellings in and around the parotid region in paediatric age group include viral infections such as mumps (epidemic parotitis), Ebstein-Barr virus and HIV. The parotid enlargement tends to be bilateral in viral causes of parotitis but may be unilateral. Acute bacterial parotitis from *Staphylococcus aureus* and anaerobes found normally in the mouth generally cause a unilateral swelling and other symptoms such as pain and fever may be present. Tuberculosis and malignancies such as lymphoma are also important differentials.

In HIV parotitis, fine needle aspiration cytology (FNAC) may show background generalized marked lymphocytosis and occasional macrophages. Some cases may show cellular aggregates suggestive of epithelial components.

Treatment

The swelling is managed conservatively with antiretroviral therapy. In one study, there was marked reduction in parotid enlargement and significant improvement in CD4 count, CD4 % and viral load following the commencement of ART in majority of the cases. Sclerosing therapy, external beam RT and surgery are other reported treatment options.

Further reading

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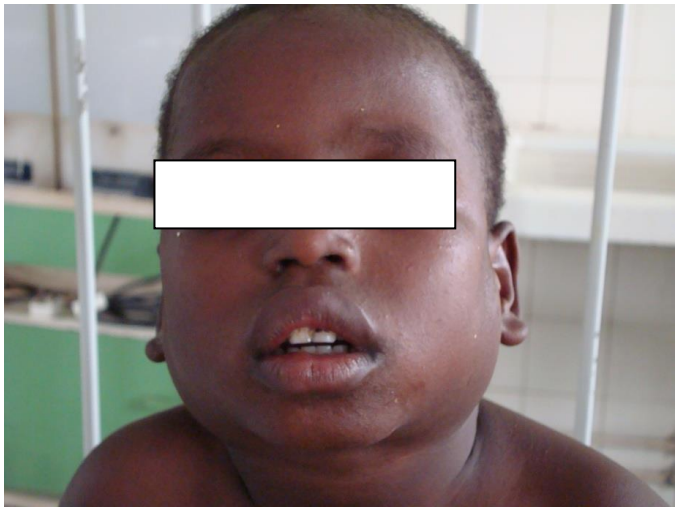

Figure 98: Bilateral parotid enlargement in a 4-year-old child erroneously diagnosed as a case of mumps. More detailed history, examination and antibody testing confirmed HIV infection.

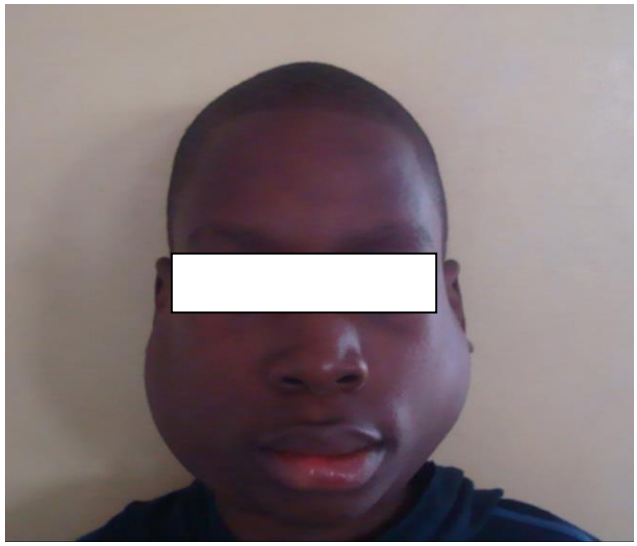

Figure 99: Bilateral parotid swelling in a 12-year-old child.

CHAPTER 10: SYSTEMIC MANIFESTATIONS OF PAEDIATRIC HIV INFECTION

HIV Associated Cardiomyopathy

HIV is an important cause of dilated cardiomyopathy (DCM). Estimated prevalence rates of between 3% and 33% have been reported among HIV-infected children. Just like other systemic conditions associated with HIV infection, cardiovascular manifestations of the disease have been altered by the introduction of ART.

DCM is characterised by dilatation and impaired contraction of one or both ventricles. Systolic function becomes impaired and may result in heart failure.

The possible mechanisms of cardiomyopathy in HIV infection include; myocardial damage by HIV itself, autoimmunity, secondary infection, drug toxicity, co-infection with cardiotropic viruses (CMV, EBV, Coxsackie virus), nutritional deficiencies (selenium, vitamin B_{12}) and low levels of growth and thyroid hormones.

Diagnosis: The child may present with features of heart failure with evidence of cardiomegaly demonstrable on clinical examination, chest x-ray and electrocardiogram.

Echocardiographic findings include left ventricular (LV) dilatation, global hypokinesia and a reduced LV ejection fraction. Mitral and tricuspid regurgitation due to annular dilation may also be present.

Treatment: Antifailure medications (frusemide, spironolactone, captopril). To be managed in conjunction with the cardiologist. ART initiation is paramount.

Further reading

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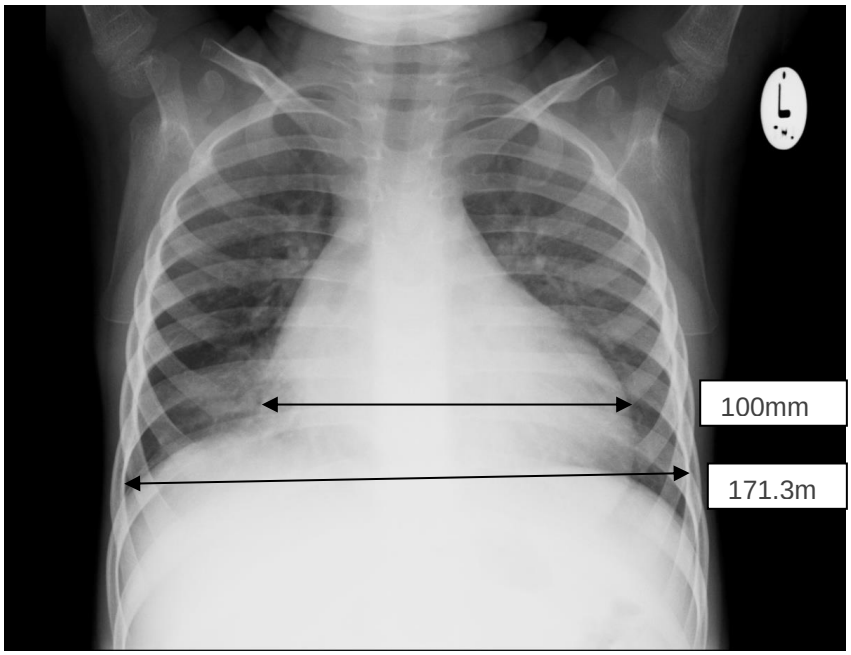

Figure 100: Chest X-ray showing enlarged heart in a child with HIV associated dilated cardiomyopathy

HIV-Associated Nephropathy (HIVAN)

HIVAN is defined by the presence of proteinuria associated with mesangial hyperplasia and/or global-focal segmental glomerulosclerosis, in combination with the microcystic transformation of renal tubules. Before the era of highly active antiretroviral therapy, more than 40% of HIV-infected children experienced renal complications. HIVAN is considered to be a renal disease induced directly by HIV-1. Black race is an established risk factor for the development of HIVAN.

Diagnosis: Patients with HIVAN typically present with significant proteinuria and rapidly progressive renal insufficiency in the setting of poorly controlled HIV infection marked by low CD4 counts and elevated HIV RNA levels. Most patients with HIVAN do not have significant oedema or hypertension. As proteinuria may be the first sign, it is advocated that all HIV-infected children should be screened for proteinuria at least once a year. Renal ultrasound may show large echogenic kidneys. However, in the case of long-standing kidney disease, there may be signs of fibrosis with small kidneys.

The definitive diagnosis of HIVAN requires a histological examination of renal tissues. In adults, HIVAN usually presents with the classic histologic findings of collapsing focal segmental glomerulosclerosis (FSGS) and tubular microcystic changes but in contrast, HIV-infected children more frequently show mesangial hyperplasia and/or classic FSGS in combination with the microcystic tubular lesions. Children with mesangial hyperplasia show a slower rate of progression of their renal disease when compared with children with classic or collapsing FSGS.

Treatment: ART is considered the best treatment for HIV. By reducing the viral load, ART may prevent progression of proteinuria and is associated with a marked improvement of HIVAN, resulting in slower progression to end stage renal disease (ESRD). HIV-infected children with HIVAN need to be managed in conjunction with a nephrologist. Diuretics, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin-receptor blockers are other forms of supportive therapy available for HIV-related kidney disease in children but need to be used with caution.

In severe kidney damage, renal replacement therapy has been shown to offer improved survival. The most appropriate modality, peritoneal or haemodialysis depends on the availability of resources and expertise for the treatment. Necessary precautions need to be taken during dialysis to prevent the transmission of HIV-1 to health care workers.

Further reading

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2. McCulloch MI, Ray PE. Kidney disease in HIV-positive children. Semin Nephrol. 2008; 28(6):585-94.
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HIV Encephalopathy (HIVE)

HIV encephalopathy (HIVE) has been postulated to result from direct damage to the brain by HIV virus as it replicates in the CNS as well as viral/host interactions that lead to CNS damage by the release of soluble neurotoxic factors. In ART naïve children, prevalence of HIVE ranges from 20%-60%.

Presentation: HIVE has a wide spectrum of manifestation and can be in form of progressive or static encephalopathy affecting motor, cognitive or language function. Motor involvement may include spasticity and movement disorder.

HIV associated progressive encephalopathy may be characterized by delay, loss or regression in developmental milestones and or neurological dysfunction. Children with static encephalopathy on the other hand have a non-progressive developmental delay and they may gain new skills but function below average.

Diagnosis: Diagnosis is clinical, however, where available, neuro-imaging of the brain may show basal ganglia calcification, cerebral atrophy, and white matter changes.

Centers for Disease Control (CDC) case definition of HIV encephalopathy is: At least one of the following progressive features present for ≥2 months:

1. Failure to attain or loss of developmental milestones or loss of intellectual ability verified by standard developmental scale or neuropsychological tests.
2. Impaired brain growth or acquired microcephaly demonstrated by head circumference measurements or brain atrophy on CT scan or MRI (serial scanning is required for children <2 years).
3. Acquired symmetric motor deficit manifested by 2 or more of the following: paresis, pathologic reflexes, ataxia, or gait disturbance.

Treatment: Improvement occurs with institution of combination ART. However, ART may not fully reverse developmental dysfunction despite demonstration of clinical, immunological and virological response to therapy.

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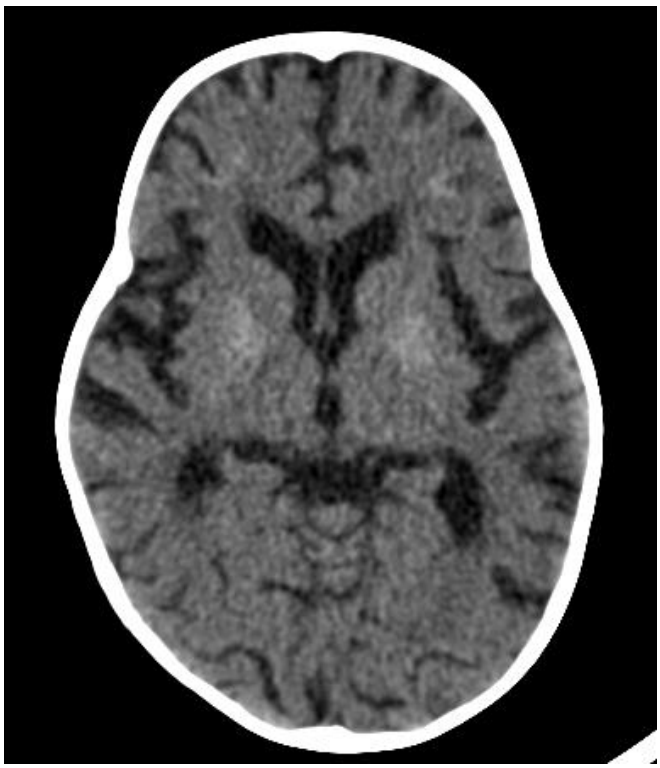

Figure 101: CT brain of an 18/12 old girl with HIV encephalopathy: The image shows global brain shrinkage, bibasal ganglia and subcortical calcification.

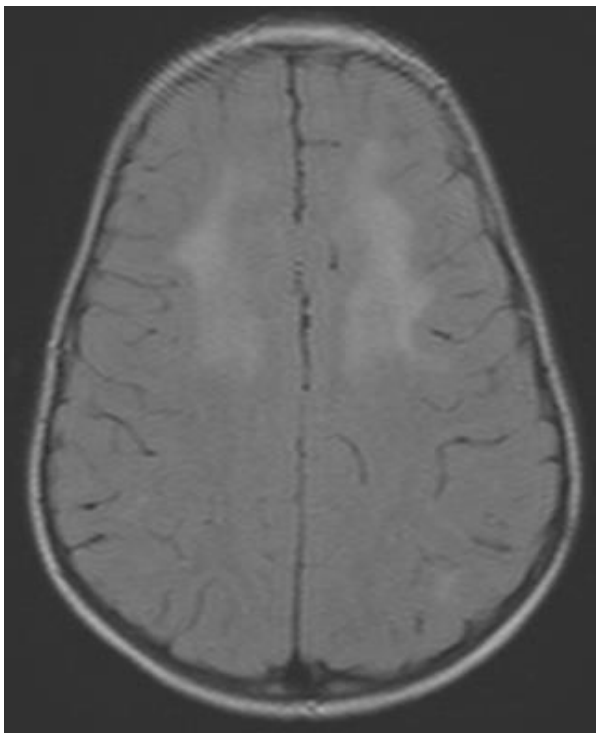

Figure 102: MRI brain of a 20-month old child with HIV encephalopathy showing white matter enhancement.

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CHAPTER 11: MALNUTRITION AND HIV

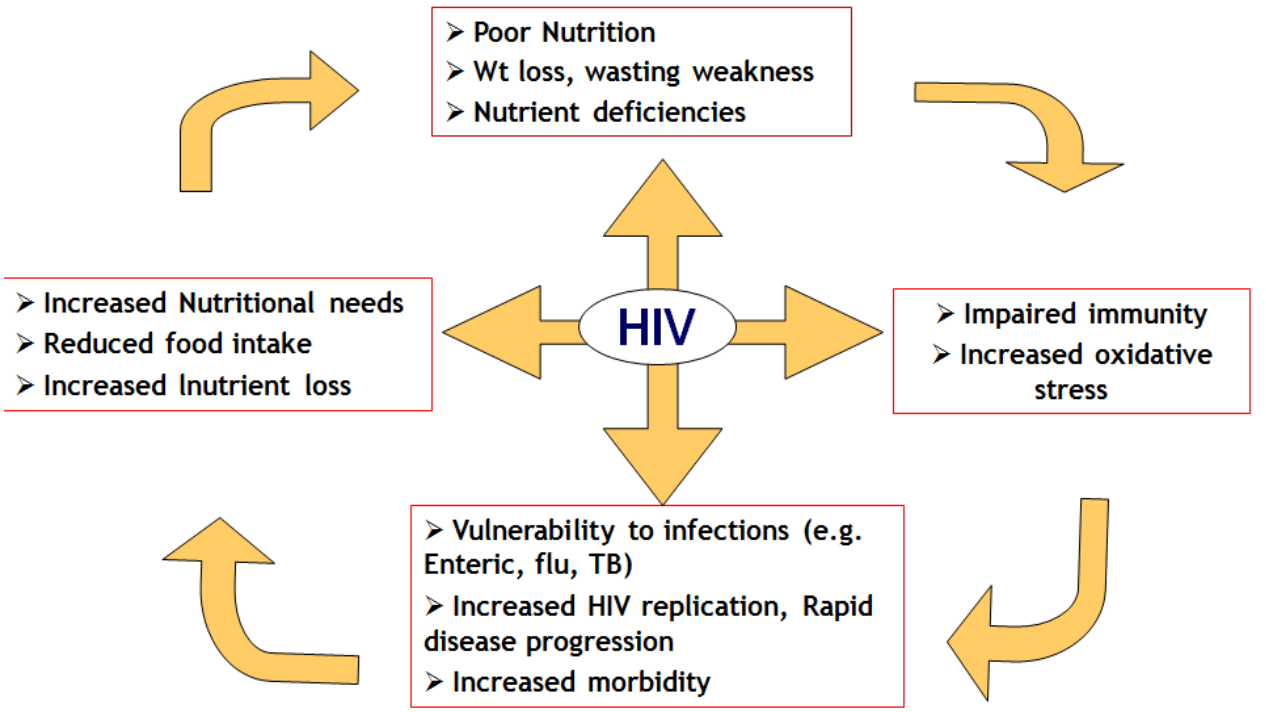

Figure 103: Interaction between HIV infection and nutritional status in children

Malnutrition is high among HIV-infected children especially in developing countries, where it is already endemic. Severe malnutrition is predictive of HIV; 30—50% of severely malnourished children are HIV-infected in settings where both conditions are endemic.

Stunting (low height for age) is a more prominent feature than wasting in HIV-associated malnutrition. Micronutrient deficiencies (low serum levels of zinc, selenium, vitamins A, E, B6, B12 and C) is also common among HIV-infected children. HIV-related malnutrition could result from reduced food intake (poor appetite, oral infections such as candidiasis), increased metabolism and poor absorption of nutrients mainly due to diarrhoeal diseases.

Unexplained moderate malnutrition not adequately responding to standard therapy is classified as stage 3 disease. Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy is a clinical stage 4 disease.

Diagnosis

1. Weight, height and occipitofrontal circumference (OFC) should be plotted on available growth charts (WHO growth standards available at *www.who.int/childgrowth/training/en).*

   SD Z scores for weight, height/length, OFC (from -2SD to -3SD is severe)
2. Severe wasting can also be demonstrated by measuring the mid upper arm circumference (MUAC):
   - <11.5 cm from 6 - 59 months of age:
   - <13.5 cm from 5-9 years
   - <16.0 cm from 10-14 years

Treatment

It is recommended that children with severe acute malnutrition (SAM) are managed in the institution until there is nutritional recovery, ≥90% weight for height. Generally, this would require admission for up to 4 weeks.

Children can be discharged once they have achieved >10 g/day weight gain, are taking a solid diet, have a good appetite, show no oedema.

Ready to use foods (RTUF) e.g. plump nuts, a new peanut butter based F100 preparation is useful as therapeutic and supplemental feed in the management of severe malnutrition.

Complications

Mortality is five times higher in severely malnourished HIV-infected than in uninfected children.

Further reading

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Figure 104: Plump nuts.

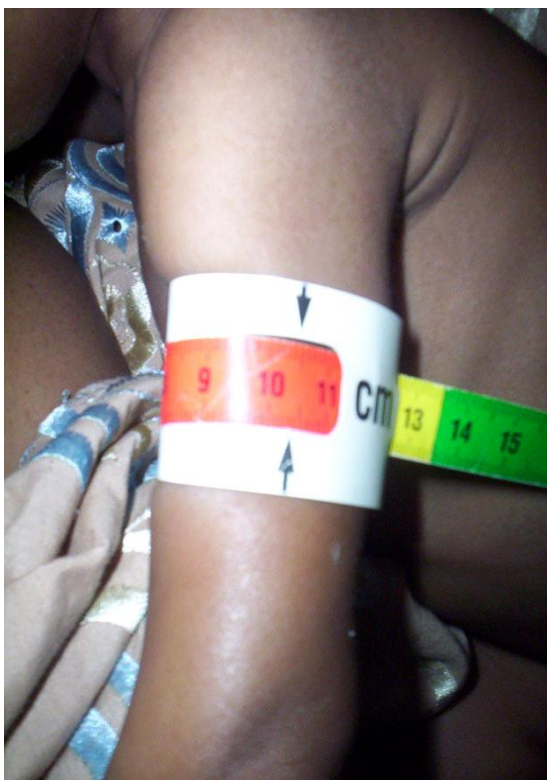


Figure 105: Severe malnutrition: MUAC 10.5 cm.

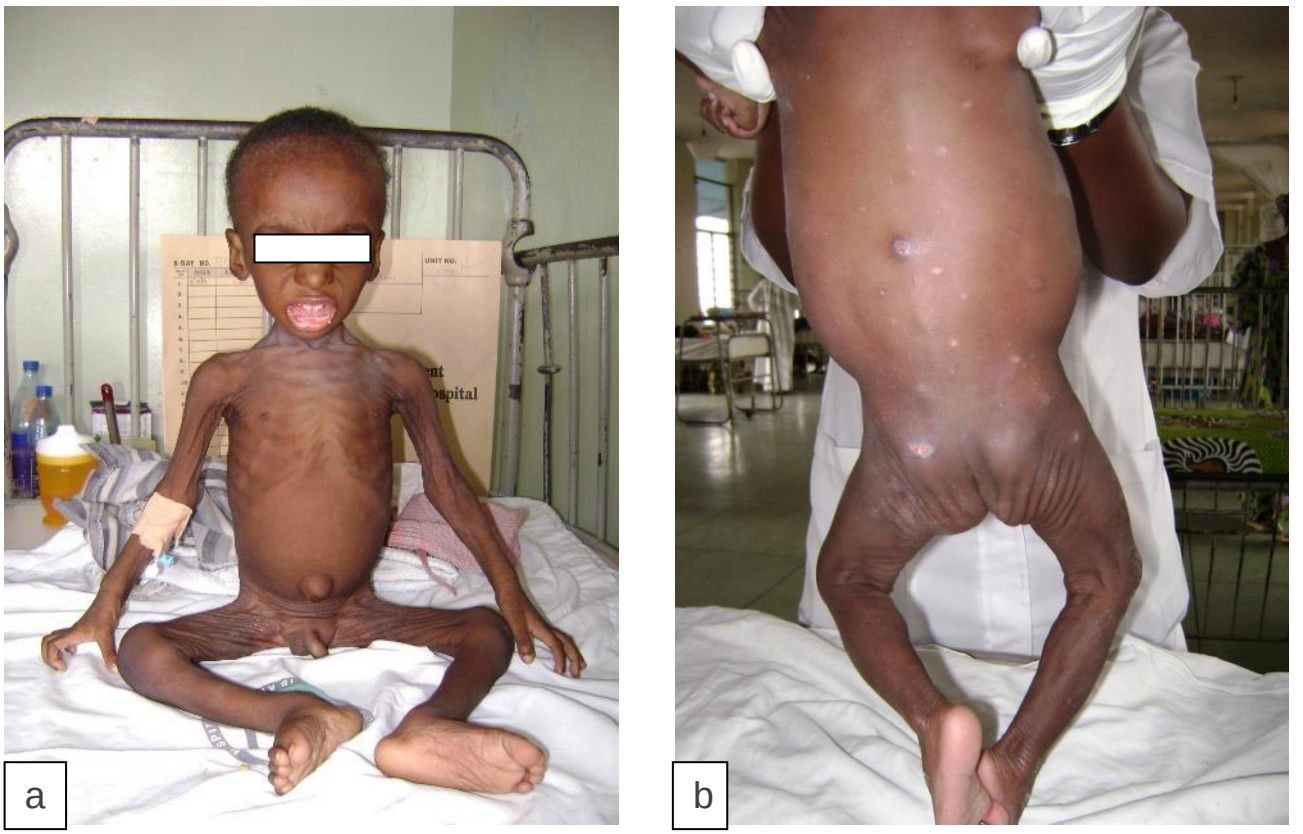


Figure 106 a and b: (a) Severe wasting, (b) Marasmus with gluteal skin folds ("baggy pants" sign).

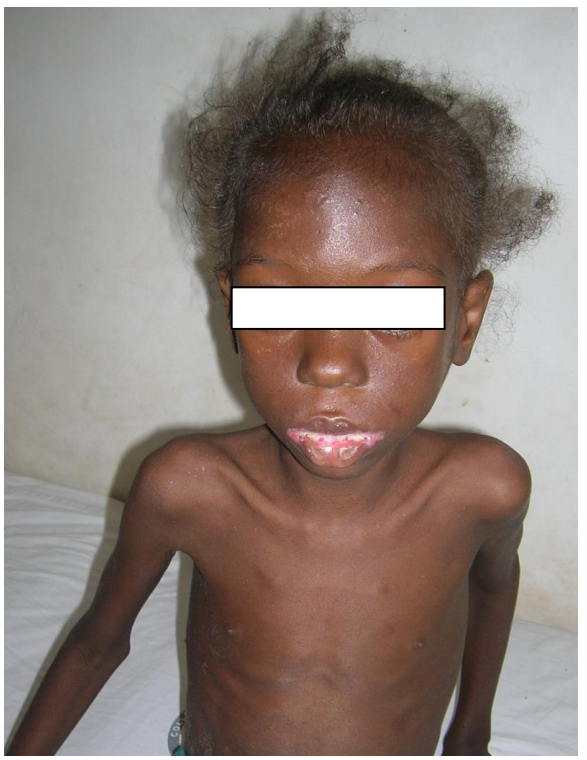


Figure 107: Severe wasting with hair changes in HIV infection.

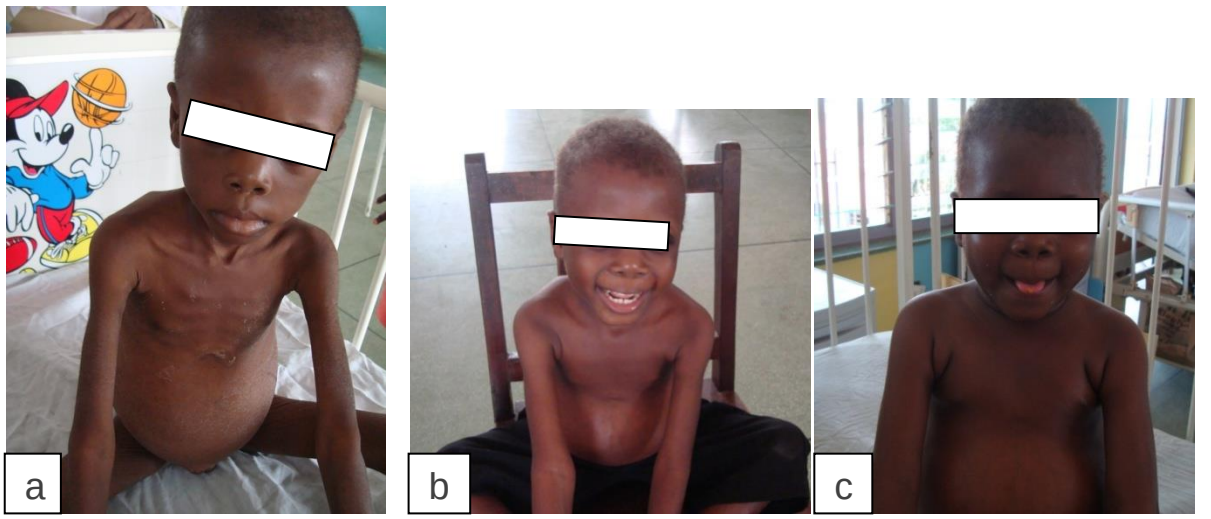


Figure 108a, b and c: (a) At first diagnosis (b) After 2 weeks on care (c) After 4 weeks on care.

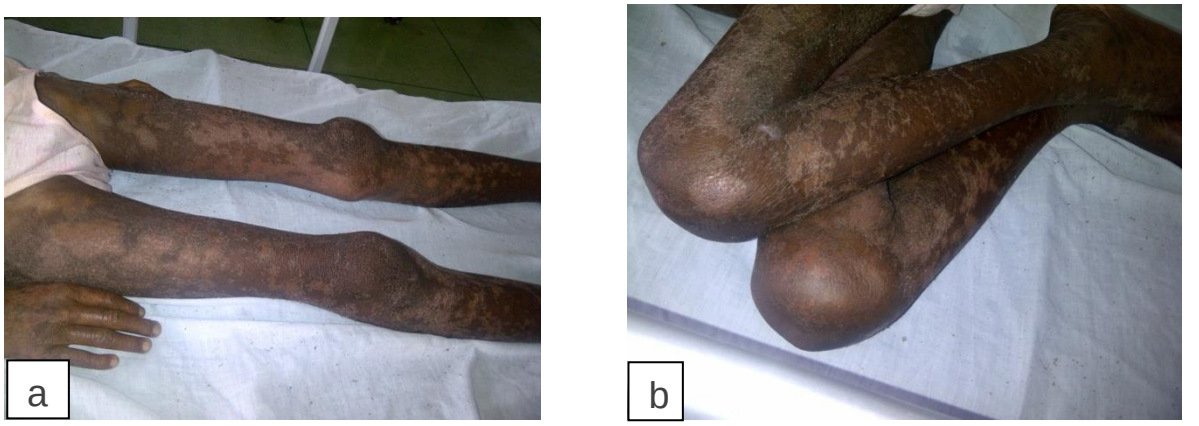
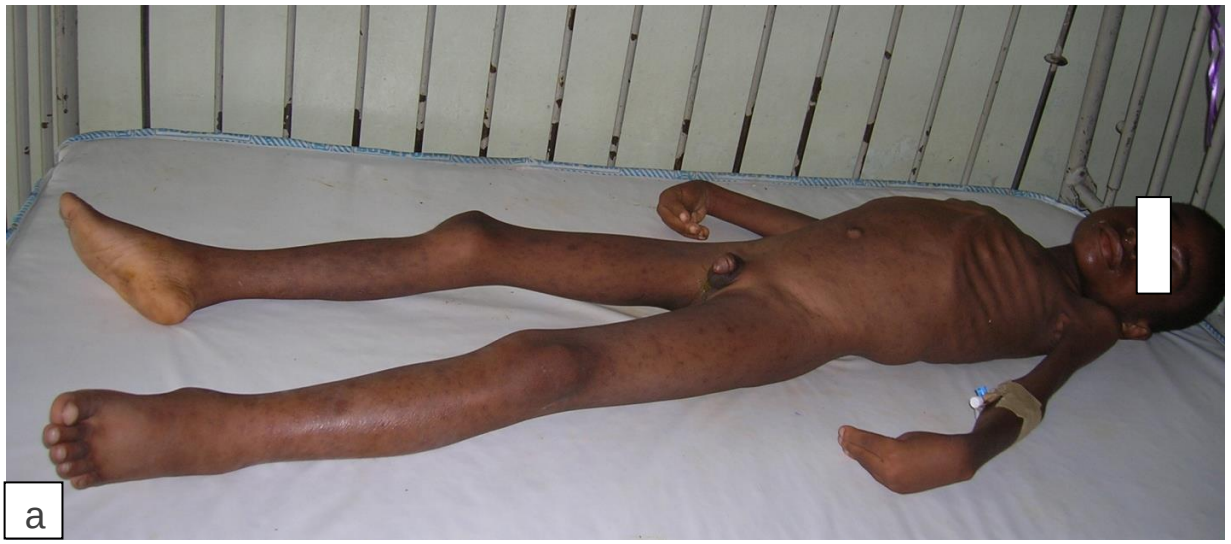


Figure 109a and b: (a, b) Severe wasting and flaky paint desquamation on the lower limbs of an HIV-infected child.



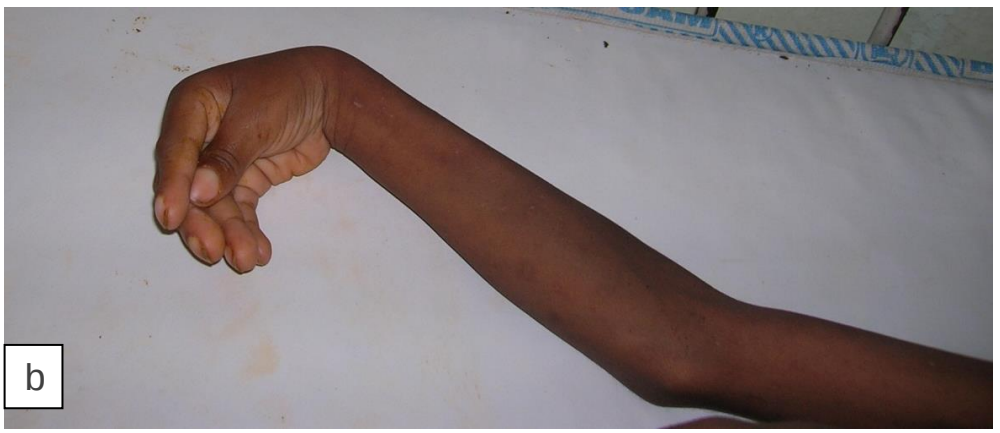


Figure 110a and b: 8-year-old boy with severe acute malnutrition plus oedema. He had symptomatic hypocalcaemia with carpal spasm demonstrated. The spasm resolved with intravenous calcium gluconate.

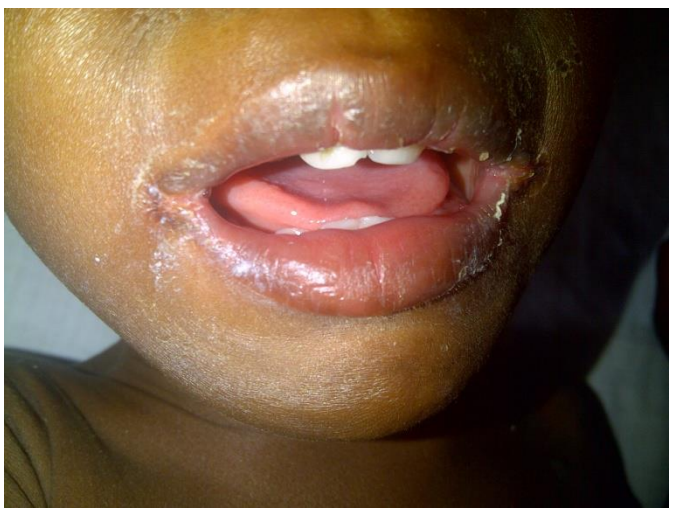


Figure 111: Angular stomatitis due to riboflavin (vitamin B2) deficiency.

CHAPTER 12: OPPORTUNISTIC INFECTIONS

Pneumocystis Pneumonia

Pneumocystis pneumonia (PCP) is caused by a fungus called *Pneumocystis jiroveci* (formerly *Pneumocystis carinii).* PCP is the major cause of severe pneumonia (15–30%) and death (30–50%) in HIV-infected infants and sometimes in older children. The highest incidence of PCP in HIV-infected children is in the first year of life, with cases peaking at ages 3 to 6 months. ART and chemoprophylaxis with co-trimoxazole have led to about 80-90% decline in PCP (cases per 100 child-years). Young infants and severely immunocompromised patients are at high risk for PCP.

Clinical presentation

Pneumocystis jiroveci pneumonia may present as hypoxic pneumonia with cough, fever difficulty in breathing, tachypnoea and cyanosis. Onset can be abrupt or insidious with nonspecific symptoms such as poor feeding and weight loss. Some patients may not be febrile, but almost all will have tachypnoea by the time pneumonitis is evident on chest radiograph.

Differential diagnoses include: cytomegalovirus (CMV), other viral pneumonias, lymphoid intestinal pneumonitis (LIP), TB and *Mycobacterium avium* complex (MAC).

Diagnosis

Induced sputum, tracheal aspirate or bronchoalveolar lavage (BAL) are suitable samples for histology, direct immunofluorescence (IF) using monoclonal antibodies or PCR to detect Pneumocystis organisms. In one study, PCP was identified in 54% children using PCR, compared to 21% using IF and Grocott staining. Sputum and nasopharyngeal aspirates (NPA) are unsuitable for detection of PCP.

Chest x-ray is not usually diagnostic but may show bilateral diffuse parenchymal infiltrates with a "ground-glass" or reticulogranular appearance, but can be normal or have only mild parenchymal infiltrates. The earliest infiltrates are perihilar, progressing peripherally before reaching the apical portions of the lung.

Treatment

Empirical treatment with co-trimoxazole 15-20 mg/kg/d ÷ q6-q8 x 21 days is advocated in an HIV positive child with suspected PCP and treatment should not be delayed while awaiting results. The co-trimoxazole is given intravenously initially (where available) and stepped down to oral therapy when there is improvement. Supplemental oxygen is useful and a short course of corticosteroids is recommended in cases of severe PCP, starting within 72 hours of diagnosis. Prednisone is given at 1 mg/kg/dose twice daily for a week and tapered off over a week.

Alternative agents include pentamidine or clindamycin + primaquine. Intravenous pentamidine isethionate (4 mg/kg) once daily is recommended for patients who cannot tolerate co-trimoxazole or who demonstrate clinical treatment failure after 5 to 7 days of therapy.

PCP prophylaxis: co-trimoxazole administered (6 mg/kg) once daily. If syrup is unavailable, tablets may be used.

Co-trimoxazole is started from 6 weeks in HIV-exposed infants until HIV diagnosis is confirmed negative.

Co-trimoxazole is also indicated in the HIV-infected child with CD4 threshold severe for age and in any child who has had PCP.

Co-trimoxazole also protects against toxoplasmosis, malaria and serious bacterial infections in HIV-infected children.

Alternatives

- Dapsone (children ≥ 1 month): 2 mg/kg PO daily
- Aerosolized pentamidine
- Atovaquone.

Further reading

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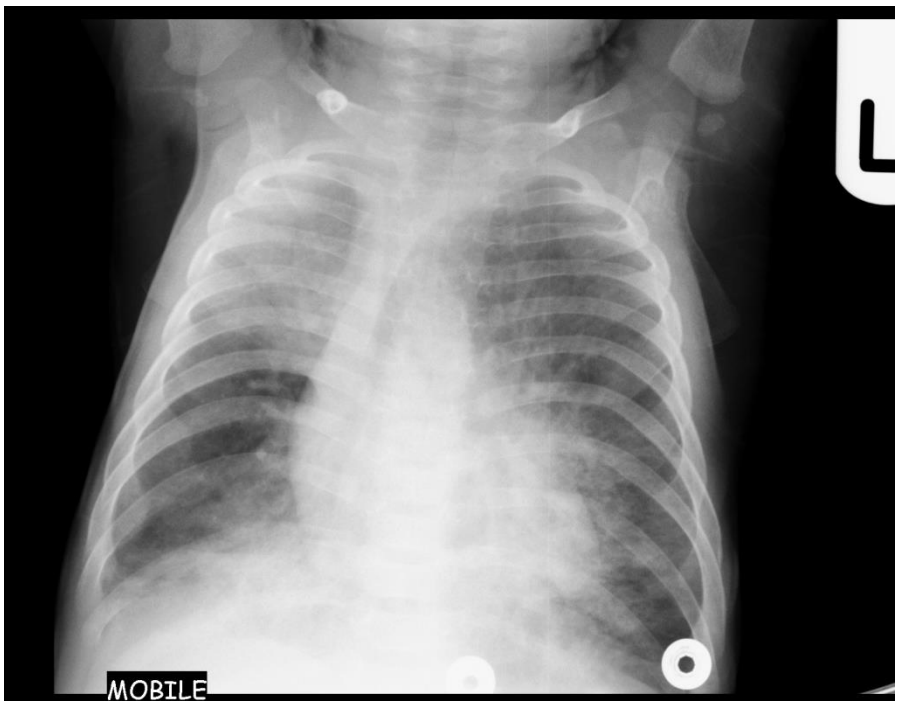

Figure 112: Chest X-ray of a 3-month-old child newly diagnosed with HIV infection. The X-ray shows confluent air space opacification in the right upper lobe and lower lobe on a background of bilateral ground-glass air space opacification. BAL specimen was positive for PCP.

Mycobacterial Infection

There is increased risk of TB among HIV-infected children partly attributable to immunosuppression. *M. tuberculosis* is believed to enhance HIV replication; CD4 T-cells reduce with progressive HIV disease, vital for immunity to TB. There is also increased exposure to TB within among close family contacts.

HIV infection increases the risk of TB disease by a factor of 20. HIV-infected children are at increased risk of TB and of more severe forms compared with immunocompetent children and TB manifestations more severe in HIV-infected children, with reduced cure rates and increased mortality. In high HIV-prevalence areas, the recommendation is to test all children with TB for HIV and HIV counselling and testing is indicated in all TB patients.

Diagnosis

Cough, fever, weight loss are some of the clinical features of TB but are not specific for diagnosis of TB as these features may be seen in HIV infection. Disease progression may be more rapid and the development of complicated or disseminated disease is more likely in HIV-infected children. HIV-infected children may also have atypical findings, such as multi-lobar infiltrates and diffuse interstitial disease, and rapidly progressive disease, including meningitis.

Apart from TB, children with HIV infection may have other lung diseases related to their HIV infection. Bacterial causes include recurrent pneumonia; fungal – PCP; viral – CMV, adenovirus; other mycobacteria; non-infectious – lymphoid interstitial pneumonitis, bronchiectasis, pulmonary Kaposi sarcoma and cardiac causes - cardiomyopathy, pulmonary artery hypertension.

Tuberculin skin test (TST) or Mantoux test - may not be sensitive especially in severely immunosuppressed patients where there may be a false negative result.

Chest X-ray (CXR): TB enlarged perihilar lymph nodes are better visualised on a lateral CXR than a PA view, therefore, it is important to obtain both PA and lateral films when evaluating a child with suspected TB.

Bacteriologic confirmation: Sputum microscopy is positive in <10-15 % of children with probable TB. Yield from culture is <30-40%. Xpert MTB/RIF identifies twice as many TB cases as smear microscopy with a sensitivity of up to 79.4% and specificity of 96.5% against culture on one induced sputum. The Xpert MTB/RIF has facilitated rapid confirmation of childhood TB and diagnosis of drug resistant TB in Africa.

Xpert MTB/RIF (GeneXpert) is an automated nucleic acid amplification test that detects simultaneously TB and rifampicin resistance (a good and reliable proxy for MDR-TB) directly from sputum and other suitable fluids.

GeneXpert test amplifies (by rapid, real-time PCR) and identifies targeted nucleic acid sequences in the TB genome in < 2 hours and is more sensitive than smear (150 bacilli/ml cf 10,000 bacilli/ml). It is useful in the diagnosis of TB in HIV co-infected persons where the sensitivity of microscopy alone is low. Results from the Xpert MTB/RIF assay indicate whether or not MTB complex was detected in the sample. If MTB complex was detected, the results will also state whether resistance to RIF was detected, not detected, or indeterminate.

Line probe Assay (LPA), culture or Drug Sensitivity Testing (DST) is still required to confirm MDR-TB and perform other drug testing. LPA is a nucleic acid amplification test just like Xpert but is only performed on AFB smear positive and/or culture positive specimens. LPA can identify MTB and report on mutations that confer resistance to Rifampicin and INH.

Culture remains the gold standard for TB diagnosis. Culture is more sensitive than microscopy and Xpert, requiring a low organism load (10 bacilli/ml). Solid culture may require up to 6-8 weeks for incubation.

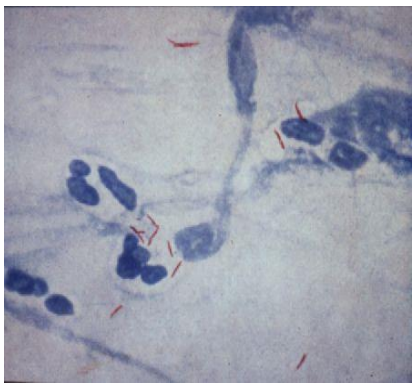

Figure 113: Acid fast bacilli (AFB) on smear microscopy

Figure 114: GeneXpert machines

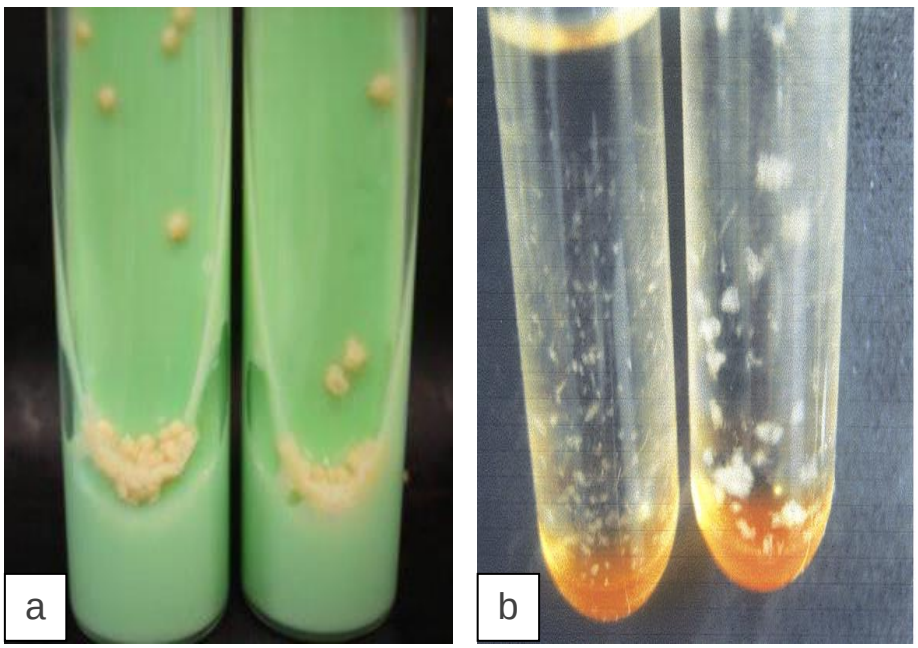

Figure 115a and b: a) Lowenstein Jensen (solid) medium -Culture positive TB. b) MGIT (liquid) medium – Culture positive TB.

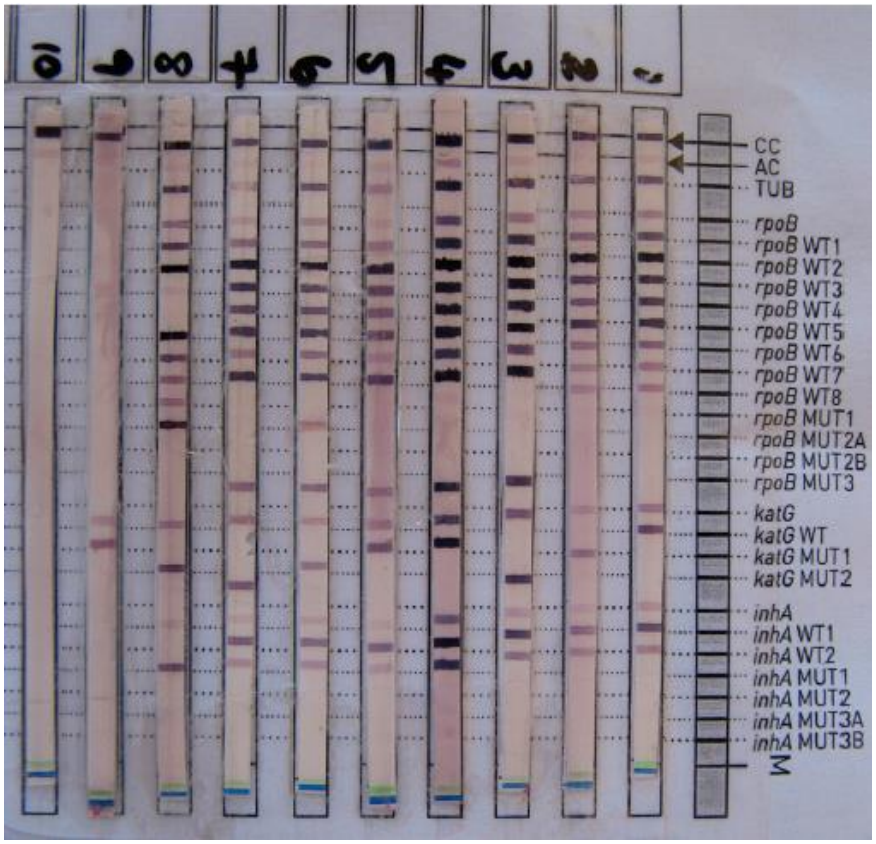

Figure 116: PCR Line Probe Assay. There are 27 bands per strip consisting of 6 controls plus wild and resistant probes (rpoB probes: 8 wild type susceptible + 4 resistant mutants), (katG probes: 1 wild type (susceptible) + 2 resistant mutants), (inhA probes: 2 wild type (susceptible) + 4 resistant mutants).

Interpretation: Resistance = 1. Absence of a wild type probe 2. Presence of any mutant probes

Treatment

Any child with active TB disease should begin TB treatment immediately (4 drug regimen – RHZE), and start ART as soon as tolerated in the first 8 weeks of TB therapy, irrespective of CD4 count and clinical stage.

Rifampicin can affect pharmacokinetics of some ARV medications especially non-nucleoside reverse transcriptase inhibitors (nevirapine) and protease inhibitors (lopinavir). Co-administration may result in sub-therapeutic ARV drug levels. Options for antiretroviral therapy in TB co-infection include optimising the dose of nevirapine at 200 mg/m^2, use of triple nucleoside reverse transcriptase inhibitor (AZT/3TC/ABC) or boosting with additional ritonavir for a lopinavir/ritonavir based regimen.

Further reading

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3. Palme IB, Gudetta B, Bruchfeld J et al. Impact of human immunodeficiency virus 1 infection on clinical presentation, treatment outcome and survival in a cohort of Ethiopian children with tuberculosis. Pediatr Infect Dis J. 2002; 21(11):1053-61.
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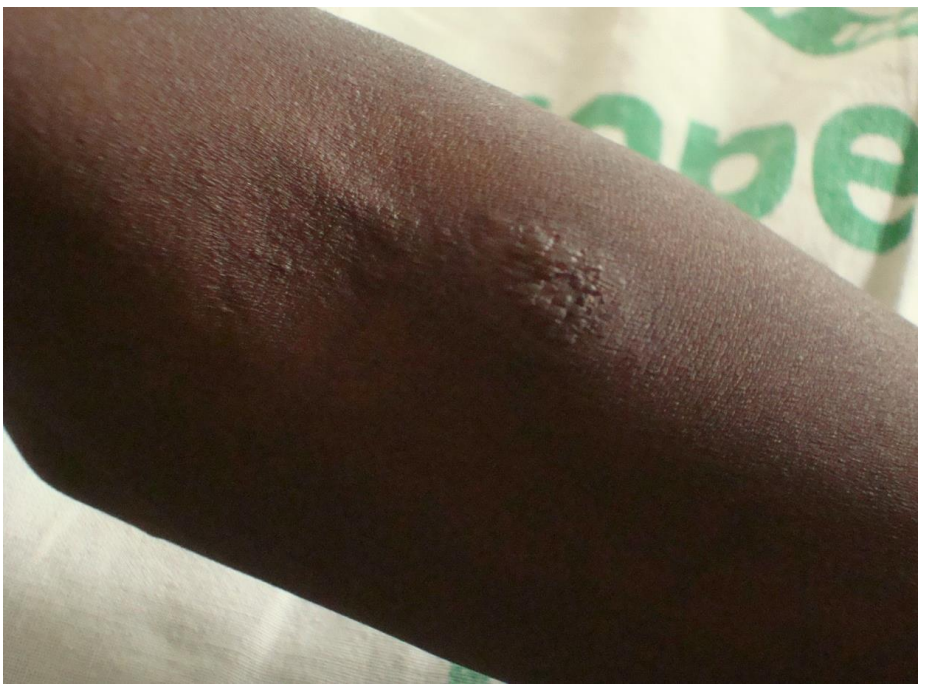


Figure 117: Positive Mantoux test. Mantoux test may be negative in HIV-infected children as a result of immunosuppression.

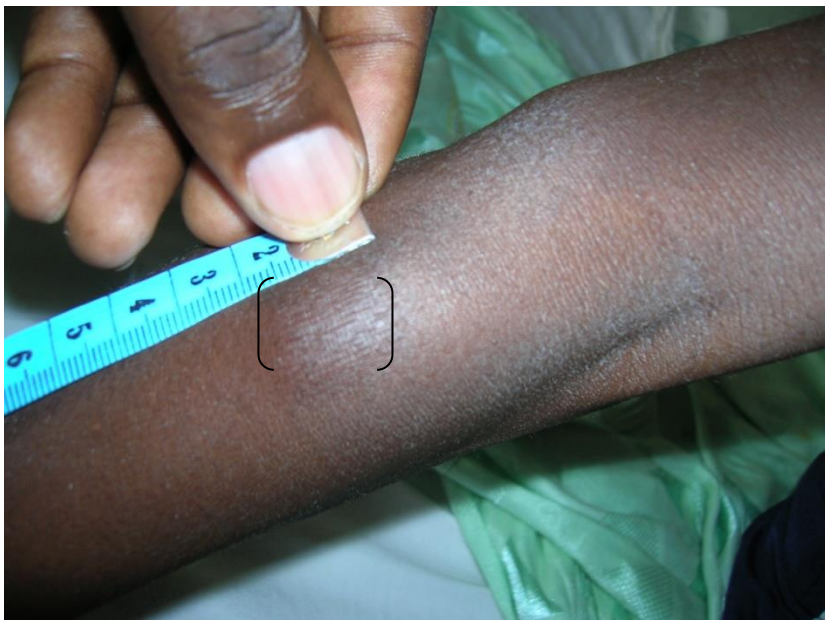


Figure 118: Positive Mantoux test in a very dark-skinned child.

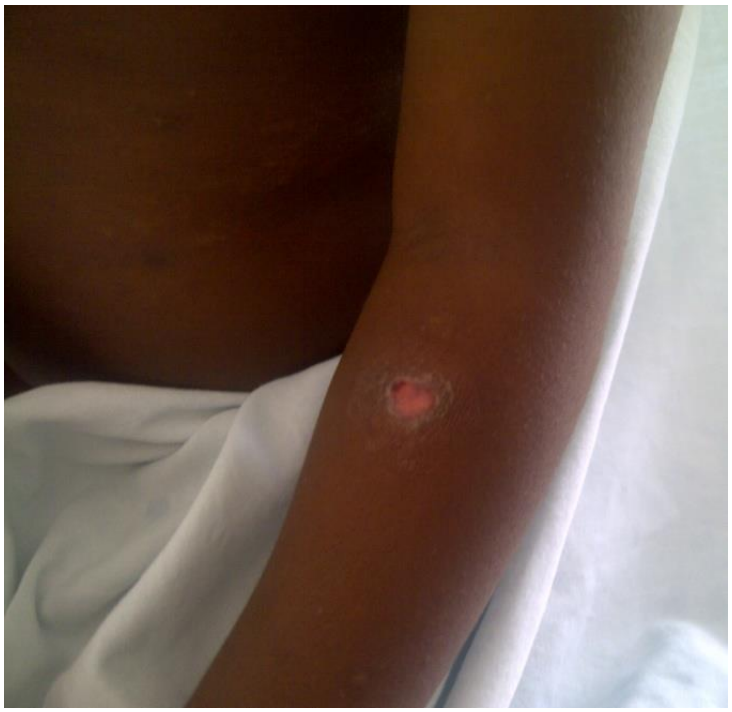


Figure 119: Ulcerated Mantoux test.

Figure 120: This 8-year-old girl presented with phlyctenular conjunctivitis at time of diagnosis of HIV with no features of active TB. Many months after commencement of ART, she presented with disseminated tuberculosis involving the lungs and abdomen.

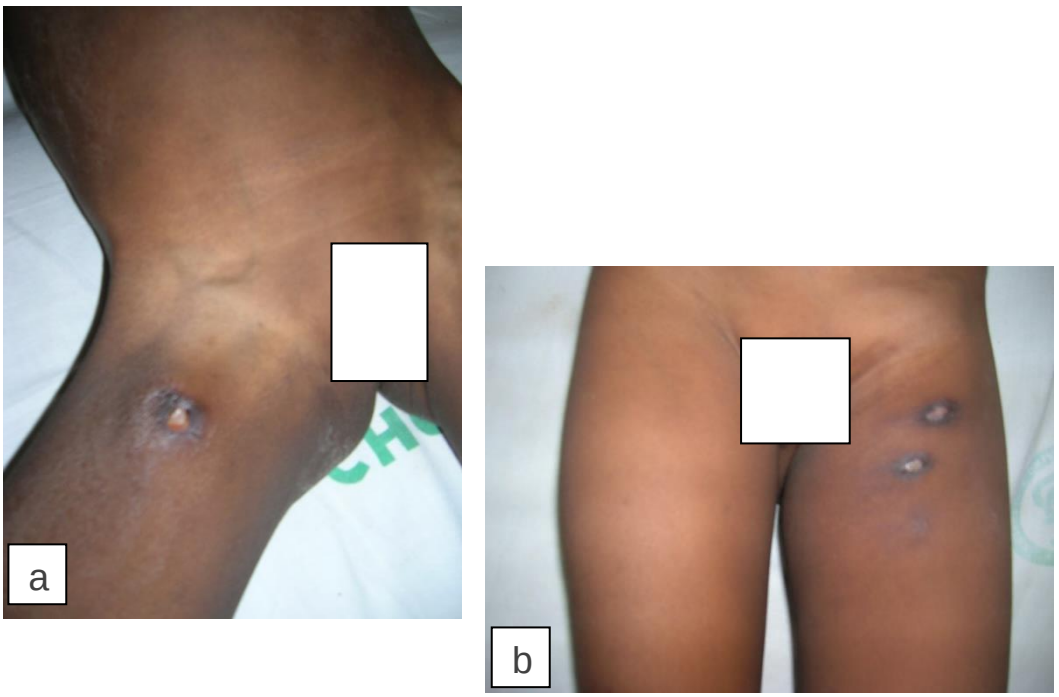
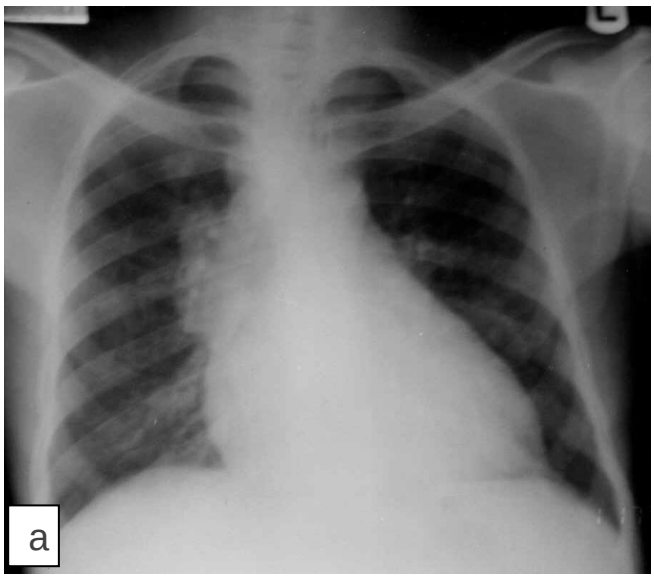


Figure 121: TB-HIV co-infection. Tuberculous lymphadenitis with formation of sinuses (scrofula).



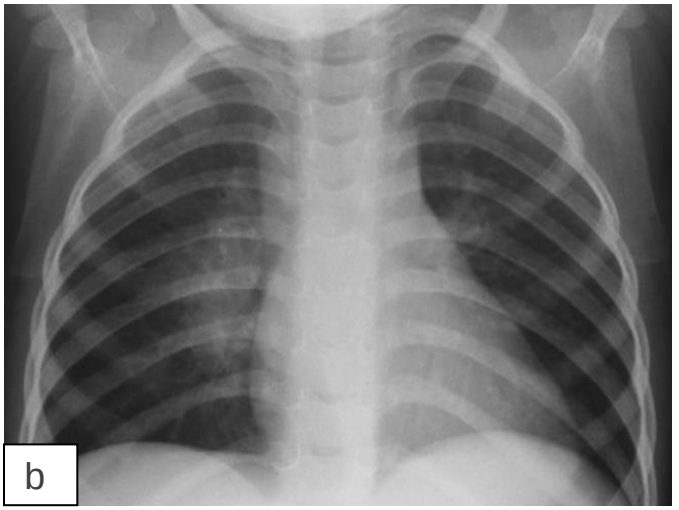
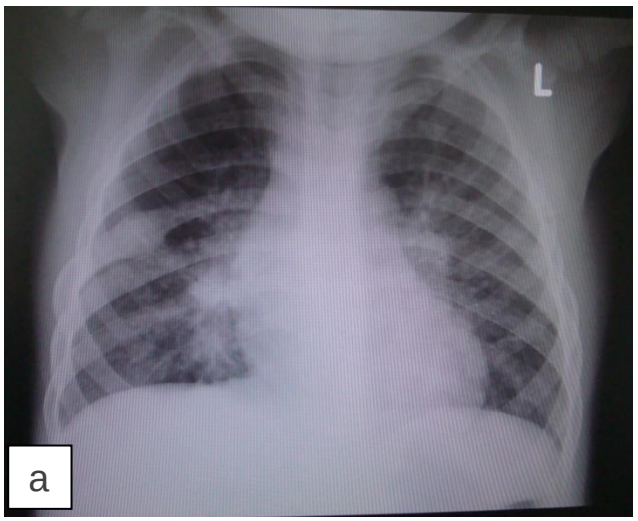


Figure 122a and b: CXR - Primary pulmonary tuberculosis.



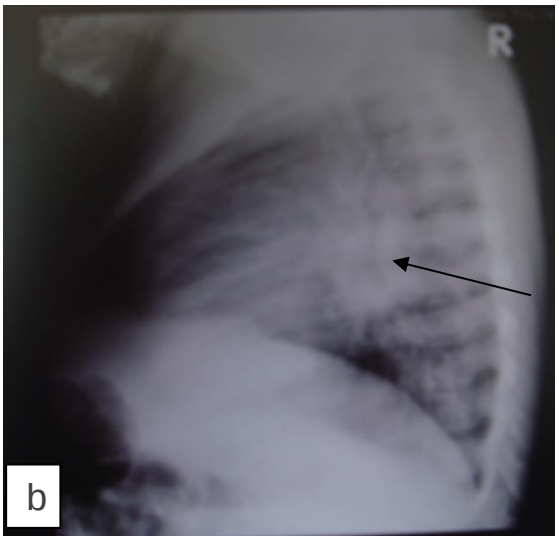


Figure 123a and b: Black arrow demonstrates perihilar and sub-carinal enlarged lymph nodes encircling the carina with some airway obstruction ("doughnut" or "hamburger" sign) as seen on the lateral view.

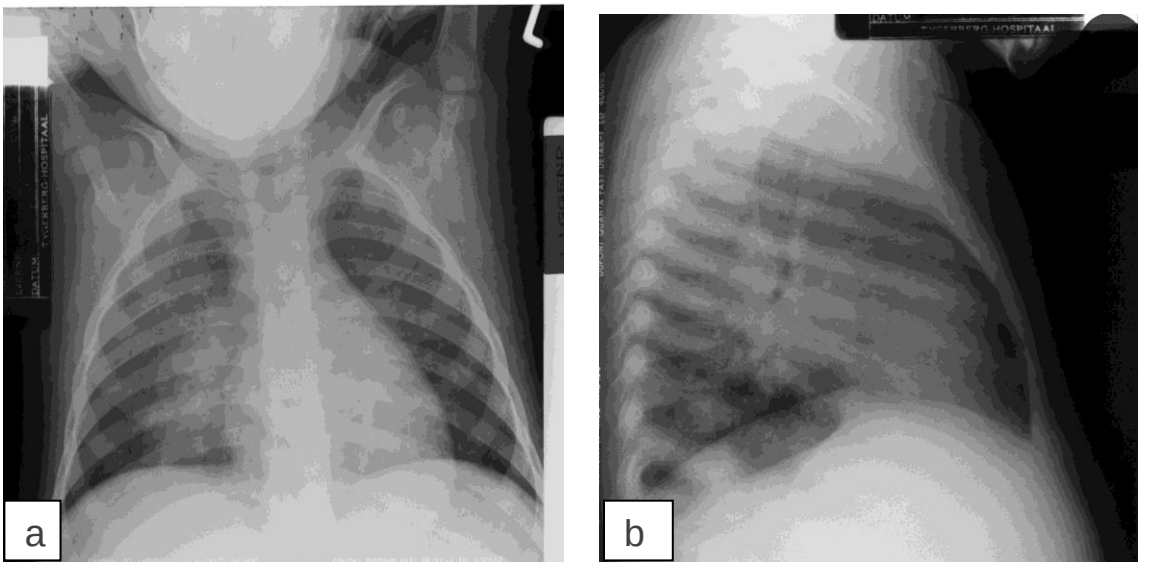


Figure 124: CXR: Perihilar opacities in PA and lateral views.

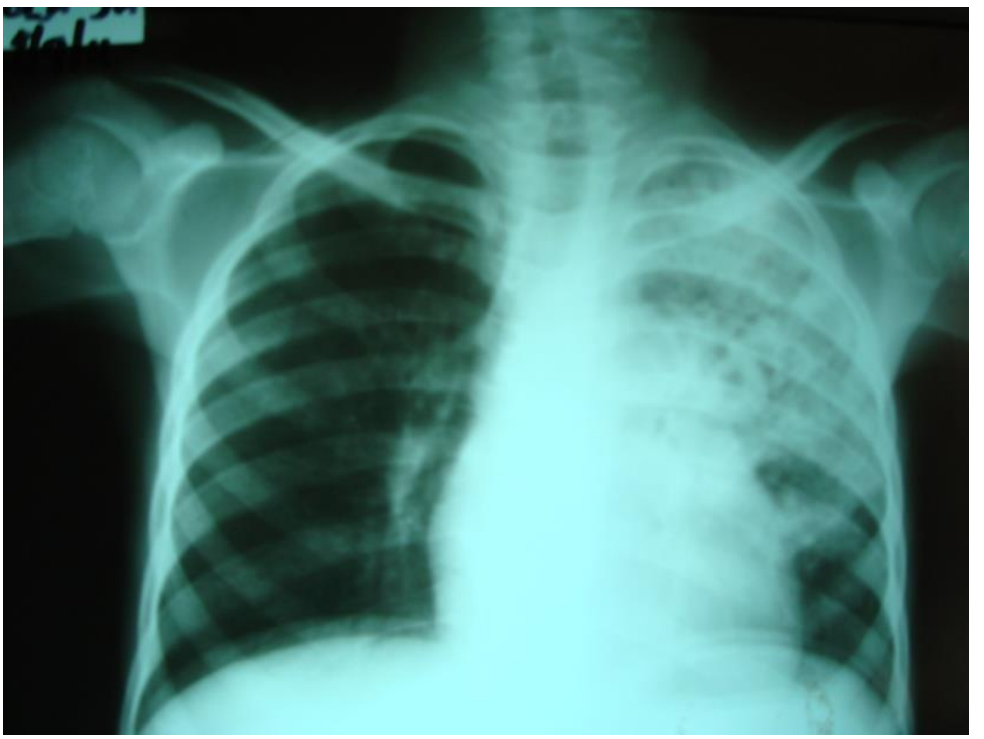


Figure 125: Chest radiograph showing cavities in the left hilar region in a 10-year-old girl that presented with chronic cough and wasting.

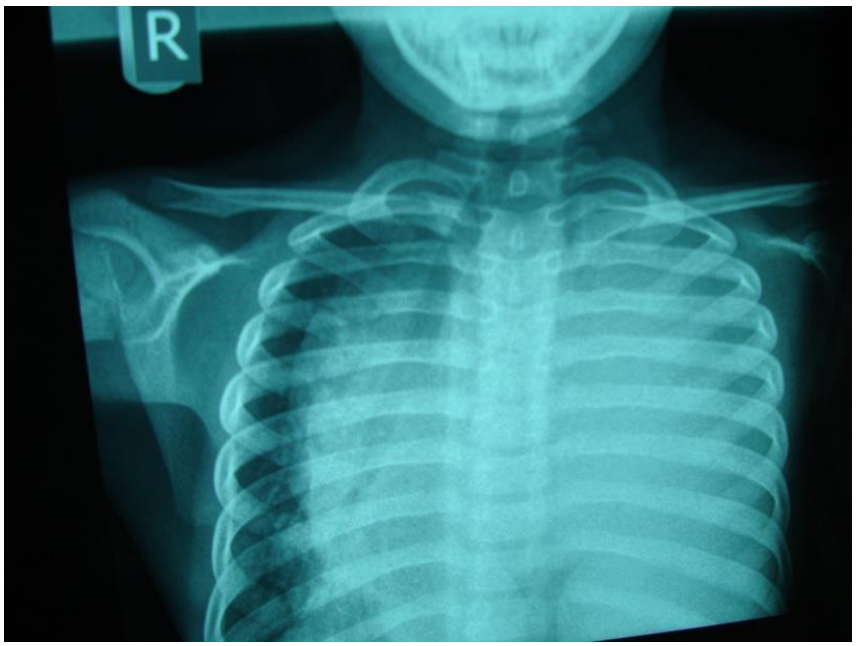


Figure 126: Massive left pleural effusion. The trachea is deviated to the left.

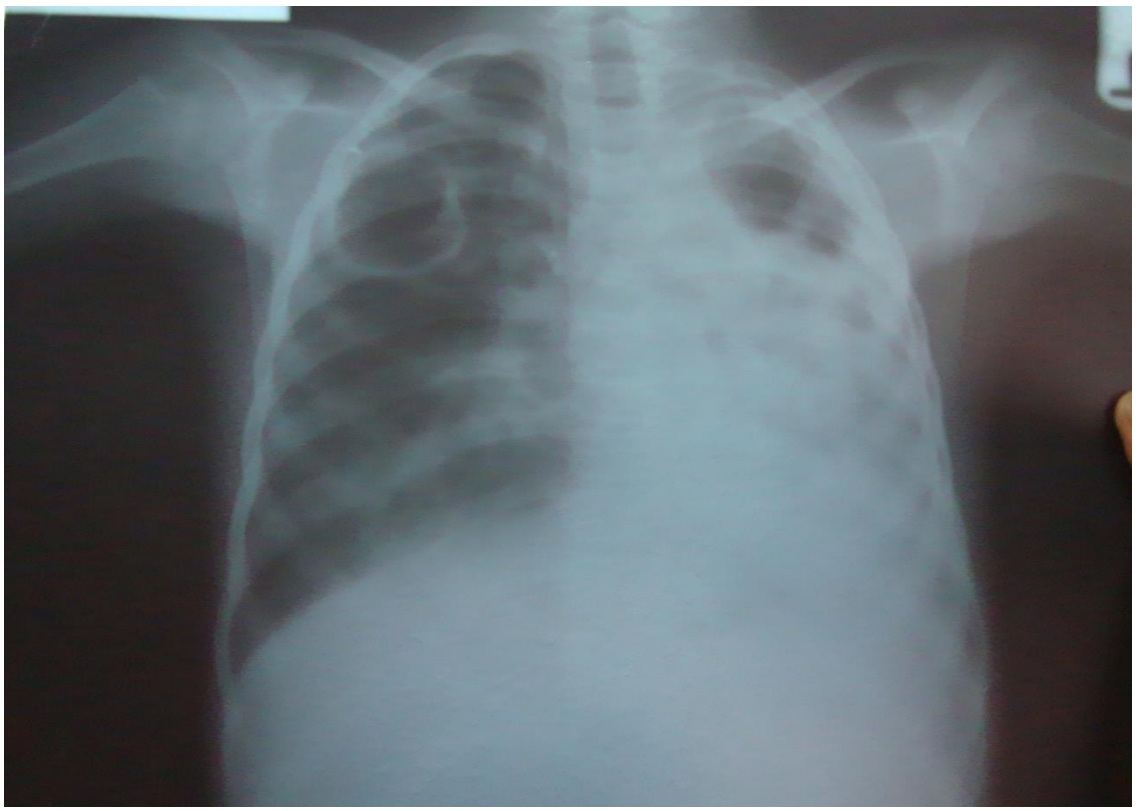


Figure 127: Chest radiograph of a 12-year-old HIV-infected child with MDR TB. Note the cavity on the right upper zone.

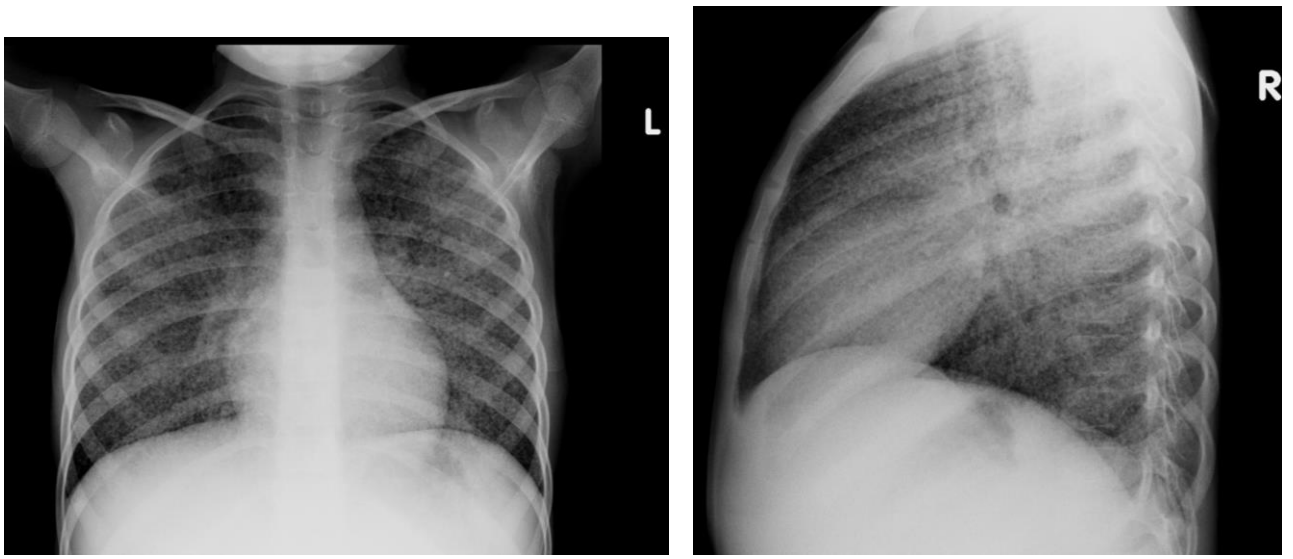


Figure 128: CXR - PA and lateral views showing multiple micro nodules in keeping with miliary TB. Differential diagnosis - LIP in the HIV-infected child.

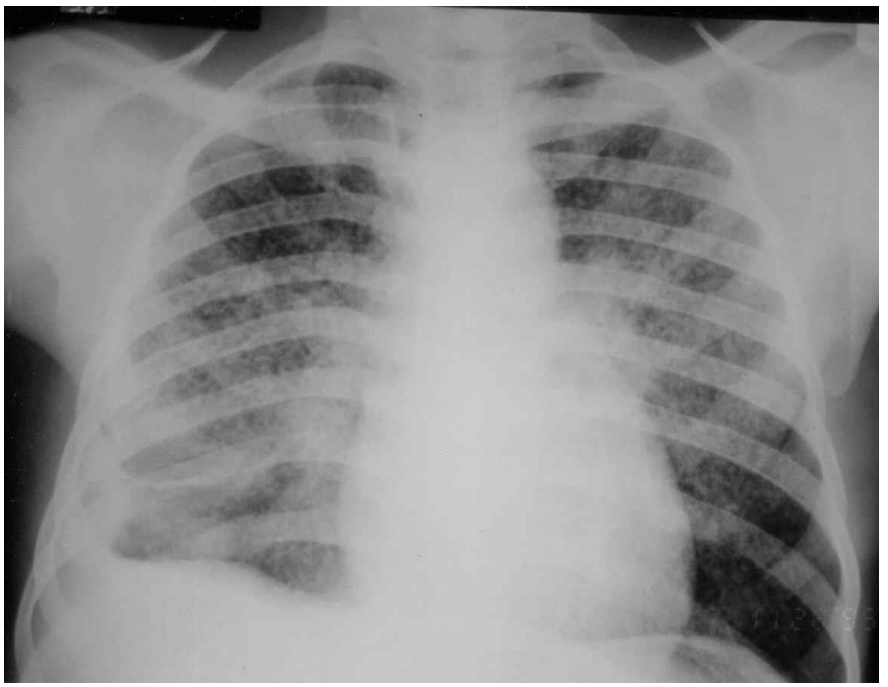


Figure 129: CXR - Miliary shadow.

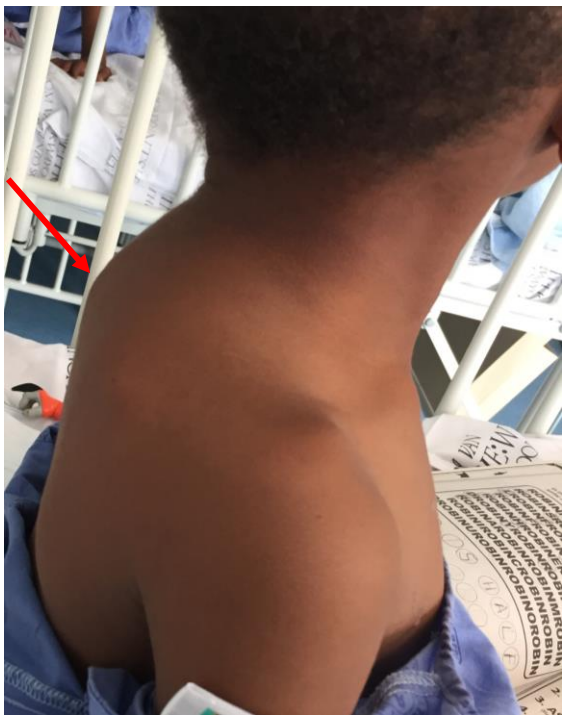


Figure 130: TB spine - Gibbus formation involving the upper thoracic spine (red arrow).

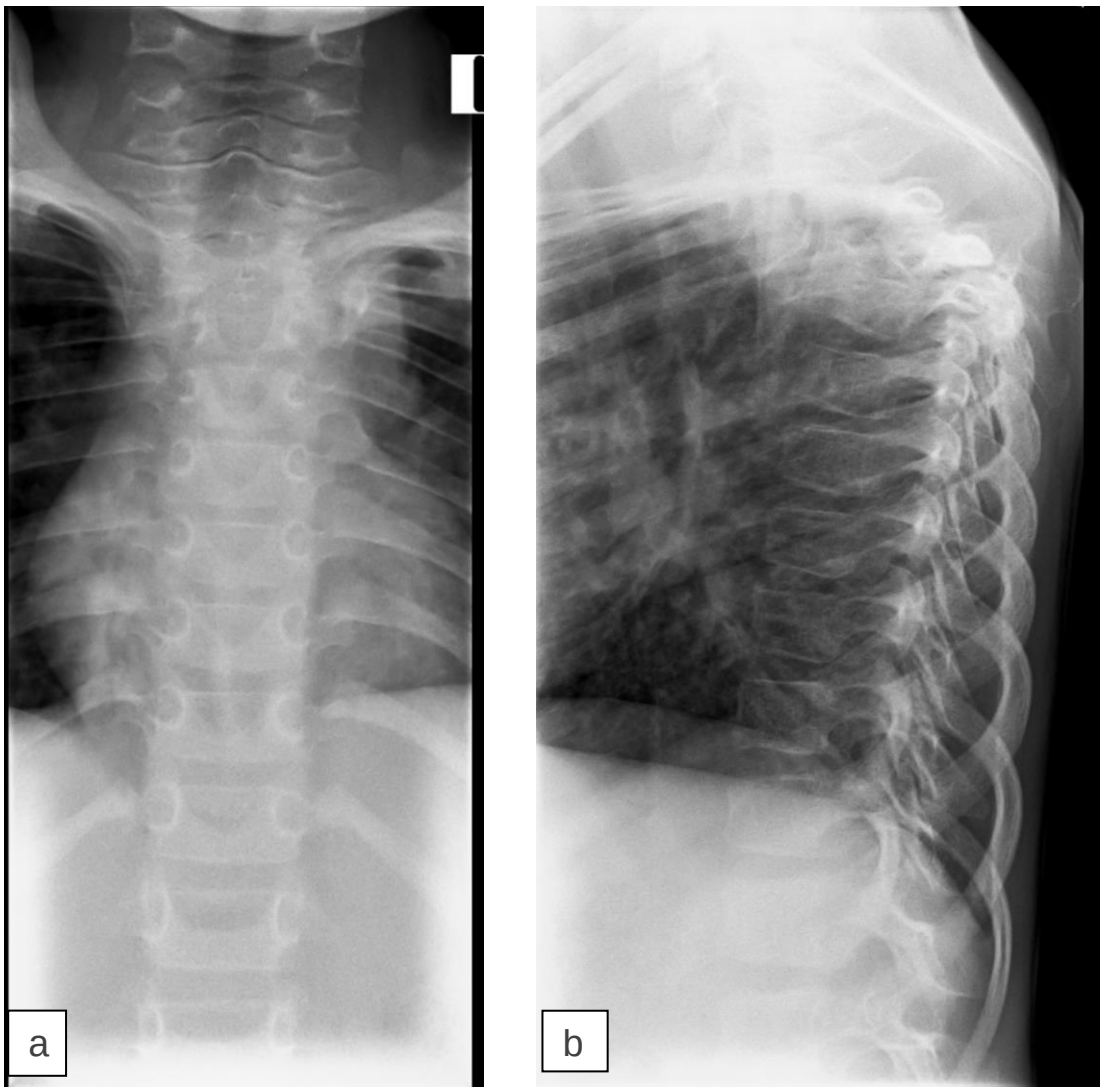


Figure 131a and b: Thoracolumbar spine X-rays (AP and lateral views) of the child above: TB spine involving T3, T4, T5 and T6 with vertebral body destruction and gibbus formation. Paraspinal mass demonstrated on the lateral.

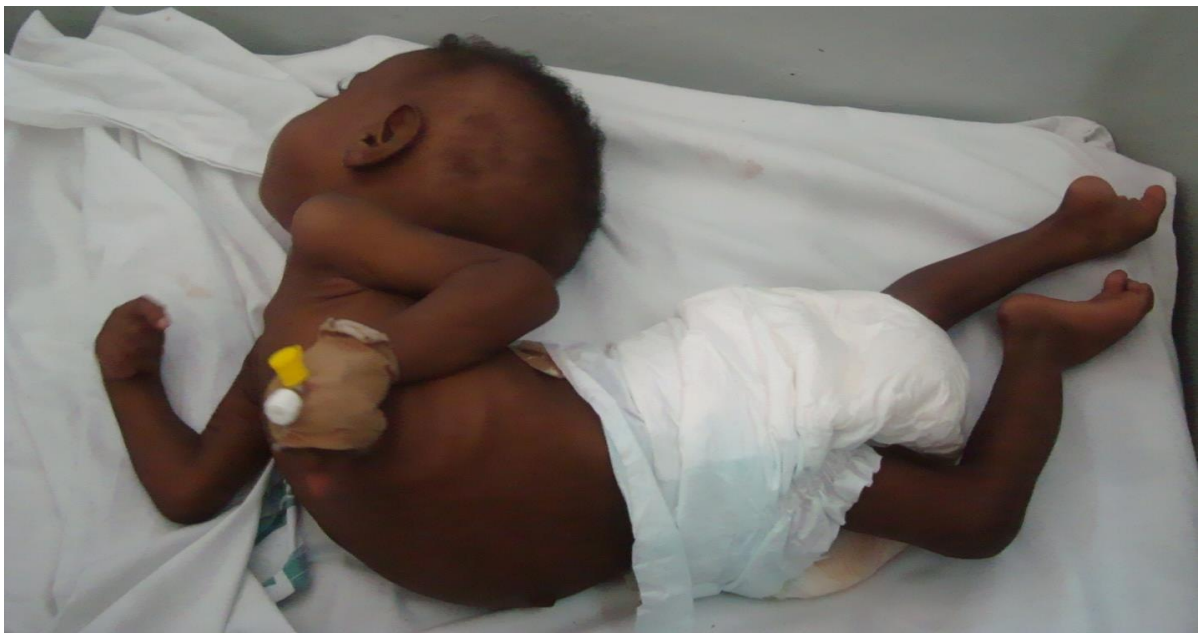


Figure 132: 12-month-old child with late diagnosis of HIV infection, presented with TB meningitis.

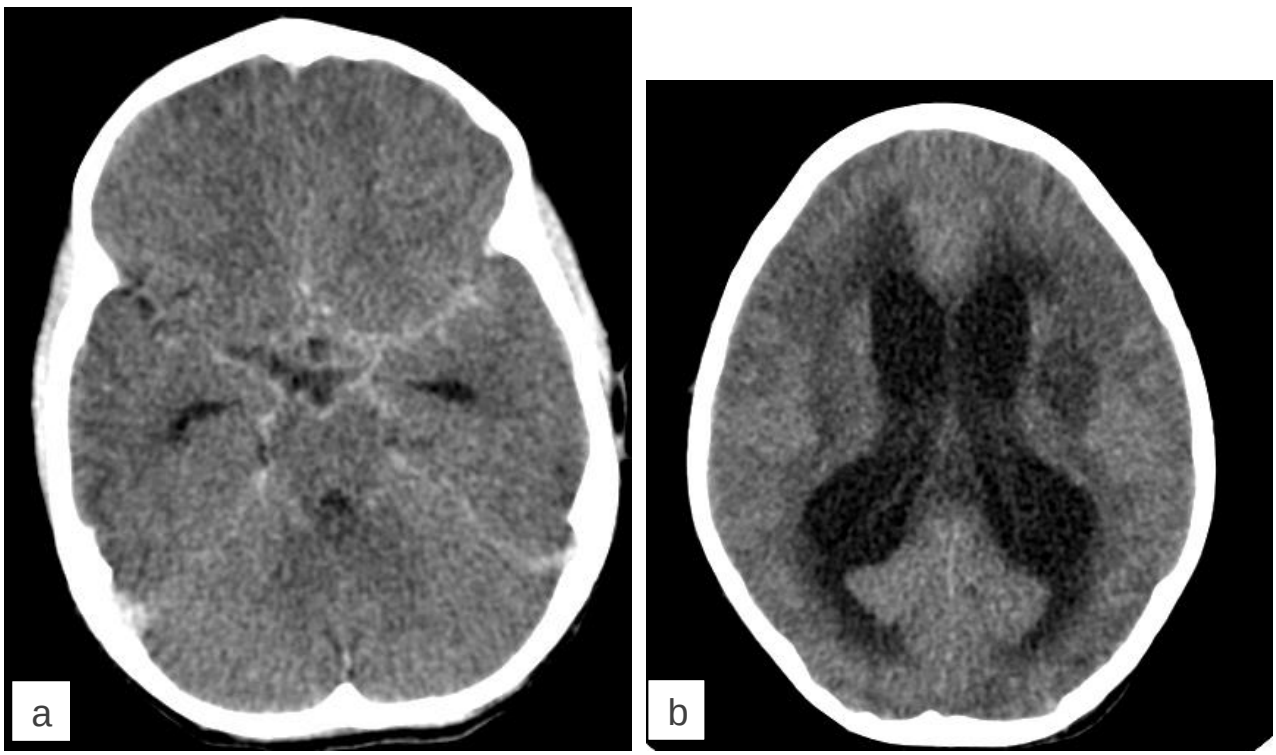


Figure 133a and b: (a) CT brain of a child with TBM showing basal meningeal enhancement. However, TBM imaging may be atypical with the usually typical signs absent or more subtle. (b) CT brain of the same child as above with TBM, showing hydrocephalous and basal ganglia infarct.

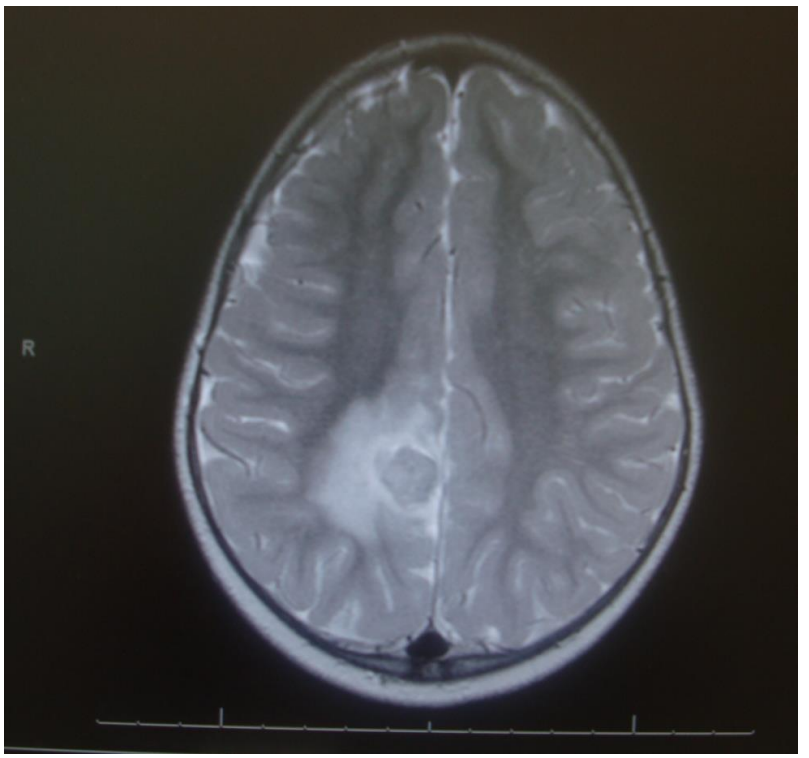


Figure 134: Tuberculoma. Magnetic Resonance Imaging showing rim-enhanced granulomas in the right para-falcine region posteriorly. The centre of the lesion is hypodense. Note the surrounding vasogenic oedema.

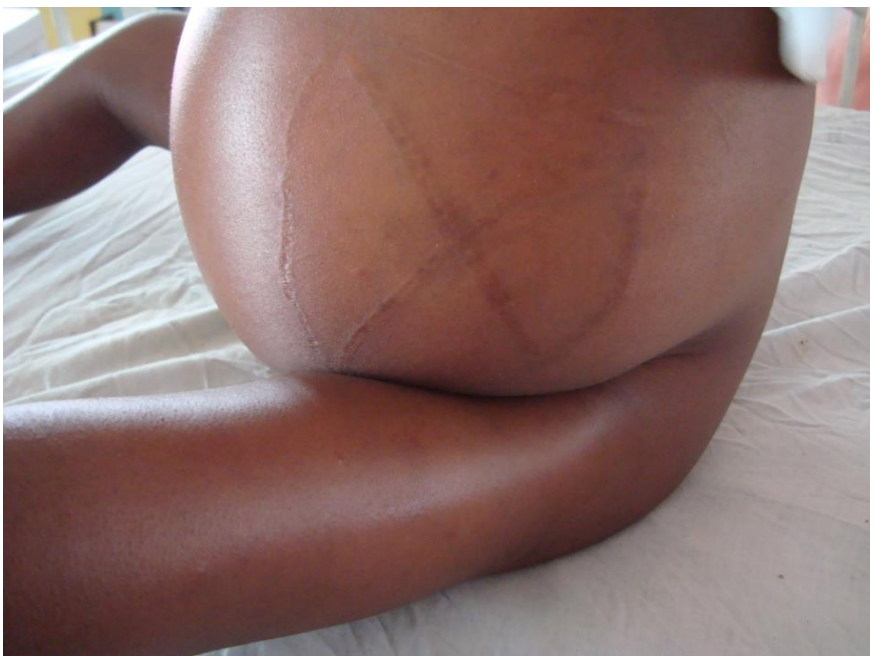


Figure 135: Local scarification marks on the abdomen of a 4-year-old boy newly diagnosed with HIV infection. He had hepatosplenomegaly and ascites from TB abdomen.

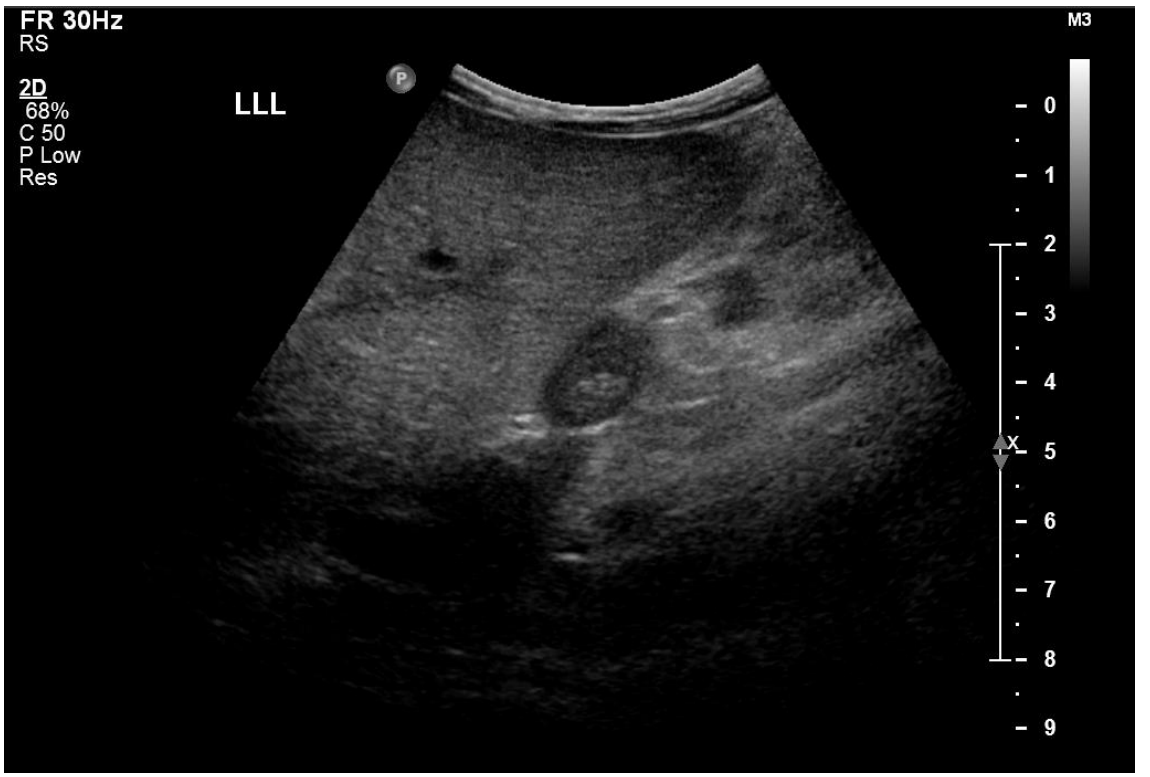


Figure 136: TB abdomen - Significant perioral, para-aortic and splenic hilar lymph nodes. Numerous splenic microabscesses are also shown.

BCG Disease

The bacillus Calmette-Guerin (BCG) vaccine contains a live attenuated strain of *Mycobacterium bovis*. There can be complications of immunization with bacillus Calmette-Guerin (BCG) in children in the setting of HIV infection. The World Health Organization in a revised consensus statement recommended that HIV infection in infants should not receive BCG vaccination. In practice, HIV DNA PCR testing is rarely performed during the first few weeks of life by which time immunization with BCG would have occurred.

In one study, 6% of HIV-infected children who received intradermal BCG vaccination at birth developed clinically significant BCG complications after starting HAART, believed to be manifestations of the immune reconstitution inflammatory syndrome (IRIS). BCG complications occurring in HIV-infected children not receiving HAART usually involve localized disease manifesting as ulceration of the vaccine site with or without ipsilateral axillary lymphadenitis, and less frequently disseminated forms of disease in which *M. bovis* BCG is confirmed in one or more anatomical sites far from both the site of injection and regional lymph nodes.

Diagnosis: The spectrum of presentations includes ulceration or abscess formation at the BCG vaccination site (right deltoid) and/or abnormally enlarged axillary lymph nodes with or without suppuration (regional disease). There may be spontaneous discharge of pus from the axillary abscesses. Abscesses in the ipsilateral supraclavicular and lower cervical regions (progressive regional disease) may also occur. Disseminated disease to other sites has also been reported.

Mycobacterial culture of material obtained from abscesses at the vaccination site, suppurative regional lymph nodes, or gastric lavage specimens may yield positive cultures for M. bovis. However, further identification of *Mycobacterium bovis* BCG by PCR is required. GeneXpert diagnoses mycobacterial species and is not specific to *Mycobacterium tuberculosis* (MTB). Therefore, if mycobacterial species are positive on GeneXpert, further identification should be requested if BCG disease is suspected.

Treatment: Spontaneous perforation and sinus formation usually occur if the abscess is left untreated. Needle aspiration helps to prevent these and shorten the duration of healing, apart from offering valuable diagnostic information. Sometimes repeated aspirations are required for optimal management, and wider-bored needles are preferred for ease of evacuation of thick inflammatory materials. Incision and drainage should be avoided as it increases the risk of sinus formation and delayed wound healing and unsatisfactory scar formation.

Antimycobacterial drugs for systemic disease:

Isoniazid (INH) 15 mg/kg/day

Rifampicin (RIF) 15 mg/kg/day

Pyrazinamide (PZA) 20 – 25 mg/kg/day (NB: BCG is resistant to PZA. If MTB is excluded, stop PZA)

- Ethambutol (EMB) 20 – 25 mg/kg/day
- Levofloxacin (≤8 years) or Moxifloxacin (> 8 years) 15 mg/kg/day.

Further reading

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3. Hesseling AC, Marais BJ, Gie RP et al. The risk of disseminated Bacille Calmette–Guerin (BCG) disease in HIV-infected children. Vaccine 2007; 25:14–18.
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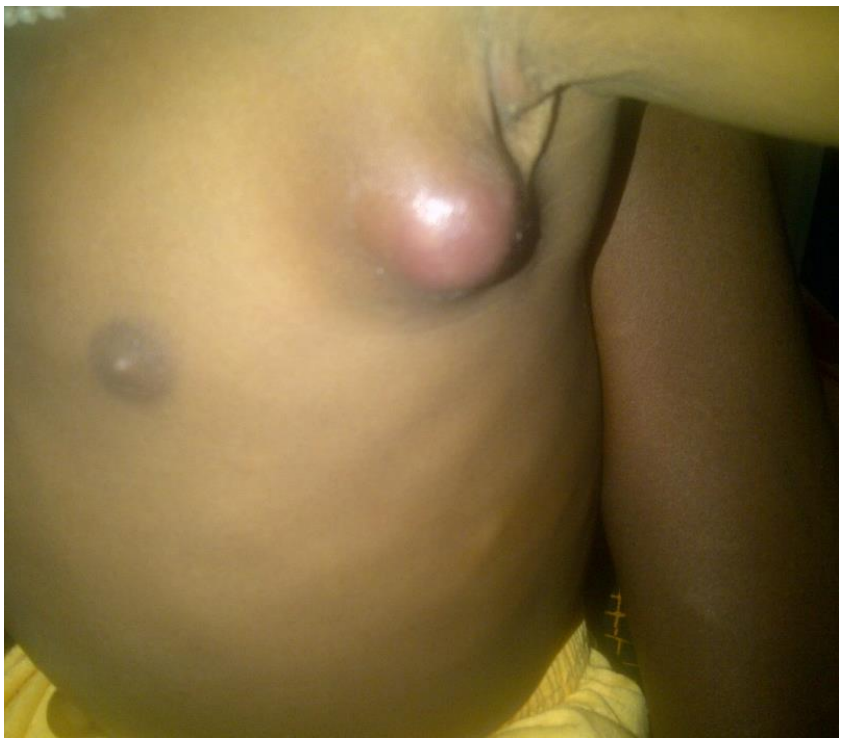

Figure 137: BCG disease of the axillary lymph node with abscess formation.

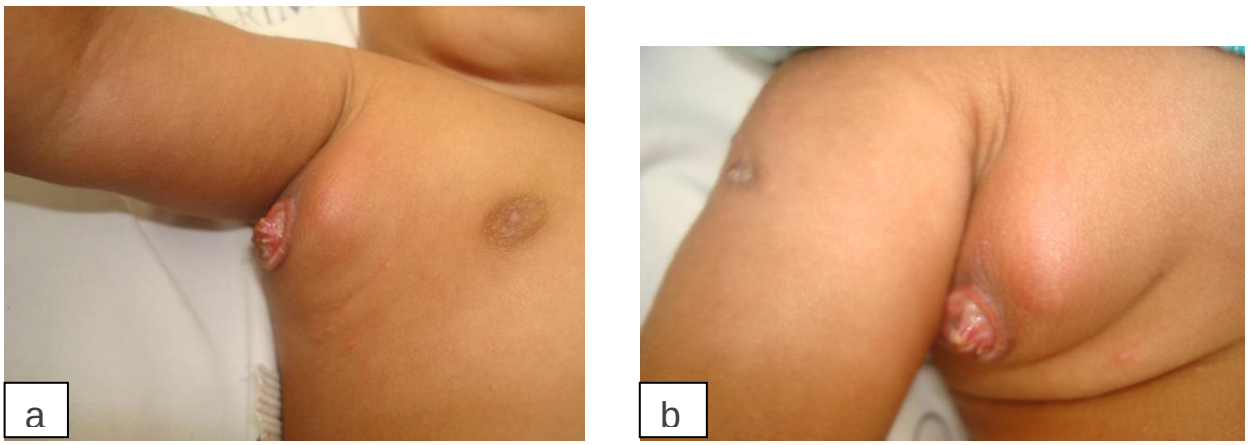

Figure 138: BCG adenitis in a 3 month old HIV exposed infant. Incision and drainage of the lesion was carried out 2 weeks previously resulting in a fungating ulcer. HIV DNA PCR was negative.

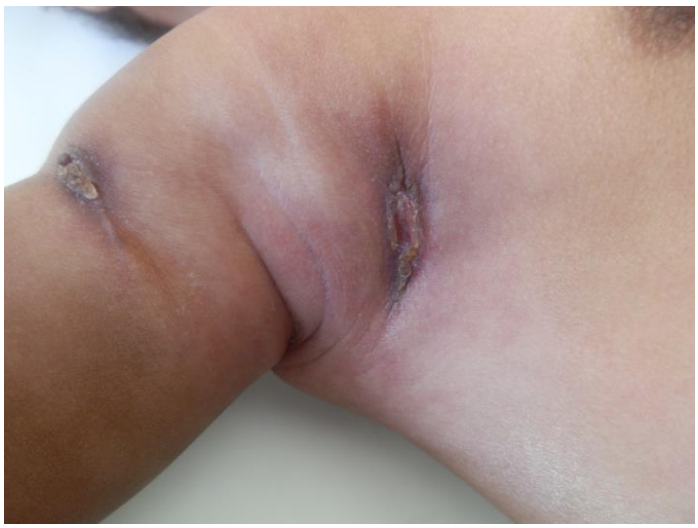

Figure 139: Scrofuloderma – ulceration in the axilla and arm of an HIV-infected child with BCG vaccination.

Mycobacterium Avium Complex (MAC)

Mycobacterium avium complex (MAC) refers to multiple related species of non-tuberculous mycobacteria (NTM) (e.g., *Mycobacterium avium*, *Mycobacterium intracellulare*, and *Mycobacterium paratuberculosis*) that are widely distributed in the environment. MAC can appear as isolated lymphadenitis in both HIV-infected and HIV-uninfected children. Disseminated infection with MAC in paediatric HIV infection rarely occurs during the first year of life; its frequency increases with age and declining CD4 cell count, but can occur at higher CD4 counts in younger HIV-infected children than in older children or adults.

Clinical Manifestations: Respiratory symptoms are uncommon in HIV-infected children who have disseminated MAC, and isolated pulmonary disease is rare. Early symptoms can be minimal and may precede mycobacteraemia by several weeks.

Symptoms commonly associated with disseminated MAC infection in children include persistent or recurrent fever, weight loss or failure to gain weight, sweats, fatigue, persistent diarrhoea, and persistent or recurrent abdominal pain. Mesenteric adenitis may mimic acute appendicitis. Gastrointestinal symptoms can occur alone or in combination with systemic findings. Lymphadenopathy, hepatomegaly, and splenomegaly may occur.

Laboratory abnormalities include anaemia, leukopenia, and thrombocytopenia. Although serum chemistries are usually normal, some children may have elevated alkaline phosphatase or lactate dehydrogenase levels.

Diagnosis: Diagnosed by isolation of the organism from blood or from biopsy specimens from normally sterile sites (bone marrow, lymph node). Multiple mycobacterial blood cultures over time may be required to yield a positive result.

The volume of blood sent for culture also influences yield, with increased volume leading to increased yield. While histology demonstrating macrophage-containing acid-fast bacilli is strongly indicative of MAC infection, culture is essential to differentiate nontuberculous mycobacteria from *M. tuberculosis*, to determine which non-tuberculous mycobacterium is causing infection, and to perform drug-susceptibility testing. Testing of MAC isolates for susceptibility to clarithromycin or azithromycin is recommended.

Treatment: Combination therapy of MAC with a minimum of 2 drugs is recommended to prevent or delay the emergence of resistance, since monotherapy with a macrolide results in emergence of high-level drug resistance within weeks.

HAART should be initiated in children with MAC disease, considering the risk of IRIS. The drugs include either clarithromycin or azithromycin plus ethambutol; with clarithromycin as the preferred first agent, reserving azithromycin for patients with substantial intolerance to clarithromycin or when drug interactions with clarithromycin are a concern.

Candidiasis

Candida spp causes the commonest fungal infections in HIV-infected children, which include oropharyngeal and oesophageal disease, vulvovaginitis, and diaper dermatitis. Once the organism penetrates the mucosal surface and widespread haematogenous dissemination occurs, invasive candidiasis ensues. This can result in candidaemia, meningitis, endocarditis, renal disease, endophthalmitis, and hepatosplenic disease. Oral thrush and diaper dermatitis occur in 50% to 85% of HIV-infected children.

Candida albicans is the most common cause of mucosal, oesophageal, and invasive candidiasis, but approximately 50% of reported cases of bloodstream infections in HIV-infected children are caused by non-albicans *Candida* spp., including *Candida tropicalis*, Candida *pseudotropicalis*, *Candida parapsilosis*, *Candida glabrata*, *Candida krusei*, and *Candida dubliniensis*. The non-*albicans Candida* species are important to recognize because several are resistant to fluconazole and other antifungals.

Clinical Manifestations: Thrush appears as creamy white, curd-like patches with inflamed underlying mucosa that is exposed after removal of the exudate. It can be found on the oropharyngeal mucosa, palate, and tonsils. Hyperplastic candidiasis comprises raised white plaques on the lower surface of the tongue, palate, and buccal mucosa and cannot be removed. Angular cheilitis occurs as red fissured lesions in the corners of the mouth.

Oesophageal candidiasis often presents with odynophagia, dysphagia, or retrosternal pain, and unlike adults, many children experience nausea and vomiting. Suspect oesophageal candidiasis when patients with oropharyngeal thrush have odynophagia or dysphagia. It may manifest in young children as drooling. Infants struggle to swallow when feeding.

Renal candidiasis presents with candiduria and ultrasonographically demonstrated renal parenchymal lesions, often without symptoms related to renal disease.

Diagnosis: Oral candidiasis can be diagnosed clinically as a whitish plaque on the buccal mucosa that comes off with difficulty on scraping. The yeast cells may also be seen with a potassium hydroxide preparation and culture with microscopic demonstration of budding yeast cells in wet mounts or biopsy specimens.

Oesophageal candidiasis has a classic cobblestoning appearance on barium swallow. Endoscopy is also helpful for ruling out other causes of refractory oesophagitis, such as HSV, CMV, and *Mycobacterium avium* complex. Candidaemia is best diagnosed with blood culture.

Treatment

Oropharyngeal candidiasis (OPC)

Early, uncomplicated infection can be effectively treated with topical therapy using clotrimazole troches or oral nystatin suspension 100 000u 4 to 6 hourly x 7 to 14 days. Oral therapy with fluconazole for 7 to 14 days is recommended for moderate to severe OPC. For fluconazole-refractory OPC, itraconazole oral solution should be used.

Oesophageal disease

Oral fluconazole 6 – 12 mg/kg/day x 14 to 21 days is effective for treatment of *Candida o*esophagitis. IV fluconazole, amphotericin B, or an echinocandin should be used for patients who cannot tolerate oral therapy. For fluconazole-refractory disease, itraconazole solution, voriconazole, amphotericin B, or an echinocandin are alternatives. Suppressive therapy with fluconazole three times weekly is recommended for recurrent infections.

Invasive disease

For invasive disease, investigation for a deep tissue focus of infection is important- in the form of echocardiogram, renal or abdominal ultrasound. Central venous catheters may need to be removed when feasible in HIV-infected children with candidaemia. The treatment of choice for invasive disease in HIV-infected children depends on severity of disease, previous azole exposure, and *Candida* isolate obtained (if known). Recommended duration of therapy for candidaemia is 14 days after documented clearance from the blood.

Further reading

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6. Stevens DA. Diagnosis of fungal infections: current status. J Antimicrob Chemother. 2002;49 Suppl 1:11-19.

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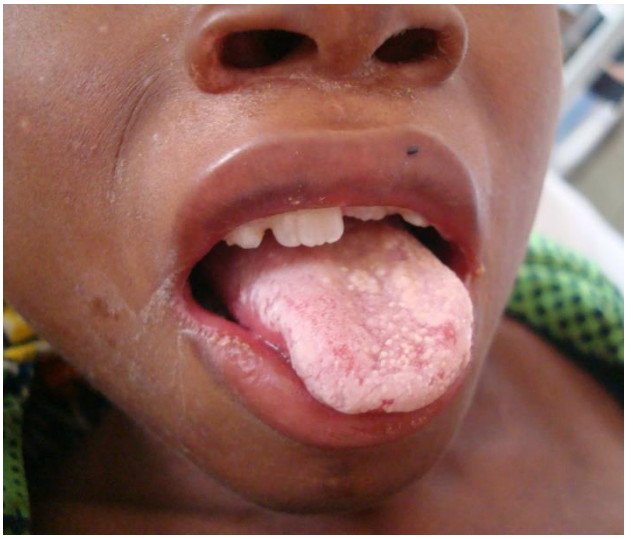

Figure 140: Oral candidiasis.

Figure 141: Oesophageal candidiasis

Cytomegalovirus (CMV) Infection

The prevalence of CMV infection among HIV-infected pregnant women is higher than in the general population and the HIV-infected infants have a 3-fold higher risk for symptomatic congenital CMV infection. CMV causes a wide range of diseases in HIV-infected children, including pneumonitis hepatitis, retinitis, encephalitis, oesophagitis and colitis.

Presentation: The signs and symptoms of CMV disease often overlap with other infectious processes, therefore, the diagnosis of CMV disease in HIV-infected children should take into consideration clinical presentation and radiological finding along with laboratory testing. CMV pneumonia presents with fever, dyspnoea and hypoxemia. A chest radiograph shows diffuse pulmonary infiltrates (ground glass appearance) as seen in other viral pneumonias and PCP. The isolation of CMV from isolates including BAL does not prove that the child has CMV pneumonia. Co-infection with both PCP and CMV is common.

CMV produces a necrotic rapidly progressing retinitis with characteristic white perivascular infiltrate with haemorrhage (brushfire retinitis). Peripheral lesions may be asymptomatic, and even advanced disease does not cause pain. In children, strabismus or failure to fix and follow objects may be important clues to the diagnosis.

Diagnosis: Laboratory tests need to be interpreted in the clinical context as the virus, CMV DNA, and CMV antigen can all be detected in some patients who do not have active disease.

Quantitative PCR tests and the CMV pp65 antigenaemia test are available for detecting viral DNA and antigen, respectively. CMV viral load in blood is more useful for the diagnosis and monitoring of patients with CMV. There are no established cut-off values to definitively diagnose active CMV infection. Some experts base their decision to initiate antiviral therapy at viral load values of ≥4.0 log copies/ml in the presence of suggestive clinical features. In tissue invasive disease, the gold standard for diagnosing CMV disease is the identification of CMV inclusions or positive CMV-specific immuno-histochemistry staining on histopathology.

Treatment: Ganciclovir 5 mg/kg/dose IV 12 hourly, instituted in addition to ART. May switch to valacyclovir 15 mg/kg/dose 12 hourly when there is improvement and the patient can tolerate oral therapy. Total duration of therapy is 4 – 6 weeks.

An alternative drug for treating CMV disease or for use in ganciclovir-resistant CMV infections in HIV-infected children is foscarnet.

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3. Panel on opportunistic infections in HIV-exposed and HIV-infected children. Guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/oi_guidelines_pediatrics.pdf.

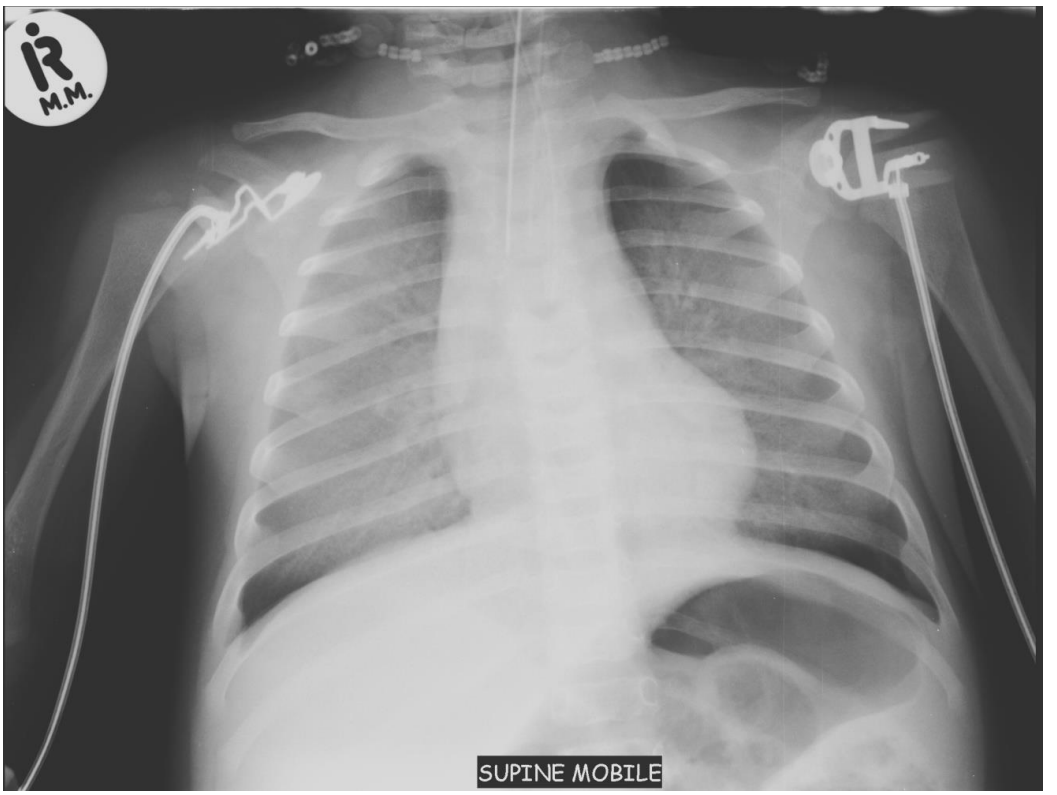

Figure 142: CMV pneumonia: Acute care setting with cardiac monitoring leads in place; widespread confluent ground-glass opacification with associated air bronchograms in a perihilar and diffuse distribution. Features are in keeping with a viral pneumonia. Differential diagnoses include PCP, other viral pneumonias.

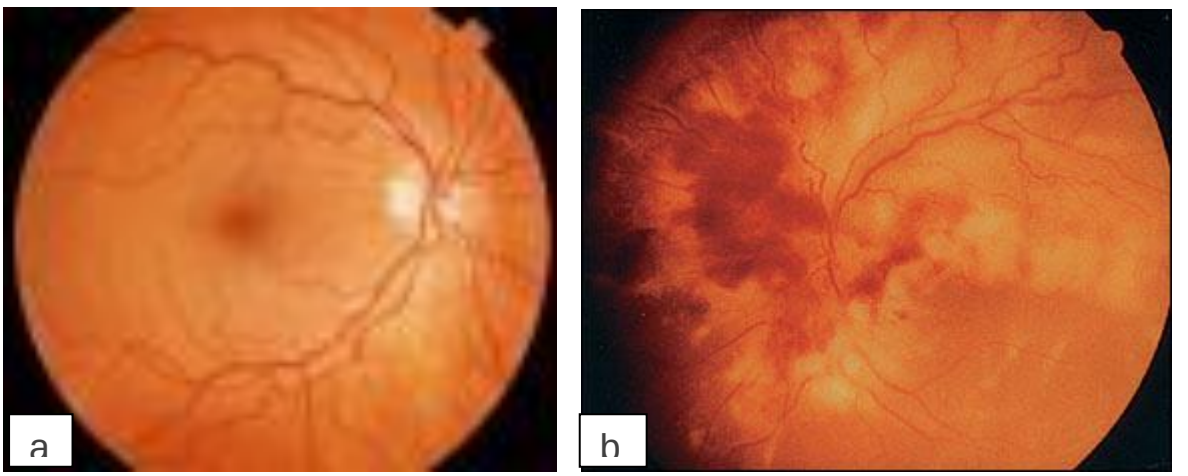

Figure 143a and b: (a). Normal retina (b) CMV retinal pathology showing necrosis and haemorrhage.

Cryptoccocosis

Cryptococcosis is fungal opportunistic infection caused by *Cryptococcus neoformans* which predominantly affects HIV-infected individuals with very severe immunosuppression. The use of potent antiretroviral therapies has resulted in a general decrease in the incidence of opportunistic infections associated with AIDS. Cryptococcosis is less frequent in children than in adults. Median age is about 10 years and median CD4/ cell count of <100 cells/µl at the time of diagnosis.

Clinical presentation: Most frequent – Meningoencephalitis typically presenting as a subacute process characterised by headache, fever, and later altered mental status as well as meningeal signs. Other manifestations include pneumonia and cutaneous diseases.

Laboratory evaluation: Culture of the organism is the gold standard for confirmation of the diagnosis of initial cryptococcal disease, confirmation of relapses or cases refractory to treatment, and adequate response to treatment.

Rapid diagnostic CrAg assays, either latex agglutination (LA) or lateral flow assay (LFA) to be used in cerebrospinal fluid (CSF), serum or plasma.

For cryptococcal meningitis prompt lumbar puncture (LP) with measurement of CSF opening pressure and rapid CSF CrAg assay is recommended or if access to CrAg assay is not available, CSF India ink test examination. In settings without immediate access to LP, or when it is clinically contraindicated, rapid serum or plasma CrAg is recommended.

Treatment

Meningeal and disseminated non-meningeal

Induction (x2 weeks) - Amphotericin B (0.7 – 1.0 mg/kg/dose/ daily IV) + flucytosine or Amphotericin B + fluconazole (12 mg/kg/day).

Alternatively, where amphotericin B is not available:

(a) fluconazole + flucytosine, or

(b) high-dose fluconazole monotherapy (12 mg/kg/day up to 800 mg/day if < 19 years).

N.B: Amphotericin B-related toxicities – Ensure adequate hydration. Monitor renal function for hypokalaemia and nephrotoxicity.

Management of raised ICP – May require serial lumbar punctures.

Consolidation (x 8 weeks): Fluconazole PO (6-12 mg/kg/day up to 400-800 mg/day if below 19 years).

Maintenance (secondary prophylaxis): Fluconazole PO (6 mg/kg/day up to 200 mg/day if < 19 years)

≥2 years of age: At least one year + evidence of immune reconstitution with optimal ART (CD4 >25% or absolute count >750 cells/µl).

<2 years of age: Anti-fungal maintenance treatment should NOT be discontinued.

Timing of ART initiation: To be deferred until there is evidence of a sustained clinical response to anti-fungal therapy, and after 2-4 weeks of induction and consolidation treatment with amphotericin B-containing regimens (+ flucytosine or fluconazole), or after 4-6 weeks of treatment with a high dose oral fluconazole induction and consolidation regimen.

Localized non-meningeal disease

12 mg/kg/day up to 800 mg/day if < 19 years) x 2 weeks, 6 mg/kg/day up to 400-800 mg/day if < 19 years) x 8 weeks, and continued maintenance with fluconazole 200 mg/day.

Further reading

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2. WHO. Rapid Advice Diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. Available at: http://www.who.int/hiv/pub/cryptococcal_disease2011/en/.
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Progressive Multifocal Leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system that results from infection with JC virus (JCV), a neurotropic polyomavirus. Asymptomatic primary infection with JC virus occurs in childhood and antibodies can be found in 86% of adults. JCV remains latent in kidneys and lymphoid organs, but, in the context of profound immunosuppression as occurs in HIV infection, JCV can reactivate, spread to the brain, and induce a lytic infection of oligodendrocytes, the CNS myelin-producing cells. PML is relatively uncommon among children. Median age at HIV-associated PML diagnosis was 12 years in one review.

Clinical features: Paresis, speech abnormalities, gait disturbances, ataxia, cranial nerve palsies and seizures. CSF white cell count, protein and glucose are usually normal to slightly elevated in patients with PML.

On cranial CT, PML lesions may appear as hypodense patchy or confluent white matter regions. Typical MRI features include single or multiple non-enhancing, non-space-occupying, predominantly white matter lesions commonly involving the frontal and parieto-occipital subcortical white matter.

Definitive diagnosis of PML can be established by detection of JCV DNA in the CSF or viral proteins on brain biopsy. Sensitivity of JCV DNA CSF PCR is as low as 59% but the specificity is about 100%.

Differential diagnosis: HIV encephalopathy, TB meningitis, tuberculoma, CMV infection, herpes simplex virus, cryptococcal meningitis and toxoplasmosis.

Treatment: The main stay of treatment is the initiation of effective ART which has been shown to improve survival in adults. PML-associated IRIS may occur which is a severe, often fatal, complication. Other antiviral agents have not shown any consistent benefits.

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2. Berger JR, Scott G, Albrecht J et al. Progressive multifocal leukoencephalopathy in HIV-1-infected children. AIDS. 1992 ; 6(8):837-41.
3. Dankner WM, Lindsey JC, Levin MJ et al. Correlates of opportunistic infections in children infected with the human immunodeficiency virus managed before highly active antiretroviral therapy. Pediatr Infect Dis J. 2001; 20 (1):40-8.
4. Nuttall JJ, Wilmshurst JM, Ndondo AP et al. Progressive multifocal leukoencephalopathy after initiation of highly active antiretroviral therapy in a child with advanced human immunodeficiency virus infection: a case of immune reconstitution inflammatory syndrome. Pediatr Infect Dis J. 2004 ;23 (7):683-5.

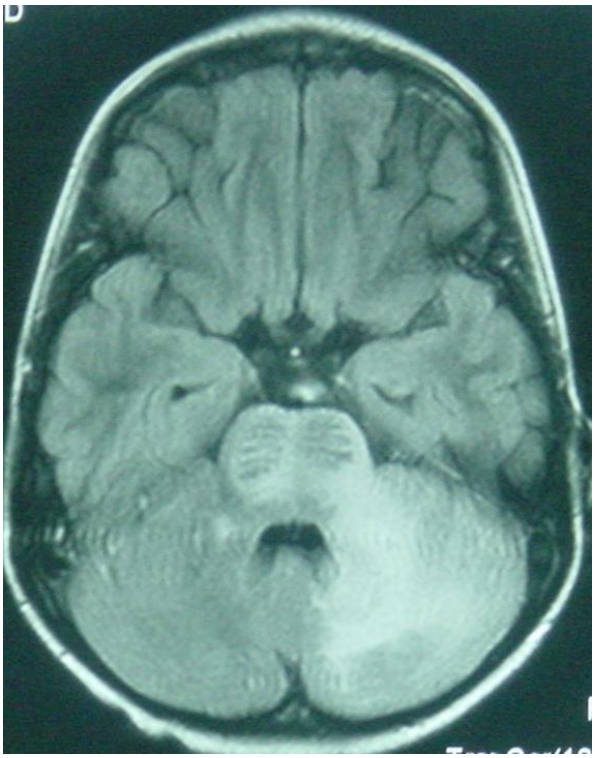

Figure 144: Brain MRI demonstrating hyperintensity of the left cerebellum extending into the middle cerebellar peduncle.

CHAPTER 13: OTHER IMPORTANT INFECTIONS IN HIV-INFECTED CHILDREN

Pneumonia

Acute pneumonia is associated with increased mortality in HIV-infected children, especially if they are not on antiretroviral therapy (ART) or if they have chronic lung disease, including bronchiectasis and lymphocytic interstitial pneumonitis.

Bacterial Pneumonia

HIV-infected children usually have a higher risk of pneumococcal infection than HIV-uninfected children. The incidence and hospitalization due to invasive pneumococcal disease (IPD) in HIV-infected children decreases markedly by up to 80% when ART and pneumococcal conjugate vaccine are co-administered.

Lower CD4 counts, high viral load, and not being on ART increase the risk. *Streptococcus pneumoniae (pneumococcus)* is the most common cause in addition to *staph aureus* and gram negatives such as *Haemophilus influenzae* type b (Hib).

Diagnosis: Same as for HIV negative children

Treatment: β lactam antibiotics with gentamycin. Consider treating for pneumocystis pneumonia especially in very young children requiring oxygen therapy.

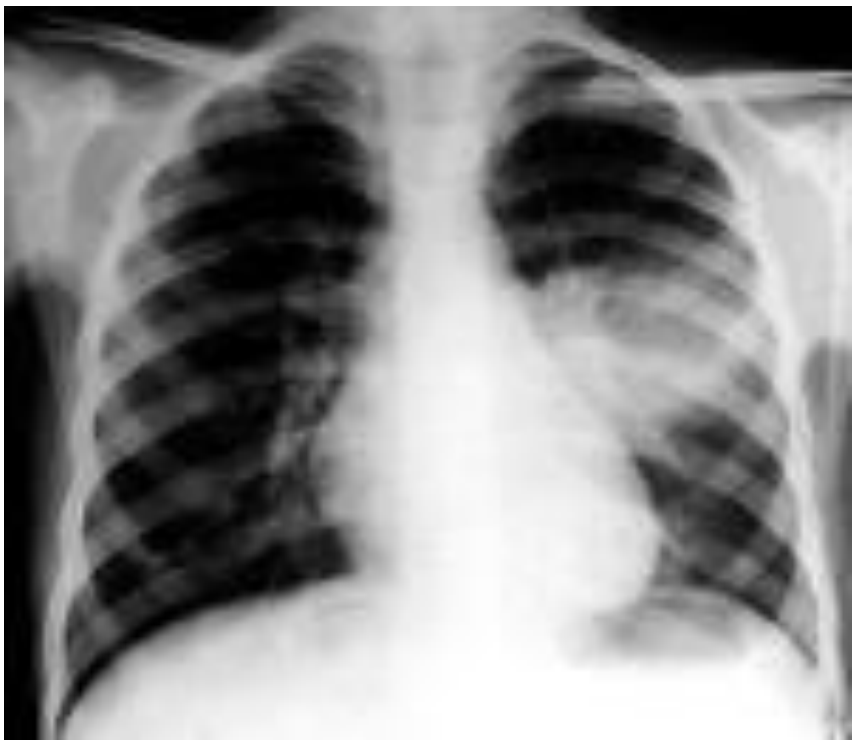

Figure 145: Pneumonia

Measles

Both measles and HIV infection cause immunosuppression. The immunosuppression in measles is transient with depression of cellular immunity while HIV infection causes progressive immunodeficiency of both humoral and cellular immunity.

Severe complications and death may occur in children with HIV co-infection with mortality rates varying from 40 to 70%.

Clinical features

Case definition for measles: Fever with a generalized maculopapular rash and one of the following - Cough, coryza (runny nose) and conjunctivitis (red eyes). A history of contact with someone with the disease is useful.

A pathognomonic enanthema (Koplik spots) may be seen at the corner of the cheek at the prodromal phase. The rash is usually preceded by the fever, has a cephalocaudal distribution, appearing behind the ears and face and later spreading to the trunk and lower limbs. The rash is desquamating disappearing in the order of its appearance.

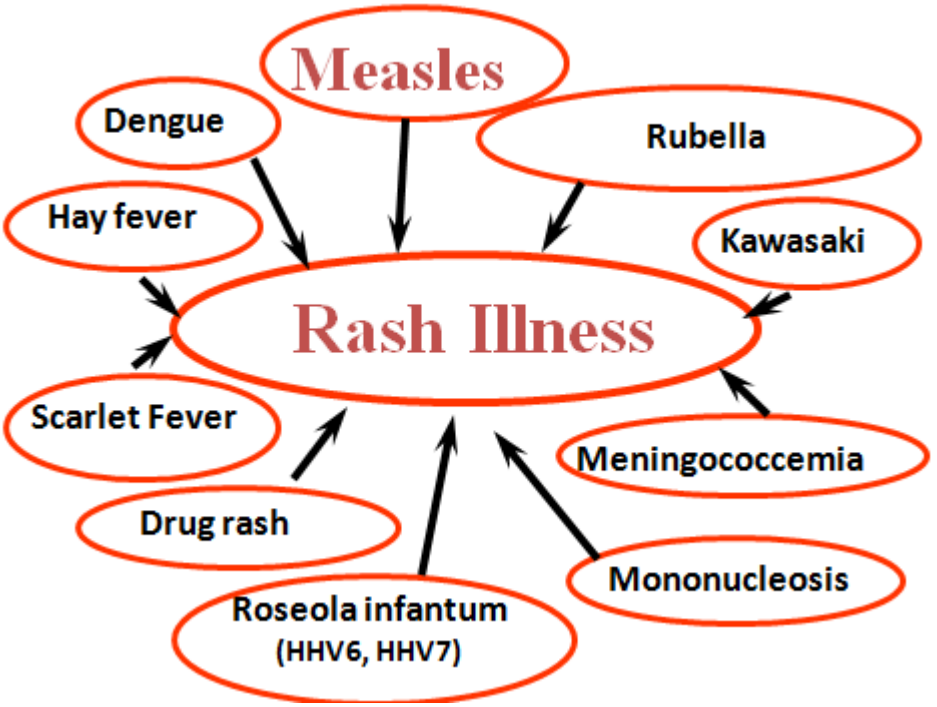

Figure 146: Differentials for rash illness

Diagnosis

The diagnosis of measles is mainly clinical. For surveillance purposes, serological test to confirm the presence measles IgM in the blood is required.

Complications

The most common complication is pneumonia which requires antibiotics as >50% of all cases of pneumonia in measles have secondary bacterial infection (*Staph aureus, Strep pneumonia, Haemophilus influenza and Klebsiella pneumonia).*

Other complications are otitis media, diarrhoea, laringotracheobronchitis (croup), corneal and retinal damage from the infection or from instillation of harmful local remedies. Mouth ulcers, neurological complications –short term: convulsions, encephalitis and long term sub-acute sclerosing pan-encephalitis (SSPE) characterised by personality changes and gradual cognitive deterioration, are other important complications. Severe acute malnutrition may result as measles is a severely catabolic disease.

Prevention

The WHO recommends that in areas where there is a high incidence of both HIV infection and measles, the first dose of a measles-containing vaccine is offered as early as age 6 months, with two additional doses of measles vaccine administered to the children.

Measles vaccine is not recommended when the CD4 percentage <15% at any age or CD4 count <200/mm^3 for persons aged >5 years since several severe and fatal measles cases have been reported in severely immunosuppressed HIV-infected persons after measles vaccination.

Administration of immunoglobulin to HIV-infected children is advocated when measles exposure has occurred, irrespective of the immunization status.

Vitamin A is indicated - 50 000 IU (if aged < 6 months), 100 000 IU (6–11 months) or 200 000 IU (1–5 years). Early initiation of antiretroviral therapy is also essential.

Recovery after acute measles is often delayed for many weeks and even months, especially in children who are malnourished.

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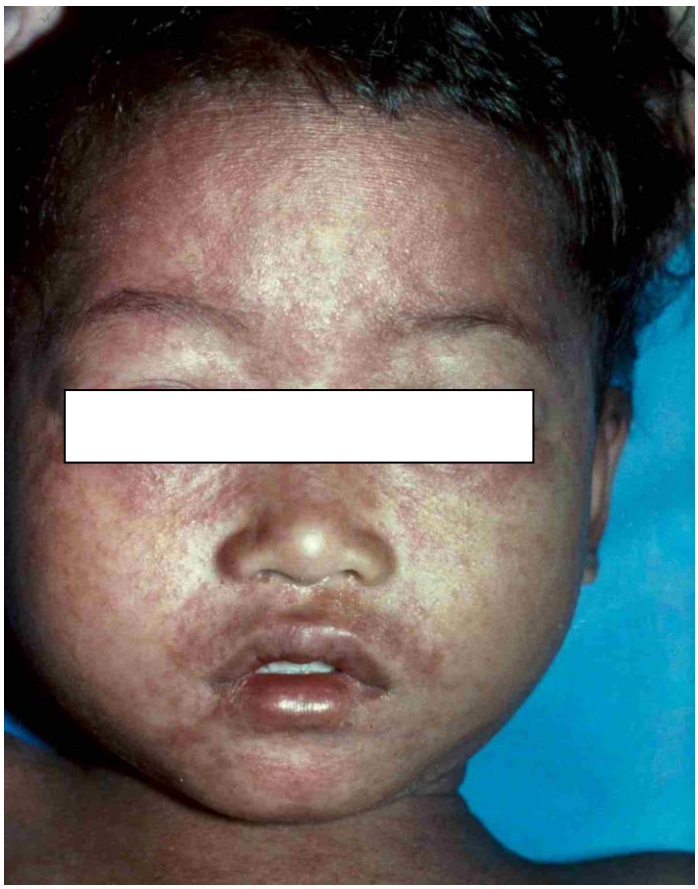

Figure 147: Confluent erythematous maculo-papular measles lesions.

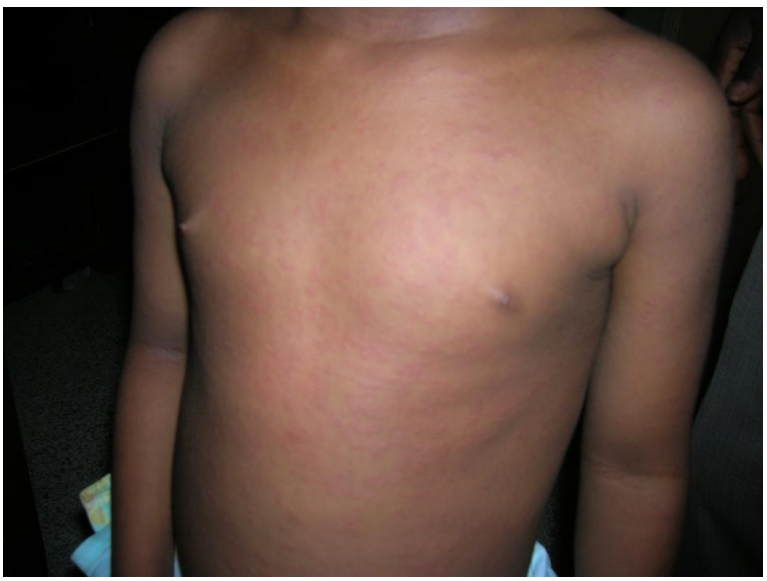

Figure 148: A case measles showing fresh maculo-papular lesions.

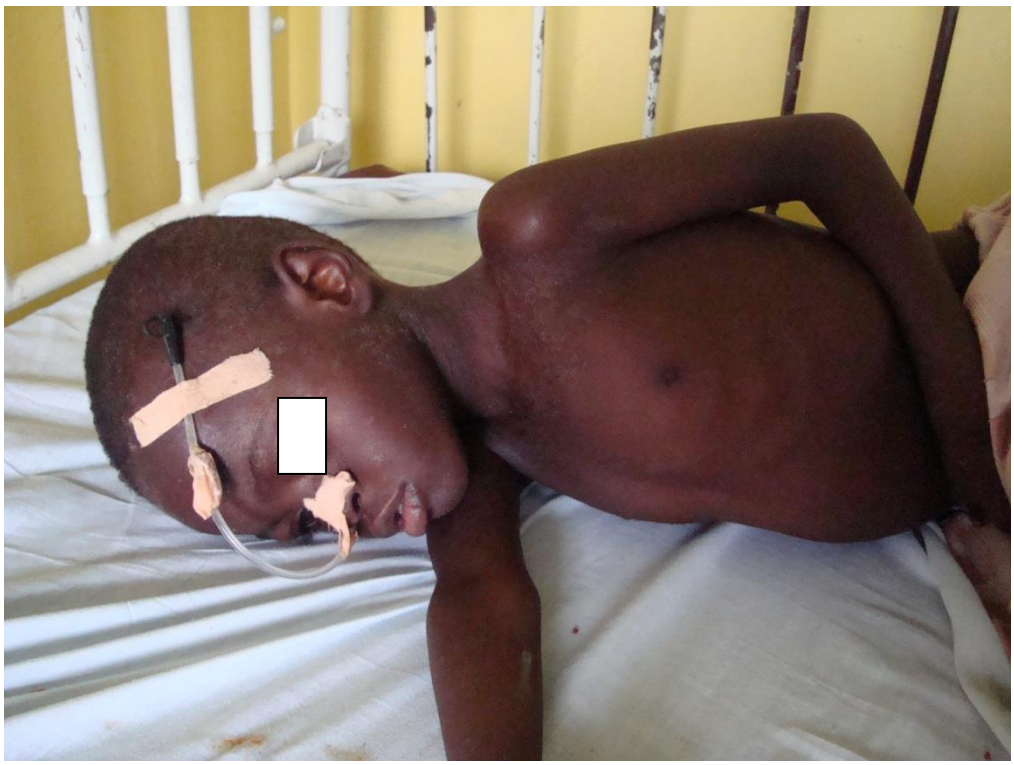

Figure 149: A case of measles shower older desquamating skin lesions.

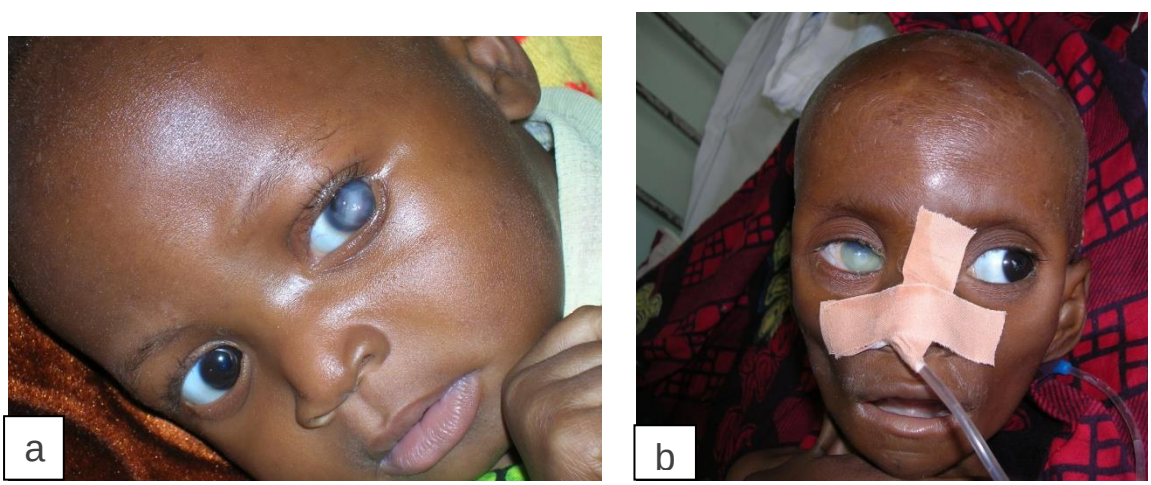

Figure 150a and b: (a) Measles keratitis (b) Post measles panophthalmitis.

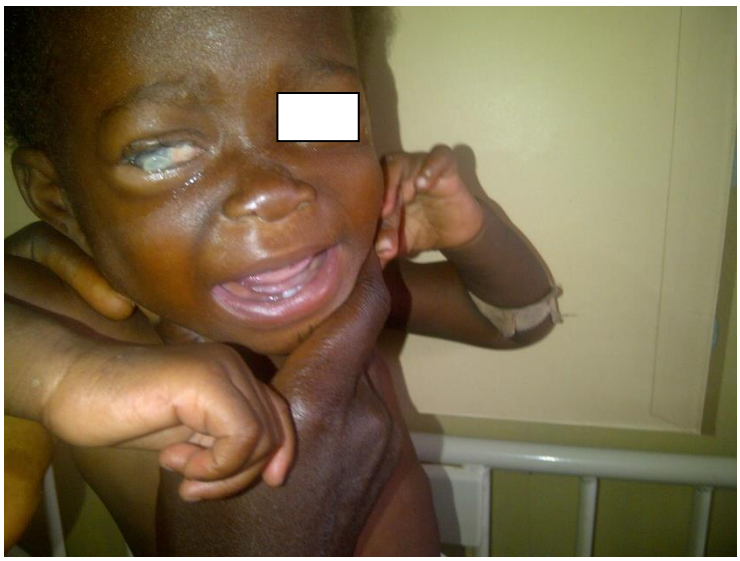

Figure 151: Uveal prolapse, post measles in a 12-month-old with newly diagnosed HIV infection.

Syphilis

Syphilis is caused by the spirochete *Treponema pallidum*, a corkscrew-shaped bacterium. Syphilis in children is usually congenital or very rarely acquired through sexual abuse. Syphilis facilitates perinatal HIV transmission. HIV-infected women have a higher prevalence of untreated or inadequately treated syphilis during pregnancy, which places their new-born children at a higher risk of congenital syphilis. Congenital syphilis is generally acquired through transplacental transmission of spirochetes in the maternal bloodstream or, occasionally, through direct contact with an infectious lesion during birth.

Untreated early syphilis during pregnancy can lead to spontaneous abortion, stillbirth, hydrops fetalis, preterm delivery, and perinatal death in up to 40% of pregnancies. *T. pallidum* is not transferred in breast milk except if the mother has an infectious lesion (e.g., chancre) on the breast.

Presentation: Manifestations in congenital syphilis are defined as early if they appear in the first 2 years of life and late if they develop after age 2 years. About 60% of neonates with congenital syphilis are asymptomatic at birth. If untreated, asymptomatic infants can develop clinically apparent disease in the ensuing 3 weeks to 6 months.

Early congenital syphilis (≤2 years): Hepatosplenomegaly, jaundice, mucocutaneous lesions (e.g., skin rash, nasal discharge, mucous patches, condylomata lata), lymphadenopathy, pseudoparalysis of an extremity, haematological abnormalities (anaemia, thrombocytopenia), pneumonia, and skeletal lesions (e.g. osteochondritis, periostitis, or osteitis). Fever, nephrotic syndrome, ophthalmologic manifestations may also occur.

Late congenital syphilis (>2 years): Involvement of the central nervous system (neurosyphilis), bone (saber shins, saddle nose), teeth (notched, peg-shaped incisors (Hutchinson teeth), eyes (interstitial keratitis), sensory-neural hearing loss (eighth cranial nerve deafness).

Differential diagnosis

Other congenital infections (toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus, neonatal sepsis), and other causes of neonatal hepatitis, hydrops fetalis, long-bone abnormalities, and cutaneous scaly lesions.

Laboratory diagnosis: Definitive diagnosis is by dark field microscopy performed on body fluids (e.g., nasal discharge) or moist skin lesions demonstrating thin, delicate, corkscrew-shaped organisms with rigid, tightly wound spirals. Failure to identify spirochetes with dark field microscopy does not exclude the diagnosis of syphilis.

The infant is evaluated with non-treponemal reaginic tests (rapid plasma reagin (RPR) and the Venereal Disease Research Laboratory (VDRL) which are quantitative, and compared with the same test done at the same laboratory on the mother's serum. The neonate's non-treponemal titre usually is

one to two dilutions less than that of the mother. A quantitative non-treponemal serologic titre in an infant that is 4-fold or (more) higher than the mother's is suggestive of infection. A reactive non-treponemal test must be confirmed by a specific Treponema test such as fluorescent Treponema antibody absorption (FTA-ABS) or *T pallidum* particle agglutination (TPPA).

Further evaluation includes a complete blood count and differential and platelet count, long bone radiographs, and CSF analysis for VDRL, cell count, and protein. A positive CSF VDRL test, elevated CSF protein, and/or elevated CSF white blood cell (WBC) count without other causes may be due to congenital syphilis. Other tests should be performed as clinically indicated (e.g., chest radiograph, liver-function tests, cranial ultrasound, ophthalmologic examination, auditory brainstem response).

Treatment: Penicillin remains the treatment of choice for syphilis, congenital or acquired, regardless of HIV status**.**

Aqueous crystalline penicillin G 100,000 to 150,000 units/kg/day, administered as 50,000 units/kg/dose intravenously (IV) every 12 hours during the first 7 days of life and every 8 hours thereafter x 10 days**.**

If congenital syphilis is diagnosed after age 1 month, the dosage of aqueous penicillin G should be increased to 200,000 to 300,000 units/kg/day IV, administered as 50,000 units/kg/dose IV every 4 to 6 hours x 10 days.

If 1 day of therapy is missed, the entire course should be restarted. An alternative to aqueous penicillin G is procaine penicillin G 50,000 units/kg/dose IM in a single dose daily x 10 days. However, penicillin G is preferred because of its higher penetration into the CSF.

Acquired syphilis in children and adolescents is treated with a single dose of benzathine penicillin G 50,000 units/kg IM (up to the adult dose of 2.4 million units) for early-stage disease. For late latent disease, 3 doses of benzathine penicillin G 50, 000 units/kg (up to the adult dose of 2.4 million units) should be administered IM once weekly for 3 doses (total 150,000 units/kg, up to the adult total dose of 7.2 million units). Neurosyphilis should be treated with aqueous penicillin G 200,000 to 300,000 units/kg body weight per dose IV every 4 - 6 hours (maximum dosage: 18–24 million units/day) x 10 - 14 days.

A sustained 4-fold decrease in titre demonstrates adequate therapy. Treponemal tests usually remain positive for life, even with successful treatment.

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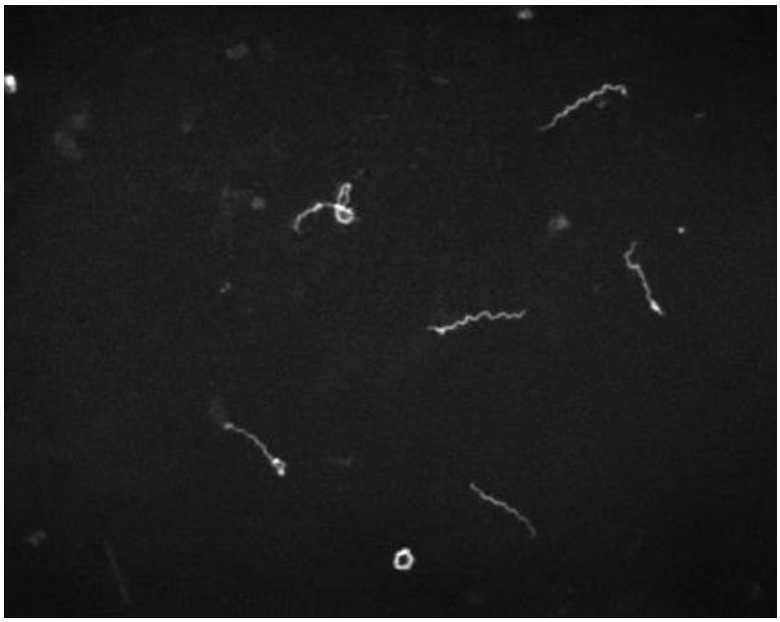

Figure 152: Treponema pallidum spirochetes on dark field microscopy.

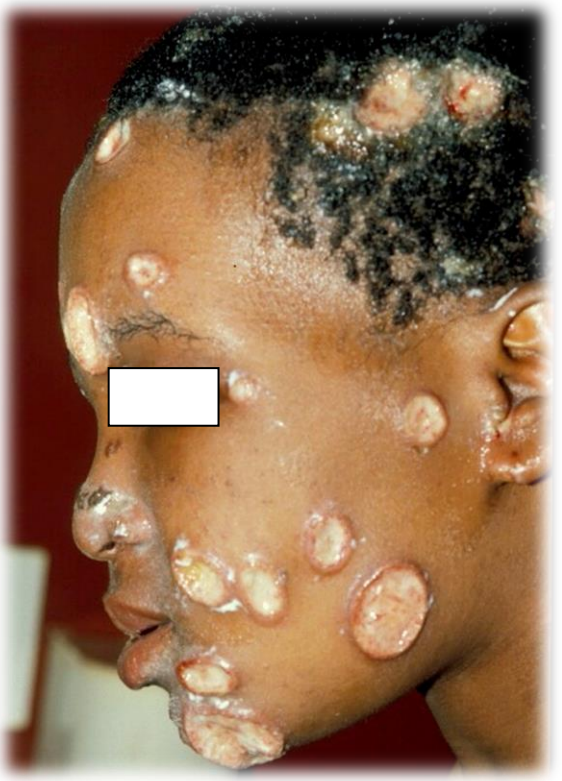

Figure 153: Extensive ulcerative nodulo-ulcerative syphilis in HIV.

Diarrhoea

Diarrhoea is more likely in children with HIV, and the leading cause of death among HIV-infected infants. Diarrhoea tends to be prolonged and usually complicated by dehydration and malnutrition.

It is classified into 3:

- **Acute diarrhoea** (if an episode of diarrhoea has lasted for ≤14 days): Causes dehydration and contributes to malnutrition.
- **Persistent diarrhoea (**if the diarrhoea lasts ≥14 days): often leading to malnutrition and weight loss.
- **Dysentery**: Diarrhoea with blood in the stool, with or without mucous — in young children, this is generally caused by *Shigella.*

The usual infective causes of acute diarrhoea are also prevalent in HIV-infected children, the commonest of which is Rotavirus. Additionally, cryptosporidiosis, isosporiasis, CMV infection, atypical *Mycobacteria species*, and parasitic infections, including *Strongyloides stercoralis and Tricuris tricuria* may be implicated.

Treatment:

- Hospitalisation is required if there is dehydration and/or malnutrition.
- Evaluating for dehydration and ensuring adequate fluids (and electrolytes) is the most important component of the management of a child with diarrhoea.
- Antibiotics to be used only when the diarrhoea is bloody or shigellosis – Drug of choice - Ciprofloxacin 15 mg/kg 12 hourly x 3 days (widespread resistance of *Shigella* to ampicillin, co-trimoxazole and nalidixic acid)
- 20 mg/day of zinc supplementation for 10-14 days (10 mg/day for infants < 6 months old).
- Anti-diarrhoeal drugs are not usually recommended.
- Metronidazole 15 mg/kg/dose 8 hourly PO for 10 days is added if fresh stool sample reveals trophozoites of *Entamoeba histolytica* within red blood cells or *Giardia lamblia.*
- Low or free lactose diet may be required in severe cases of chronic/persistent diarrhoea.

Figure 154: Bloody stool (dysentery) from a 12-month-old HIV-infected child presenting with recurrent diarrhoea.

Further reading

1. Pocket Book of Hospital Care for Children: Guidelines for the Management of Common Childhood Illnesses. 2nd ed. Geneva: World Health Organization; 2013.
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Malaria

Malaria is caused by plasmodium parasite transmitted via the female anopheles mosquito. There are five plasmodium species - *P. falciparum, P. vivax, P. ovale, P. malariae* and *P. knowlesi*. *P. falciparum* causes the most serious form of the disease and is common in the tropics. Non-falciparum malarial infections are less common in sub-Saharan Africa. In endemic areas, with repeated infections, partial immunity is developed to the disease. Parasitaemia still develops but the severity of clinical symptoms may be less.

There is a geographic overlap in malaria and HIV. HIV increases the risk of malaria and reduces the acquired natural immunity to malaria as a result of the immunosuppression. More severe manifestations of *P. falciparum* malaria including severe acidosis, anaemia, respiratory distress and hyperparasitaemia and increased mortality were reported when compared with HIV-uninfected children. Bacteraemia is an important consideration especially with non-typhi salmonella (NTS) in HIV-infected children especially in those with severe malaria anaemia.

Clinical presentation

Uncomplicated malaria – The clinical signs and symptoms of malaria are non-specific and include fever, headache, malaise, chills, anorexia, vomiting and arthralgia. On physical examination, liver and spleen may be palpable.

Severe malaria – Severe malaria is defined by clinical or laboratory evidence of vital organ dysfunction. Many of the clinical manifestations result from parasitized (and non-parasitized) red blood cells adhering to small blood vessels causing small infarcts, capillary leakage, and organ dysfunction.

Features of severe malaria (shown in the boxes below) can occur singly or, more commonly, in combination in the same patient. High parasitaemia; parasite densities >100 000/µl (~2.5% parasitaemia) in low-transmission areas and more in endemic areas is a risk factor for death.

Clinical features of severe malaria

- impaired consciousness (including unrousable coma);
- prostration, i.e. generalized weakness so that the patient is unable to sit, stand or walk without assistance;
- multiple convulsions: more than two episodes within 24h;
- deep breathing and respiratory distress (acidotic breathing);
- acute pulmonary oedema and acute respiratory distress syndrome;
- circulatory collapse or shock, systolic blood pressure < 80mm Hg in adults and < 50mm Hg in children;
- acute kidney injury;
- clinical jaundice plus evidence of other vital organ dysfunction; and
- abnormal bleeding.

Laboratory and other findings

- hypoglycaemia (< 2.2mmol/l or < 40mg/dl);
- metabolic acidosis (plasma bicarbonate < 15mmol/l);
- severe normocytic anaemia (haemoglobin < 5g/dl, packed cell volume < 15% in children; <7g/dl, packed cell volume < 20% in adults);
- haemoglobinuria;
- hyperlactataemia (lactate > 5mmol/l);
- renal impairment (serum creatinine > 265µmol/l); and
- pulmonary oedema (radiological).

Diagnosis

Microscopy (gold standard) – Thick and thin blood films to detect the malaria parasites.

Where microscopy is unavailable or not feasible, rapid diagnostic test (RDT) may be used. RDT detects HRP2 antigen in *P. falciparum.*

In more severe cases of malaria, additional tests would be required when available: Serum glucose, CSF analysis to rule out meningitis, full blood count (anaemia, thrombocytopaenia, polymorphonuclear leukocytosis may be present), serum electrolytes, urea and creatinine as well as blood culture to rule out bacteraemia.

Differential diagnoses

Urinary tract infection, tonsillitis, viral illness, pneumonia, septicaemia, meningitis, enteric fever, yellow fever, dengue fever.

Treatment

Due to widespread high-level resistance to chloroquine and sulfodoxine/pyrimethamine (SP), they are not to be used in the treatment of *P. falciparum* infections.

Uncomplicated malaria - The current treatment of choice for uncomplicated malaria is Artemisinin Based Combination Therapy (ACT) – Arthemeter/Lumefantrine or Arthemeter/Amodiaquine. ACT has minimal side effects and is effective against all stages of the parasite.

For *P. vivax* and *P. ovale* disease, primaquine treatment is added to clear the liver stages of the parasites to prevent relapse: 0.25–0.5 mg base/kg body weight in two divided daily doses should be given for 14 days.

Table 6: Dosage regimen for Arthemeter/Lumefantrine (CoartemR)

Weight	Number of tablets / dose
5 - <15 kg	1 tab twice daily x 3 days
15 - <25 kg	2 tabs twice daily x 3 days
25 - <35 kg	3 tabs twice daily x 3 days
>	4 tabs twice daily x 3 days

Severe malaria -IV artesunate given at 0, 12, 24 hours and then daily.

Revised dose recommendation for parenteral artesunate:

Children <20 kg: 3 mg/kg/dose

≥20 kg: 2.4 mg/kg/dose

Parenteral therapy must be given for a minimum of 24 hours. Follow on treatment once the patient can tolerate orally consists of a complete course of ACT.

Alternative treatment for severe malaria is IV Quinine starting with a loading dose of 20 mg/kg, then 10 mg/kg 8 hourly for 7 days. Toxicity of quinine includes nausea, vomiting, hypoglycaemia, tinnitus and cardiac arrhythmias.

Other supportive therapy to correct hypoglycaemia, treatment of seizures with anticonvulsants and ensuring adequate fluid balance is important. Therapeutic response needs to be monitored 12-hourly with parasite count.

Prevention

Mosquito bite prevention

- Reduced outdoor exposure between dusk and dawn (when Anopheles mosquitoes feed)
- Protective clothing
- Wearing insect repellent
- Sleeping within bed nets treated with insecticide (e.g., permethrin)
- Staying in well-screened rooms.

Chemoprophylaxis (for travellers)

- Atovaquone/Proguanil daily, starting 2/7 before exposure, during exposure, up to one week following exposure
- Mefloquin weekly, 2 weeks prior to exposure, during exposure and up to 4 weeks after exposure
- Doxycycline: Not recommended for children< 8 years.

Immunization: A child vaccine in addition to existing malaria interventions is desirable for an improved malaria control. The RTS S malaria vaccine candidate has been developed and is awaiting policy recommendations.

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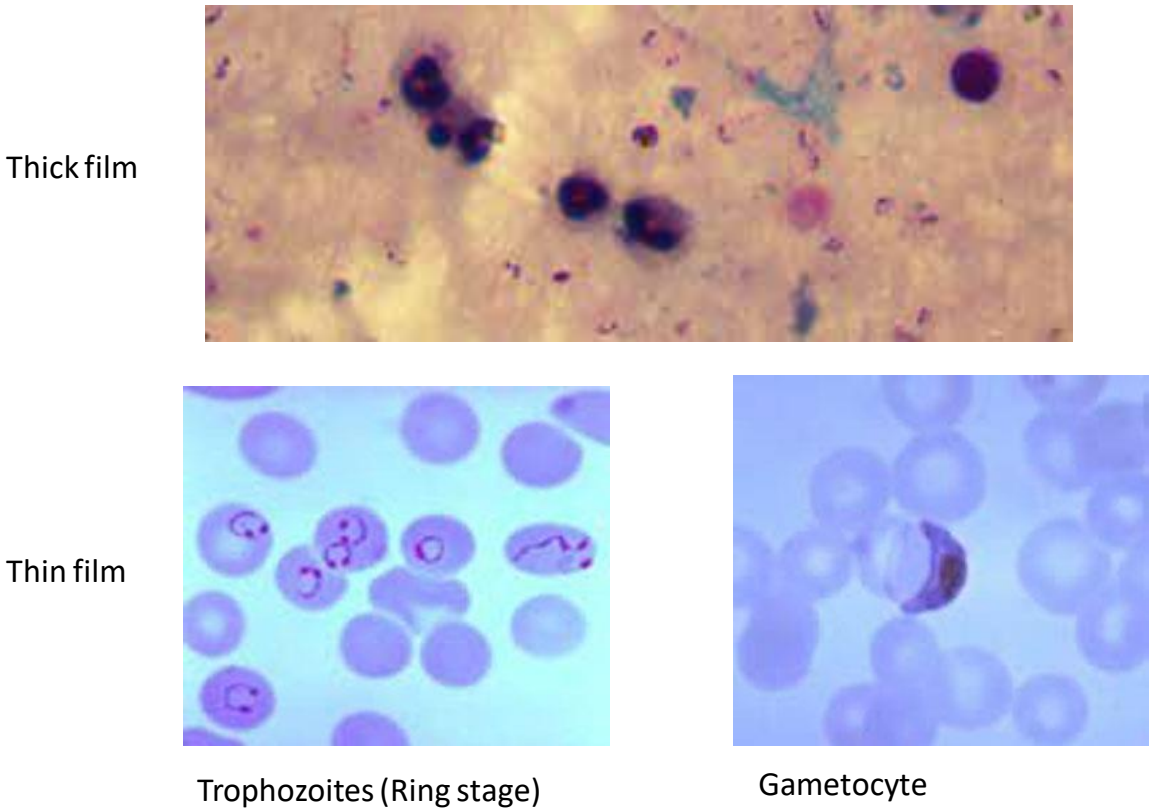

Figure 155: Appearance of P. falciparum parasite stages in Giemsa-stained thin and thick blood films.

CHAPTER 14: HIV ASSOCIATED LUNG DISEASES

Lymphoid Interstitial Pneumonitis (LIP)

LIP is a slowly progressive interstitial lung disease seen in HIV-infected children. LIP is rare in non-HIV-infected children and in HIV-infected adults. The usual age of presentation is older than 2 years of age. The pathogenesis is thought to be due to primary infection with Epstein-Barr virus, which initiates a lymphoproliferative response from co-infection with HIV.

Clinical presentation: Children with LIP usually present with chronic respiratory symptoms of cough and slowly progressive hypoxia, tachypnoea, exertion fatigue and reduced oxygen saturation. There may be an acute-on-chronic presentation with fever and tachypnoea, when there is superimposed bacterial pneumonia. Apart from the lungs, there is also lymphoproliferation in other organs, hence LIP may be associated with bilateral non-tender parotid enlargement, persistent generalised and symmetrical lymphadenopathy, hepatosplenomegaly, and/or adenoidal and tonsillar hypertrophy.

Digital clubbing is commonly associated with LIP.

Characteristic chest radiographic findings of LIP include bilateral, diffuse, reticulonodular infiltrates that are more prominent in the lower lobes, and bilateral hilar adenopathy. Distinguishing LIP from PTB or miliary TB can be a challenge.

Differential diagnoses: Bacterial pneumonia, PCP, Tuberculosis, CMV pneumonitis, other viral pneumonia, e.g., RSV, influenza, parainfluenza, adenovirus; malignancy, e.g., Kaposi sarcoma, lymphoma, fungal pneumonia, MAC infection and nocardiosis.

Treatment: Institution of ART is necessary. Additionally, oral prednisone 2 mg/kg/day for 2–4 weeks followed by reduced dosage are indicated in children with dyspnoea and hypoxia. Additional treatment with antibiotics may be required when secondary bacterial infection is suspected.

Further reading

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2. Graham SM. Non-tuberculosis opportunistic infections and other lung diseases in HIV-infected infants and children. Int J Tuberc Lung Dis 2005; 9(6):592–602

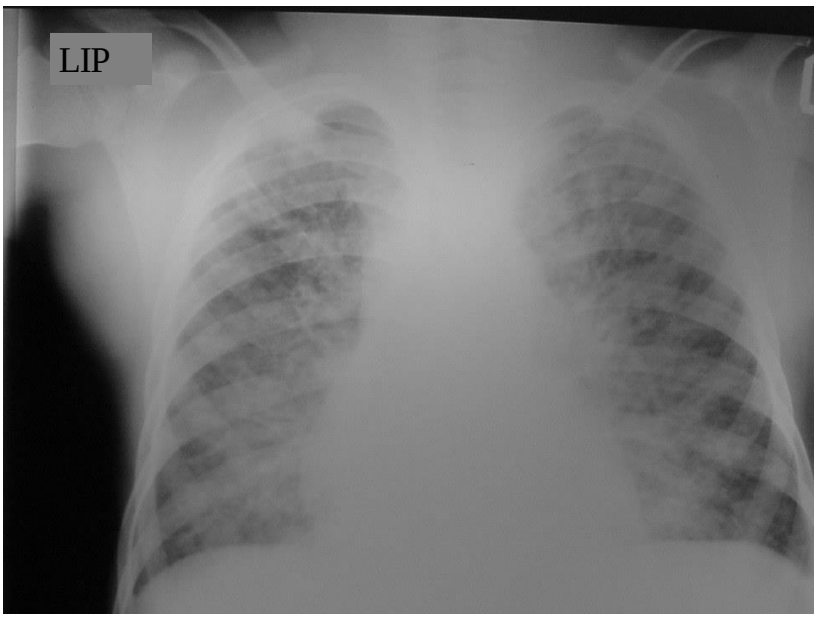

Figure 156: Bilateral reticulonodular interstitial pattern and adenopathy. LIP can be particularly difficult to differentiate from miliary TB

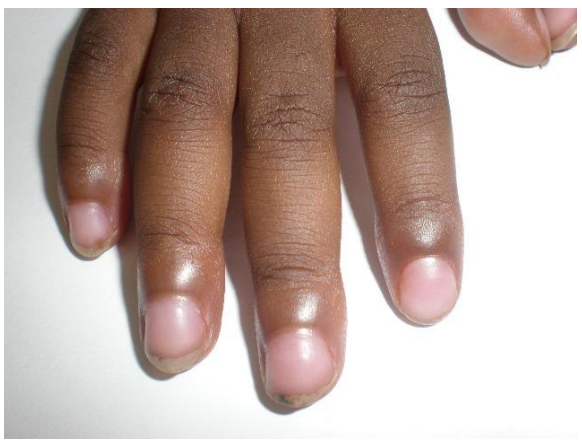

Figure 157: Digital clubbing in a child with LIP.

Bronchiectasis

Bronchiectasis is defined as an abnormal dilatation of airways. Recurrent or persistent lung disease associated with HIV e.g. recurrent or unresolved bacterial pneumonia, LIP and PTB, can be complicated by bronchiectasis.

Clinical presentation: Chronic cough productive of copious purulent sputum, digital clubbing, focal abnormalities on auscultation, usually coarse crackles, and halitosis.

Diagnosis: CXR usually shows focal abnormalities with bronchial dilatation as shown in the figure below. TB may have a similar radiological picture to bronchiectasis and in a high TB burden area where there is over-reliance on radiological diagnosis for PTB, bronchiectasis may be missed or frequent retreatments of TB may occur. Almost a quarter of a cohort of children with HIV-related bronchiectasis in one study received two courses of anti-tuberculosis treatment. In a high TB burden area, the differential diagnosis of an abnormal chest X-ray in children with chronic cough or previously treated TB should include bronchiectasis.

Where available a High-resolution computed tomography (HRCT) scanning is the standard test for diagnosis especially in the absence of characteristic chest radiograph findings of dilated airway, with thickened airway walls.

Key features on CT scan: Enlarged internal bronchial diameter with bronchi that appear larger than the accompanying artery. Other findings include the failure of the larger airways to taper while progressing to the lung periphery, air fluid levels in the dilated airways, and the identification of airways in the extreme lung periphery.

Other testing may be indicated to diagnose underlying conditions.

Treatment: Broad spectrum antibiotics to treat recurrent infections and chest physiotherapy. Long-term low dose therapy with azithromycin has been found to be beneficial in patients with bronchiectasis as it has anti-inflammatory effects but was accompanied by increased carriage of azithromycin-resistant bacteria in one study.

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4. Valery PC, Morris PS, Byrnes CA et al. Long-term azithromycin for Indigenous children with non-cystic-fibrosis bronchiectasis or chronic suppurative lung disease (Bronchiectasis Intervention Study): a multicentre, double-blind, randomised controlled trial. Lancet Respir Med. 2013; 1(8):610-20.
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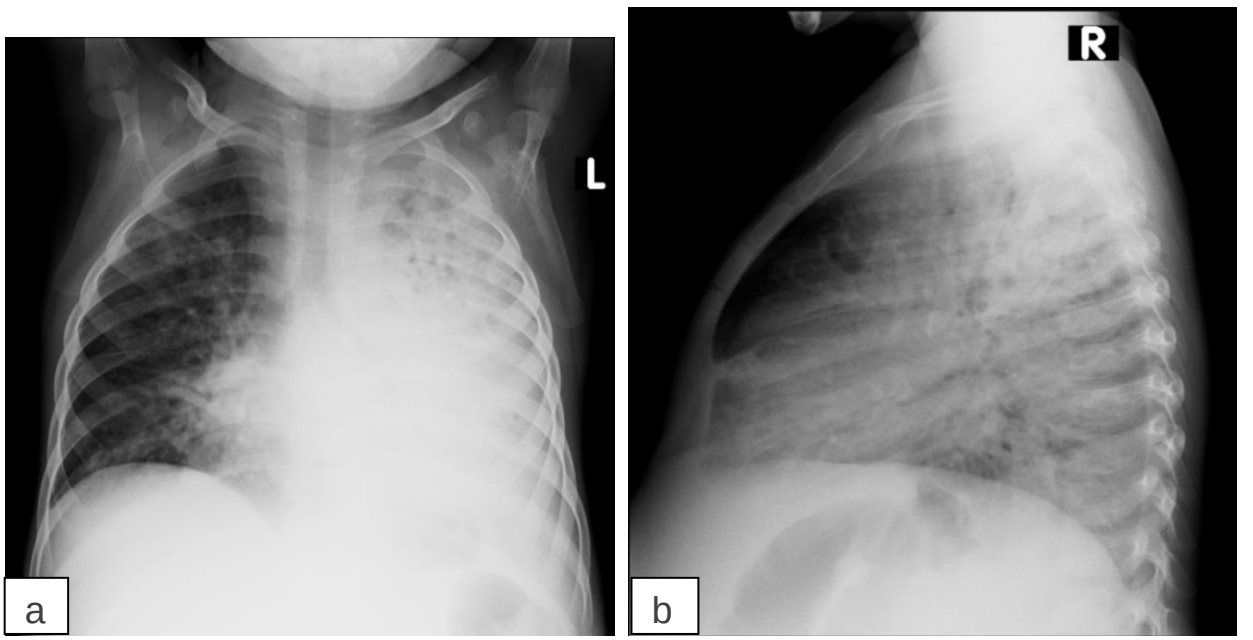

Figure 158: AP and lateral views of CXR showing widespread right-sided bronchiectasis: There is marked apical pleural thickening and underlying cystic lung disease indicative of a destroyed left lung.

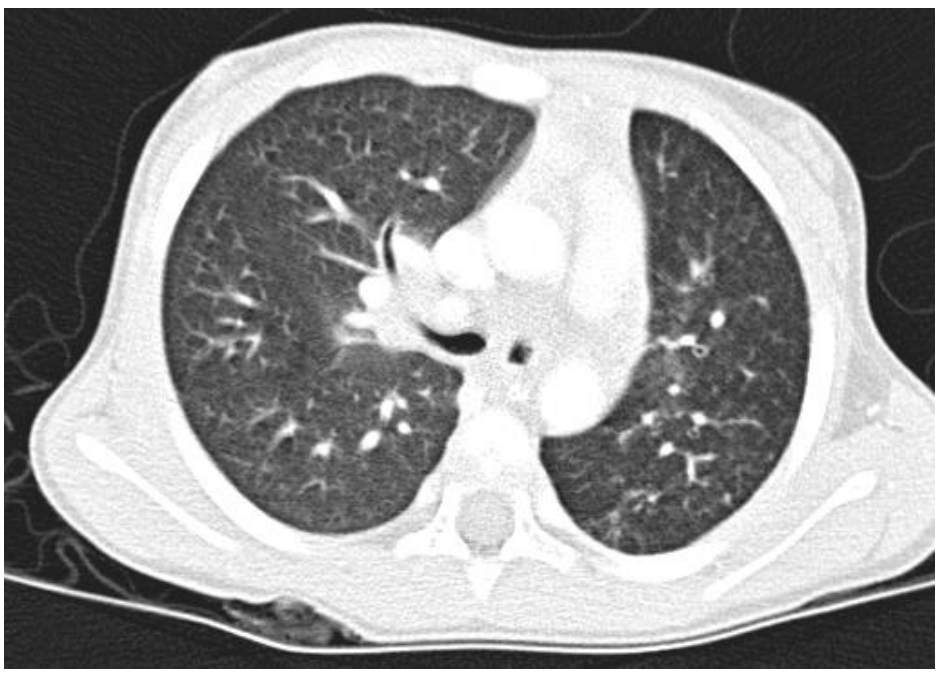

Figure 159: Bronchiectasis complication PTB. Left hemithorax is contracted from destruction and volume loss. Subcarinal lymphadenopathy is also evident.

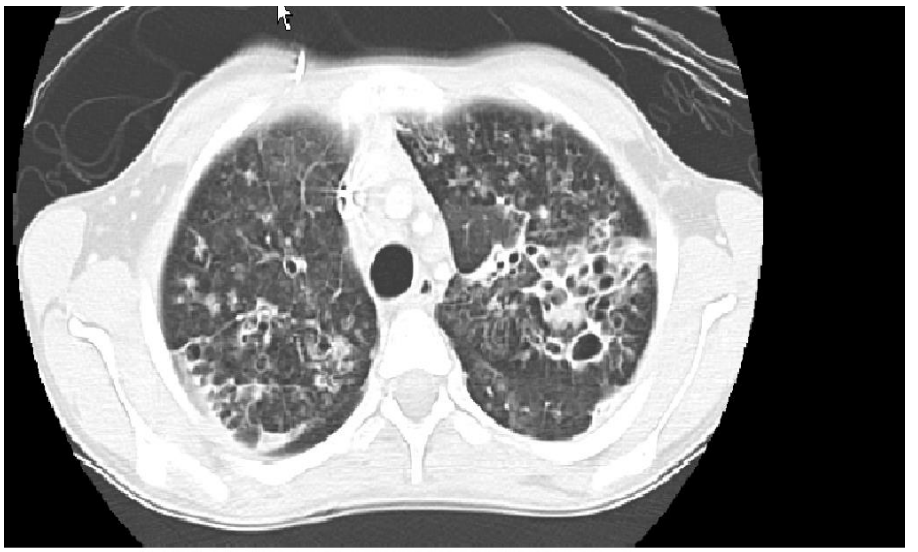

Figure 160: CT scan of a child with bronchiectasis

CHAPTER 15: MALIGNANCIES

Kaposi Sarcoma (KS)

Kaposi sarcoma and Non-Hodgkin lymphoma are two of the greatest contributors to malignancy burden among HIV-infected children. KS is an AIDS defining disease that typically occurs with lower CD4 count and high viral load.

Clinical presentation: Cutaneous lesions are the most common manifestations of KS, presenting as non-tender, purplish and indurated lesions. KS may also involve the lymph nodes, oral mucosa and the lungs. Visceral dissemination can occur, occasionally without skin lesions.

Diagnosis: Diagnosis is confirmed on histology which shows chronic granulomatous changes with cellular neoplasm composed of spindle cells with slit-like spaces containing red blood cells.

Histoimmunochemistry test may be positive for HHV 8 which further confirms the diagnosis of KS.

Differentials: Pyogenic granuloma, tuberculosis, lymphoma, bacillary angiomatosis and dermatofibromata

Treatment: ART is the first line of management. ART may lead to regression of the lesions but referral for chemotherapy (vincristine and bleomycin or liposomal preparations of danorubicin and doxorubicin) in an experienced cancer-treatment centre is usually required for extensive lesions.

Further reading

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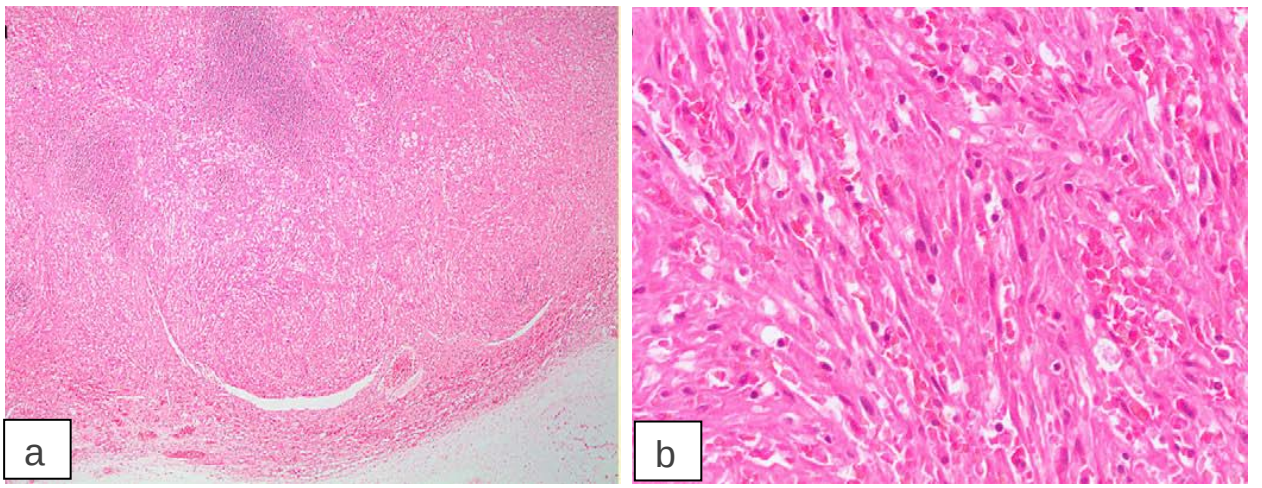


Figure 161a and b: (a) almost complete replacement of the nodal tissue by (b) a proliferation of spindle cells with slit-like vascular spaces. (Courtesy: Dr. Komala Pillay. Paediatric pathologist, Red Cross Children's Hospital, Cape Town).

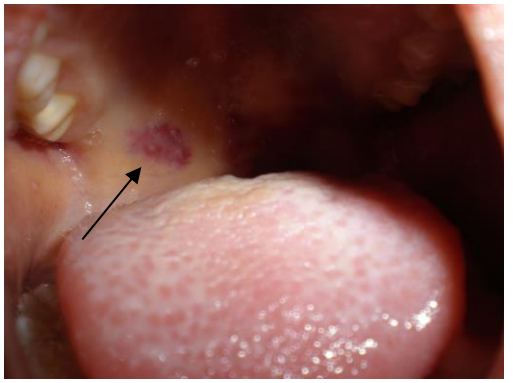


Figure 162: Kaposi sarcoma lesion (black arrow).

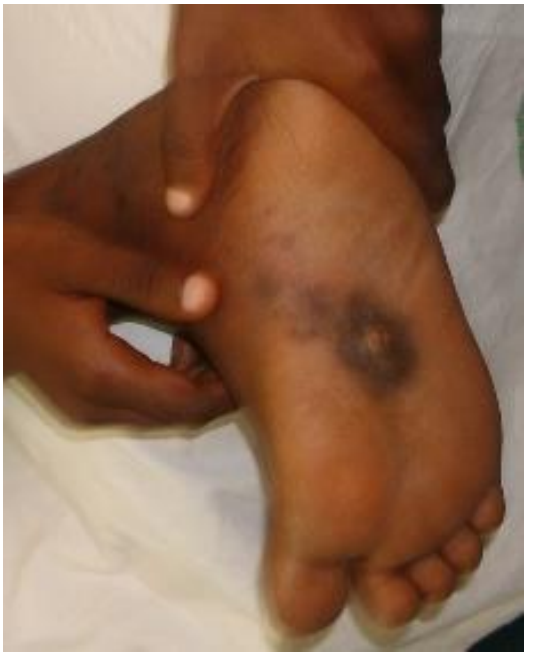


Figure 163: Kaposi sarcoma on the sole of the right foot.

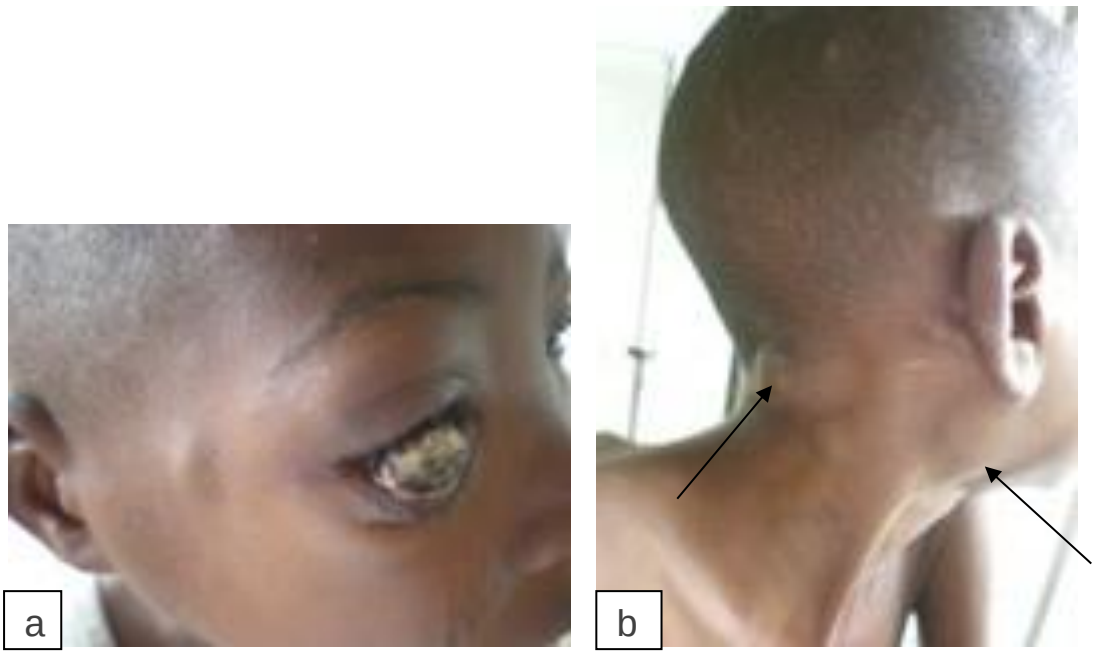
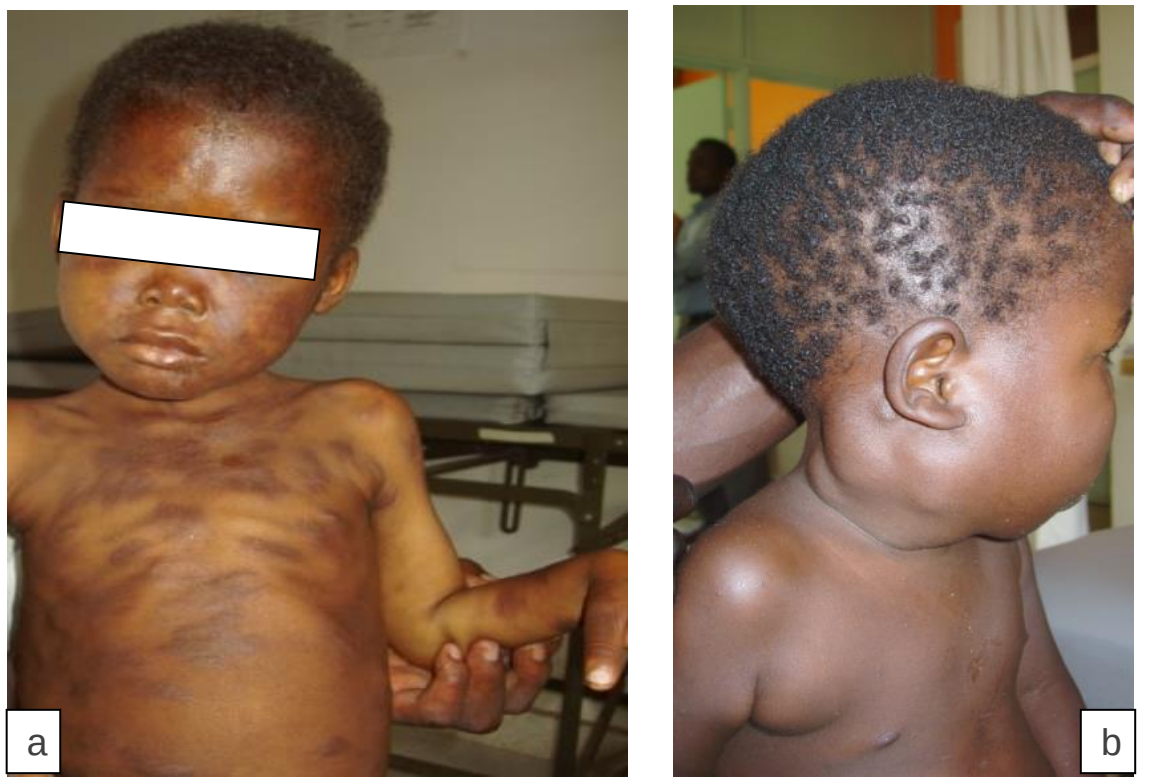


Figure 164a and b: Fungating eye tumour and lymph node in an 8 year old child with late diagnosis of HIV. Histology confirmed the lesion to be Kaposi sarcoma.



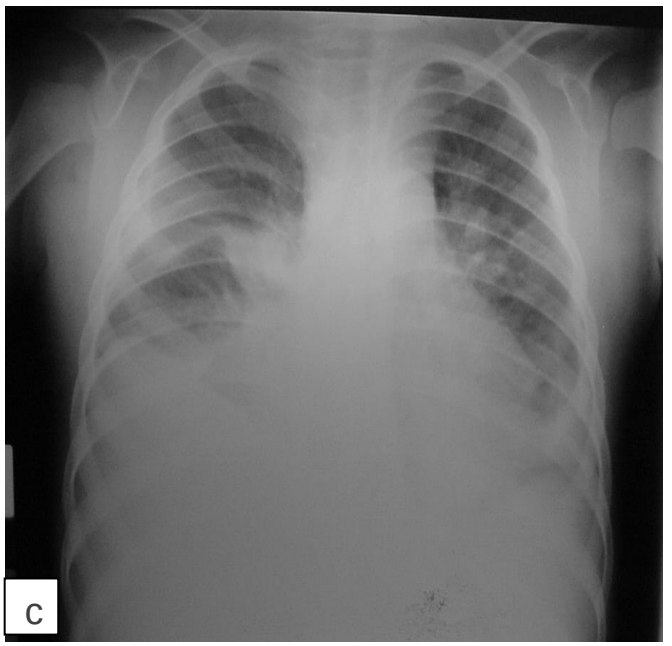


Figure 165a, b and c: Kaposi sarcoma involving the skin, lymph nodes and lungs (Courtesy of Dr George Chagaluka, Queen Elizabeth Central Hospital, Malawi).

Non-Hodgkin's Lymphoma (NHL)

HIV-infected patients are at increased risk of developing non-Hodgkin lymphoma compared with the general population. Highly active antiretroviral therapy reduces the incidence of AIDS-related non-Hodgkin lymphoma and improves overall survival. NHL cases with HIV are highest for diffuse large B-cell and Burkitt lymphomas.

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CHAPTER 16: IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

Antiretroviral therapy has greatly reduced morbidity and mortality from HIV infection. One of the complications of immune recovery following ART is IRIS which occurs especially in the first weeks of initiating therapy and majorly in patients with severe immunosuppression. Compared with adults, information on IRIS in children is limited. Incidence of IRIS in children varies between 6 and 21% depending on geographic location and case definition.

Clinical presentation: The onset of IRIS is usually acute and there are features of inflammation, which may be generalized (e.g., fever, tachycardia) or localized (e.g., lymphadenitis).

Two types of IRIS:

Paradoxical IRIS - Symptoms and signs associated with an opportunistic infection (OI), for which treatment is underway, recur or become acutely worse, despite an earlier improvement to therapy prior to ART.

Unmasking IRS - A new previously undiagnosed OI presents, unmasked by the immune recovery following ART initiation.

Conditions associated with IRIS in HIV infection:

- Mycobacterium infections: BCG, MTB, MAC
- The most commonly reported IRIS event is reaction to BCG vaccine, occurring as injection site lesions and/or ipsilateral axillary lymphadenitis with abscess.
- *Pneumocystis jiroveci* pneumonia (PCP)
- Toxoplasmosis
- Hepatitis B, hepatitis C
- Cytomegalovirus (CMV) infection
- Varicella-zoster (VZV) infection
- Cryptococcal infection
- Progressive multifocal leukoencephalopathy (PML)
- Skin conditions: Seborrheic dermatitis, molluscum contagiosum, pruritic popular eruption.

Diagnosis: Diagnosing IRIS is a challenge as there is no definitive diagnostic test for it. There should be evidence of a favourable response to ART, indicated by a falling HIV viral load. With limited laboratory support in developing country settings, IRIS is usually a diagnosis of exclusion after clinicians have treated multiple conditions that may be thought to be responsible for worsening the patient's condition.

Management and prevention of IRIS: Optimization of treatment of the underlying OI in order to quickly reduce pathogen load. It is recommended that ART should not be interrupted except in severe, life-threatening cases of CNS IRIS as there is a risk of further OIs and the emergence of ART resistance.

In the absence of contraindications, use of corticosteroids, for more severe forms of mycobacterial and fungal-associated IRIS (but not for viral-associated IRIS) may be beneficial.

IRIS may be prevented by optimal prophylaxis of OI in advanced HIV (e.g., co-trimoxazole to prevent *PCP*) and optimal screening and appropriate treatment for subclinical or clinical OI (e.g., TB screen prior to ART initiation)

Further reading

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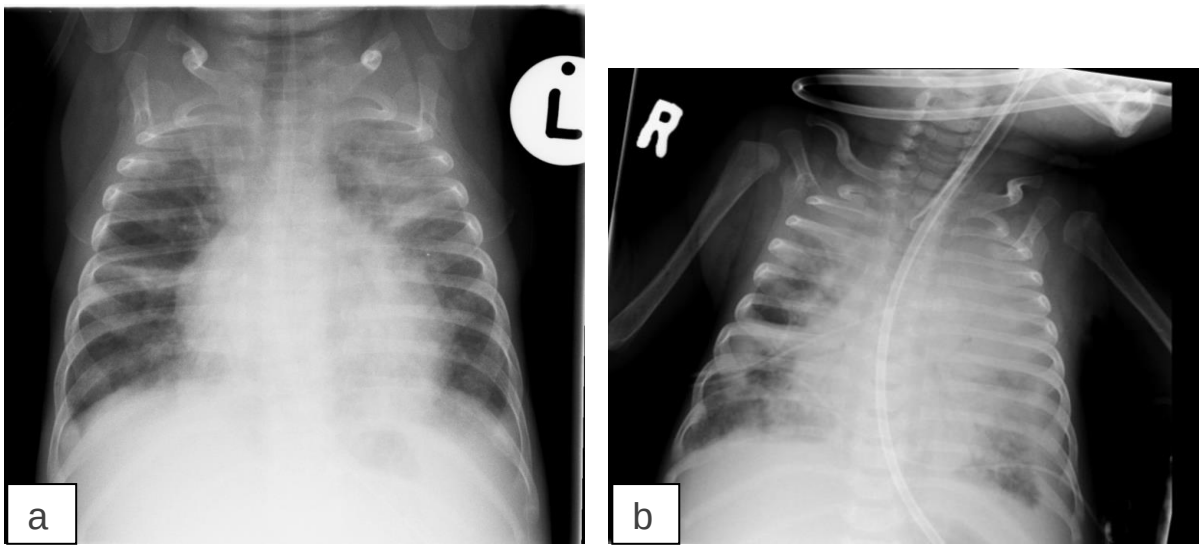

Figure 166a and b: (a) CXR taken pre-ART in a 4 month old child newly diagnosed with HIV infection. Xray shows: Multifocal airspace disease involving both upper lobes, right middle lobe, left lingular and left lower lobe. (b) CXR, 5 weeks post-ART initiation in the same child as above. He had been readmitted for worsening respiratory distress.

X-ray shows: Progressive air space disease with new more confluent left lower lobe, right lower lobe and right upper lobe consolidation plus a large pleural effusion with dense opacification of the left upper lobe as before.

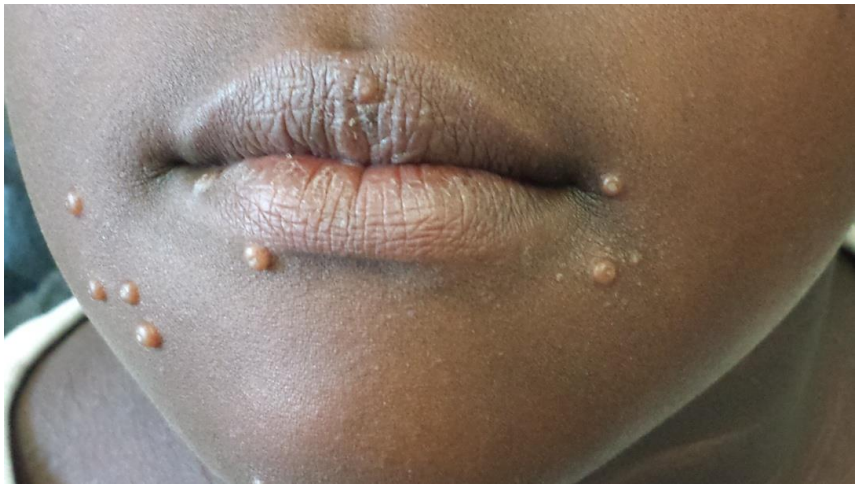

Figure 167: Molluscum contagiosum following antiretroviral therapy.