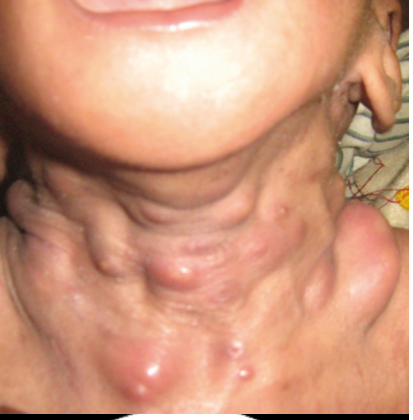
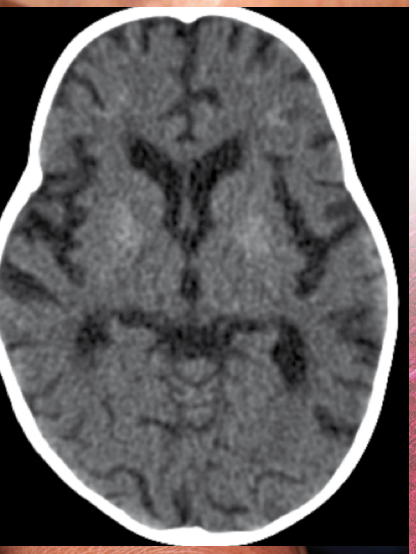
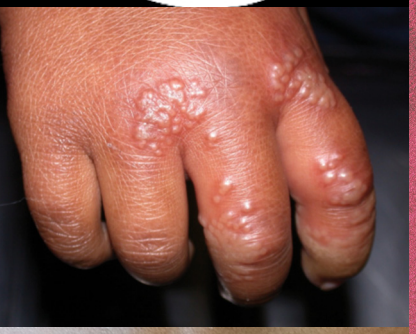
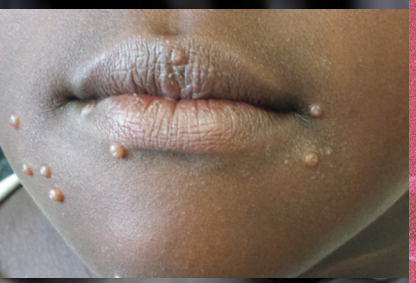
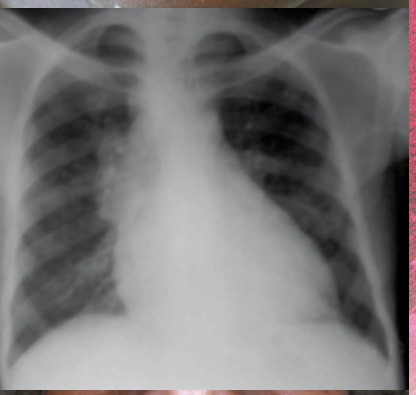
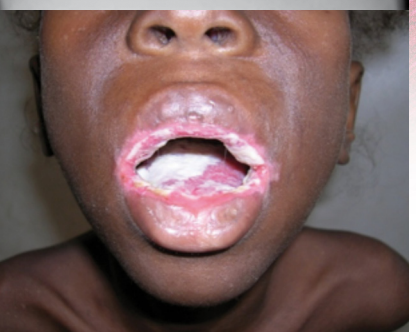

ATLAS OF PAEDIATRIC HIV INFECTION:

An illustrated guide for health care professionals

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Preface

Sub-Saharan Africa bears the greatest burden of paediatric HIV disease. This atlas is the first of its kind with photographs of varying skin, systemic conditions and opportunistic infections in the HIV-infected paediatric patient. The aim of the atlas is to illustrate conditions which were captured among paediatric patients presenting to HIV clinics and wards in an African setting. Some of the conditions are commonly seen in HIV-infected children while some are not specific to HIV.

The atlas is presented in two parts. The first part of the atlas illustrates and discusses dermatological conditions and the second part non-dermatological diseases in paediatric HIV infection. Paediatric HIV in general and HIV-associated paediatric dermatology in particular, is a grey area for many health care workers.

There is a saying that "One picture is worth a thousand words". Most published material on HIV focuses on adults and often has limited information on paediatric HIV and is deficient of pictures for illustration. We hope that this atlas with its illustrations will facilitate recognition and management of skin and non-skin conditions seen in HIV-infected children. To enrich the atlas' appeal, in most instances, photographs are featured to cover the variation in clinical spectrum and severity of the different conditions. It is essential to diagnose both skin and non-skin lesions appropriately as the skin may also be a window into systemic disease. Therefore, early recognition can often save lives. Some skin diseases are life threatening, others are disfiguring and stigmatising while others cause pronounced discomfort for HIV-infected children.

The atlas is intended for use by medical students, doctors and other healthcare professionals at different levels, either in the private sector, public institutions or university setting. Clinical features, diagnostic and treatment modalities are briefly highlighted, based on published literature and the authors' expertise. A list of references for further reading has also been included on each subject matter.

Regina Oladokun & Rannakoe J Lehloenya

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Acronyms and abbreviations

ABC	Abacavir
AIDS	Acquired immune deficiency syndrome
ART	Antiretroviral therapy
ARVs	Antiretrovirals
AZT	Zidovudine
BCG	Bacille Calmette Guerin
CDC	Centers for Disease Control and Prevention
CMV	Cytomegalovirus
CNS	Central Nervous System
CT	Computed Tomography
CXR	Chest X-ray
d4T	Stavudine
E	Ethambutol
EFV	Efavirenz
FNAC	Fine needle aspiration cytology
GI	Gastrointestinal
H	Isoniazid
HIV	Human immunodeficiency virus
OFC	Occipitofrontal Circumference
OI	Opportunistic infection
INH	Isoniazid
IRIS	Immune reconstitution inflammatory syndrome
IV	Intravenous
KS	Kaposi sarcoma
LIP	Lymphoid intestinal pneumonitis
LPV/r	Lopinavir/ritonavir
MDR-TB	Multidrug resistant tuberculosis
MAC	Mycobacterium Avium Complex

MRI	Magnetic Resonance Imaging
MTB	Mycobacterium tuberculosis
MUAC	mid upper arm circumference
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
PCP	Pneumocystis pneumonia
PCR	Polymerase chain reaction
PI	Protease inhibitor
PO	Per oral
PMTCT	Prevention of mother to child transmission (of HIV)
PTB	Pulmonary Tuberculosis
PZA	Pyrazinamide
R	Rifampicin
RIF	Rifampicin
RTUF	Ready to use foods
SAM	Severe acute malnutrition
TB	Tuberculosis
TBM	Tuberculous Meningitis
WHO	World Health Organisation
Z	Pyrazinamide

PART I: PAEDIATRIC HIV DERMATOSES

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Introduction

Human immune deficiency virus (HIV) infection can affect multiple organs, including the skin. The skin is the largest and most visible organ in the body. Skin manifestations (dermatoses) of HIV infection are variable and many HIV-associated skin conditions are often more severe and associated with worse morbidity than in HIV uninfected persons.

Infections due to fungi, bacteria and viruses, as well as infestations are either more common or more severe in this population. These infections and infestations also tend to have atypical presentations, are usually more recurrent and less responsive to conventional therapy compared to healthy children. Some malignancies, particularly haematological, inflammatory and drug-associated dermatoses are also more common. Cutaneous manifestations of nutritional deficiencies are also commonly seen in HIV-infected children.

A correlation between skin disease and underlying immune suppression has been reported in several studies, making the diagnosis of skin disease a valuable tool in the prediction of HIV infection and staging thereof.

With the increasingly early use of antiretroviral therapy (ART), there has been a decline in the incidence and prevalence of HIV-associated skin disease.

The skin is an active immune organ and contains antigen presenting cells like Langerhans and dermal dendritic cells, as well as other cells and cytokines that are involved in both the innate and acquired immunity. In AIDS, the antigen presenting cells, many of which are CD4+, are depleted together with CD4+ T cells, natural killer cells, macrophages and monocytes. These cells are usually the first line of defence, as the skin is exposed to a wide variety of pathogens and in the deficiency of this first line of defence, antigen presentation, granuloma formation and cytotoxic capabilities in the skin are markedly impaired. This results in diminished control of infections and impaired inflammatory responses. Poor control of viral infections can also be associated with uncontrolled cell replication and increased potential for malignant transformation.

The impairment of the cutaneous immune responses, which may be present early in the course of HIV-1 disease, is believed to be responsible for the high incidence of both infectious and non-infectious dermatoses, even before the development of full immunodeficiency. Fifty to eighty per cent of ART naïve children are reported to have at least one skin manifestation of HIV, prevalence being highest in those with severe immunosuppression.

Further reading

1. Calles NR, Evans D, Terlonge D. Pathophysiology of the human immunodeficiency virus. In: Baylor International Pediatric AIDS Initiative. HIV curriculum for the health professional. Baylor College of Medicine, Houston; 2006: 11-22.
2. Carvalho VO, Marinoni LP, Martins LTF et al. Dermatologic alterations in children with AIDS and their relation to clinical-immunological categories and viral load. Ann Bra Dermatol. 2003; 78:6.
3. Wananukul S, Thisyakorn U. Mucocutaneous manifestations of HIV infection in 91 children born to HIV- Seropositive women. Ped Dermatol 1999; 16(5): 359-363.
4. Katibi OS, Ogunbiyi AO, Oladokun RE et al. Mucocutaneous Disorders of Pediatric HIV in South West Nigeria: Surrogates for Immunologic and Virologic Indices. J Int Assoc Provid AIDS Care. DOI: 10.1177/2325957413502540
5. Wayne Grayson. Paediatric HIV-related skin diseases. Diagnostic Histopathology 2005; 15(5): 225-231.

CHAPTER 1: BACTERIAL INFECTIONS

Staphylococcal Infections

A high percentage of HIV-infected persons are nasal carriers of *Staphylococcus aureus*, hence the high rate of infection in this population.

Impetigo

Description: Impetigo is a superficial bacterial skin infection characterised by flaccid pustules and honey-coloured crust. It usually begins as a small painful erythematous papule.

Aetiology: The most common implicated organism is *Staphylococcus aureus*, although group A beta-hemolytic streptococcus (*Streptococcus pyogenes*) has been implicated in some cases.

Clinical presentation: Impetigo can be bullous and non-bullous, usually on the face and extremities. Primary impetigo presents as erythematous plaques with or without thin-walled vesicles that break down leaving characteristic yellow crust. Secondary impetigo can occur in other dermatoses e.g. eczema.

Epidemiology: Impetigo is common in children especially those aged 2-5 years and prevalence of 15 - 25% has been reported in the tropics. It is transmitted by contact with infected skin.

Diagnosis: Diagnosis is usually clinical but a Gram stain and culture may be required to confirm diagnosis when there is extensive disease.

Treatment: This should be guided by local antibiotics sensitivity testing but in mild and localized infection, first-line topical antibiotics like mupirocin, bacitracin or fusidic acid for 7-10 days are effective. If the infection is widespread, severe or is associated with lymphadenopathy, oral penicillins (flucloxacillin) or macrolides (erythromycin) if patient is allergic to penicillins, are indicated for 7-10 days. Parenteral antibiotics may be required if impetigo is diagnosed in a very sick child.

Complications: Cellulitis, osteomyelitis, staphylococcal scalded skin syndrome, and acute post-streptococcal glomerulonephritis can occur.

Prevention: Regular care of healthy skin and minimal skin contact with an infected child reduces the risk of transmission. Prompt diagnosis and treatment will prevent complications. In settings where impetigo is endemic among children, measures to reduce the transmission frequency should be adopted, including encouraging regular hand washing, educating the population on health matters and instituting treatment early in the course of the disease.

Further reading

1. Bangert S, Levy M, Hebert AA. Bacterial resistance and impetigo treatment trends: a review. Pediatr Dermatol. 2012; 29 (3):243-8.
2. Cole C, Gazewood J. Diagnosis and treatment of impetigo. Am Fam Physician 2007; 15: 75.
3. Steer AC, Jenney AW, Kado J et al. High burden of impetigo and scabies in a tropical country. PLoS Negl Trop Dis. 2009;3 (6):e467.
4. Odueko OM, Onayemi O, Oyedeji GA. A prevalence survey of skin diseases in Nigerian children. Niger J Med. 2001; 10 (2):64-7.
5. Kyriakos P. Kiriakis, Aline Tadros et al. Case detection rates of impetigo by gender and age. Le Infezioni in Medicina, n. 2, 105-107, 2012.

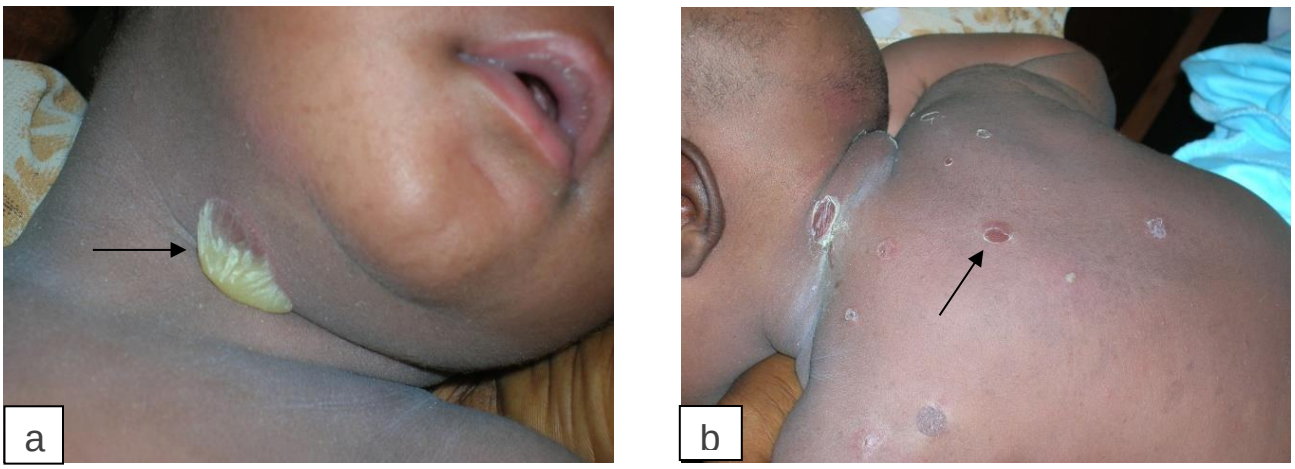


Figure 1 a and b: Bullous impetigo in a 2-month-old HIV-exposed infant. Note the flaccid pustule (left) and the older ruptured lesions (right).

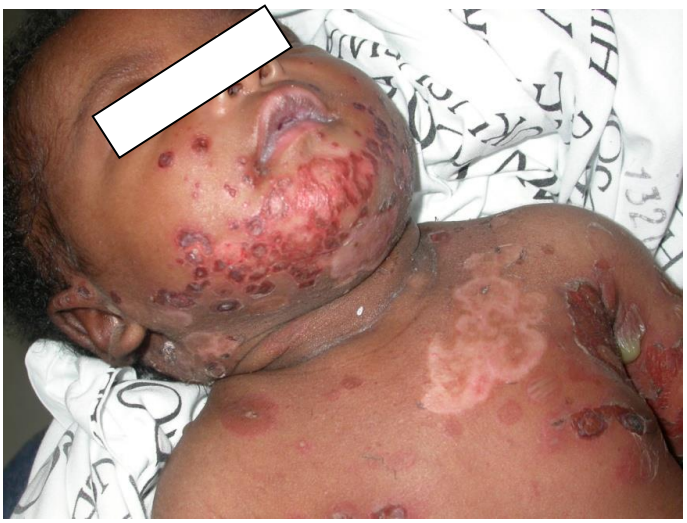


Figure 2: Bullous impetigo in a 3-month-old child. Note the lesion in different stages of evolution ranging from intact blisters, ruptured blisters and post-inflammatory hypopigmentation of healed lesions

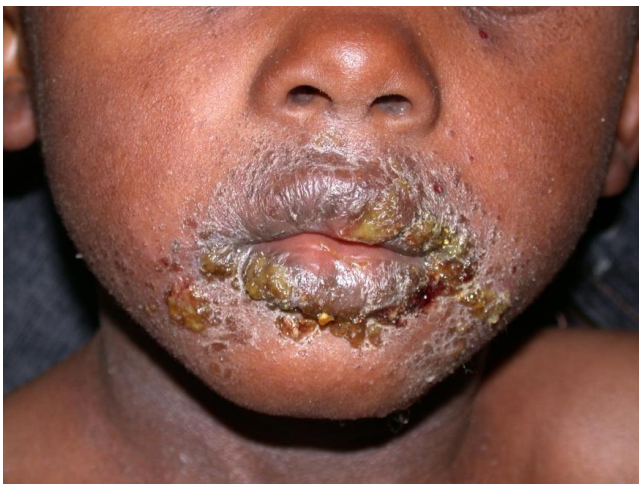


Figure 3: A child with secondarily impetiginised atopic eczema periorally.

Folliculitis

Description: Folliculitis is the inflammation of the hair follicle. It can be caused by physical injury, chemical irritation or an infection.

Aetiology: *Staphylococcus aureus* is the most frequent cause of infective folliculitis but folliculitis can also be caused by pathogenic fungi *e.g. Candida albicans*, commensal fungi such as *Malassezia furfur* and mites such as *Demodex* species. These are most often seen on the face in immunosuppressed children.

Clinical presentation: The presentation may be in the form of itchy, painless or painful papules, dome-shaped pustules (with hair shaft at the centre) often with an erythematous base. Folliculitis has predilection for the scalp, extremities, occluded areas and areas prone to excessive moisture and chafing. Systemic symptoms are not common.

Epidemiology: It is a common bacterial skin infection in childhood.

Diagnosis: It is a clinical diagnosis, but Gram stain and culture of pus may be required to confirm diagnosis.

Prevention: Prompt diagnosis and treatment reduces spread of the disease. Regular care of healthy skin reduces infection rates will prevent complications. Treatment of *Staphylococcus* carriers, particularly caregivers of affected children is important in reducing transmission and recurrence. Those who participate in sports should shower regularly and not share personal clothing.

Treatment: Mild staphylococcal folliculitis is often self-limiting, or may respond to cleansing or topical antiseptics. In more severe cases, antibiotics, topical or systemic, may be required. Topical mupirocin may suffice for mild infection. For deep-seated infection, oral antibiotics should include coverage for S. aureus, such as penicillinase-resistant penicillins e.g. flucloxacillin or macrolides – e.g. erythromycin. First-generation cephalosporins such as cephalexin may also be used.

If the infection is persistent or recurrent, the usual sites of staphylococcal carriage should be sought in the patient, contacts or caregivers and anti-staphylococcal measures initiated. Application of ½ strength hibitane cream or mupirocin cream to nostrils twice daily for 5 days is indicated. This has to be repeated monthly as re-colonization is common.

Complications: These include furuncles, carbuncles, septicaemia and osteomyelitis all of which may be recurrent.

Further reading

1. Stulberg DL, Penrod MA, Blatny RA. Common bacterial skin infections. Am Fam Physician. 2002 ;66 (1):119-24.

2. Hedrick J. Acute bacterial skin infections in pediatric medicine. Current issues in presentation and treatment. Pediatr Drugs 2003; 5 1: 35-46.

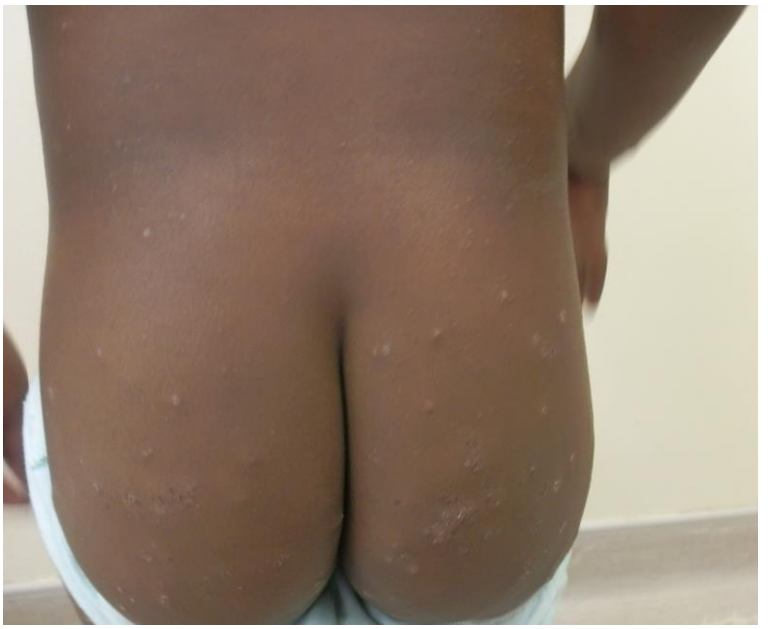


Figure 4: Folliculitis in a child. Note multiple papules and pustules on the buttocks, trunk and thighs.

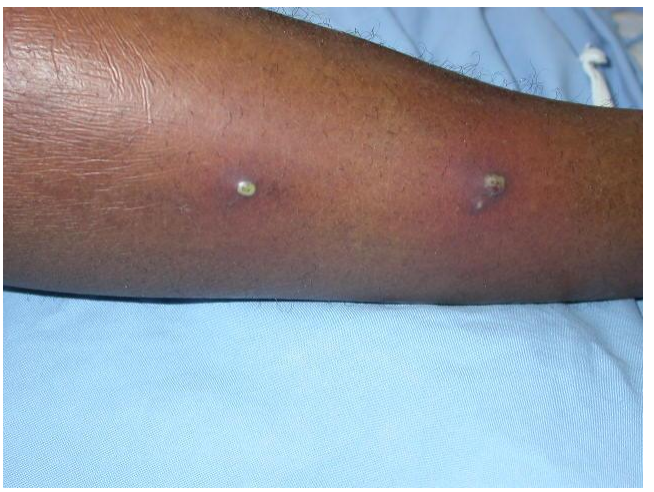


Figure 5: Folliculitis on the leg. Note the pustules and surrounding erythema. Folliculitis is often a precursor to furuncles and carbuncles.

Furunculosis

Description: Furunculosis (boil or abscess) is inflammation of the hair follicle with small abscess formation extending through the dermis into the subcutaneous layers. When furuncles aggregate to form broad, swollen, erythematous, deep, and painful masses that usually open and drain through multiple tracts they are called carbuncles.

Aetiology: Furunculosis is suppurative sequelae of a folliculitis. *Staphylococcus aureus* is the primary aetiological agent.

Clinical presentation: A furuncle appears as a red tender, firm, erythematous, often fluctuant nodule on hair-bearing parts of the body, with central purulence that may spontaneously drain. They are most often seen on the neck, face, buttocks, axillae, and groin.

Epidemiology: It is transmitted by contact with infected skin and other fomites. It is often spread to other family members. Predisposing factors include poor hygiene, overcrowding, immunodeficiency and malnutrition.

Diagnosis: Clinical but Gram stain and culture of pus may be required to confirm diagnosis.

Prevention: Family hygiene including regular hand washing, fomite cleaning, and avoiding contact with contaminated skin. In recurrent cases effort should be made to exclude diabetes and other causes of immunosuppression. Nasal and perineal carriage of *Staphylococcus aureus* in the patient and other household members should be sought and treated.

Treatment: May resolve spontaneously, but surgical drainage of pus is mainstay of therapy. If surrounding cellulitis or systemically unwell, cloxacillin IV 25 – 50 mg/Kg/dose 6 hourly or flucloxacillin PO may be indicated. Treatment of recurrent furunculosis involves therapeutic triad of antibiotics, decolonisation and decontamination.

Complications: These include carbuncles, septicaemia, osteomyelitis and scarring.

Further reading

1. Weinke T, Scherer W, Rohde I, et al. Increased carriage rate of Staphylococcus aureus among HIV patients [poster]. Presented at the VI International Conference on AIDS. San Francisco, 1990; Th.B.529.transparent image.
2. Berger TG, Jacobson MA, Becker B, et al. Nasal carriage rate of Staphylococcus aureus (SA) in AIDS and ARC patients [abstract]. In: 29th Interscience Conference on Antimicrobial Agents and Chemotherapy. Houston, 1989.
3. Stulberg DL, Penrod MA, Blatny RA. Common bacterial skin infections. Am Fam Physician. 2002; 66 (1):119-24.

4. Atanaskova N, Tomecki KJ. Innovative management of recurrent furunculosis. Dermatologic Clinics 2010; 28 (3): 479-486.
5. Hedrick J. Acute bacterial skin infections in pediatric medicine. Current issues in presentation and treatment. Pediatr Drugs 2003; 5 1: 35-46.

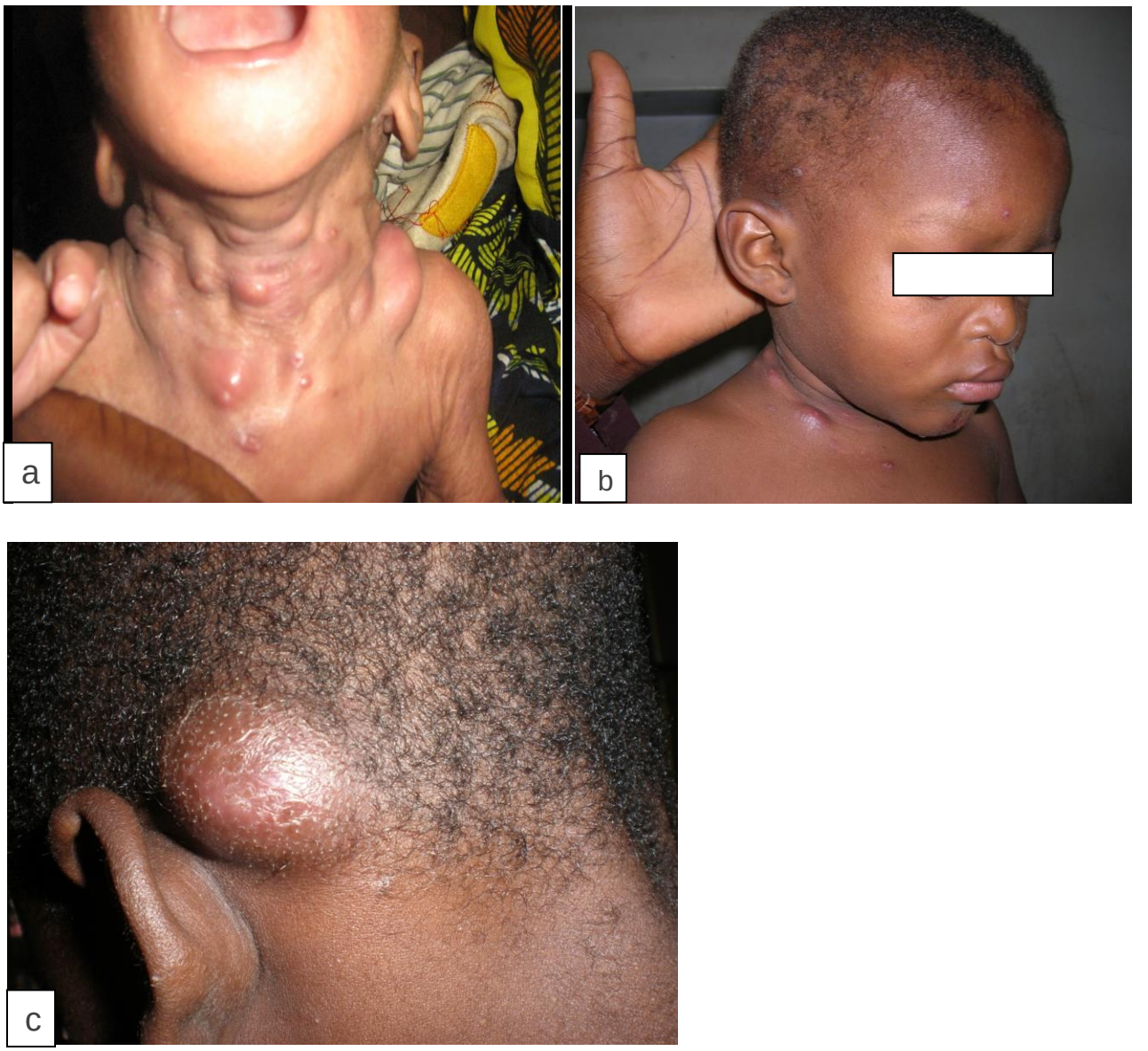


Figure 6a, b and c: Pictures showing a combination of furuncles and carbuncles in immunosuppressed children, multiple fluctuant erythrematous nodules, on neck (a), face and scalp (b), postauricular (c).

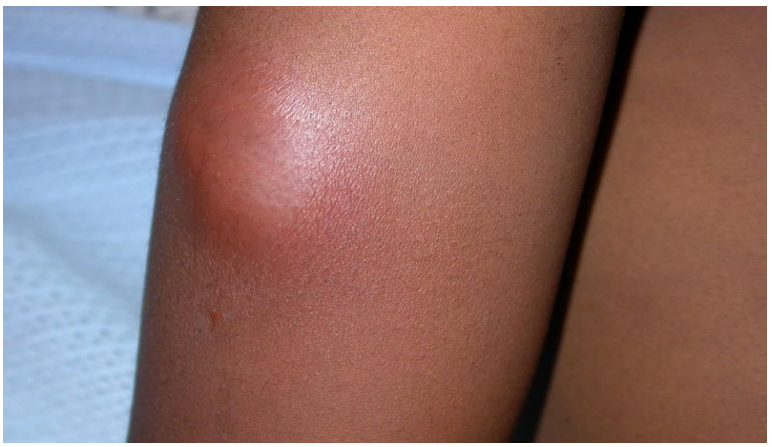


Figure 7: Another picture of a carbuncle presenting as a red nodular swelling on the upper arm.

Necrotising Fasciitis (NF)

Definition: An acute bacterial infection (also known as "flesh eating bacteria") that is characterized by necrosis of the deep fascia and subcutaneous tissues. It is a progressive and rapidly spreading infection in the deep tissue planes.

Aetiology: NF can be classified as polymicrobial (type I) or monomicrobial (type II), type I being more common. Type I NF is caused mainly by a combination of Group A *Streptococcus* (most common), *Klebsiella*, *Clostridium*, *E. coli*, *Staphylococcus aureus,* and *Aeromonas hydrophila.*

Clinical presentation: Pain, swelling and redness at the site of infection, followed by frank necrosis within days or weeks. Constitutional symptoms and signs such as fever, tachycardia and tachypnoea may be present. Presence of crepitus indicates gas produced by aerobic and anaerobic organisms is considered diagnostic of NF, but together with haemorrhagic bullae, skin necrosis, crepitus, sensory and motor deficits, it is a late sign of NF.

Epidemiology: Most common in immunocompromised hosts such as patients with HIV infection and diabetics.

Diagnosis: NF is a clinical diagnosis and Gram stain, blood and tissue cultures aid management.

Treatment: Surgical debridement, fasciotomy and broad spectrum intravenous antibiotics are the mainstay of treatment. Initial antibiotic treatment could include penicillin G and an aminoglycoside. Clindamycin may be added to cover streptococci, staphylococci, gram-negative bacilli, and anaerobes. Antibiotics are adjusted with culture results.

Complications: NF has a high mortality and other complications include necrotizing myositis, septic shock and multiple organ failure.

Further reading

1. Fazeli MS, Keramati MR. Necrotizing fasciitis: an epidemiologic study of 102 cases. Indian J Surg 2007; 69(4): 136–139.
2. Rausch J, Foca M. Necrotizing fasciitis in a pediatric patient caused by Lancefield Group G Streptococcus: Case report and brief review of the literature. Case Report Med. 2011; 67:1365.
3. CDC. Necrotizing fasciitis: A rare disease, especially for the healthy. 2012. Available from: http://www.cdc.gov/features/NecrotizingFasciitis/.

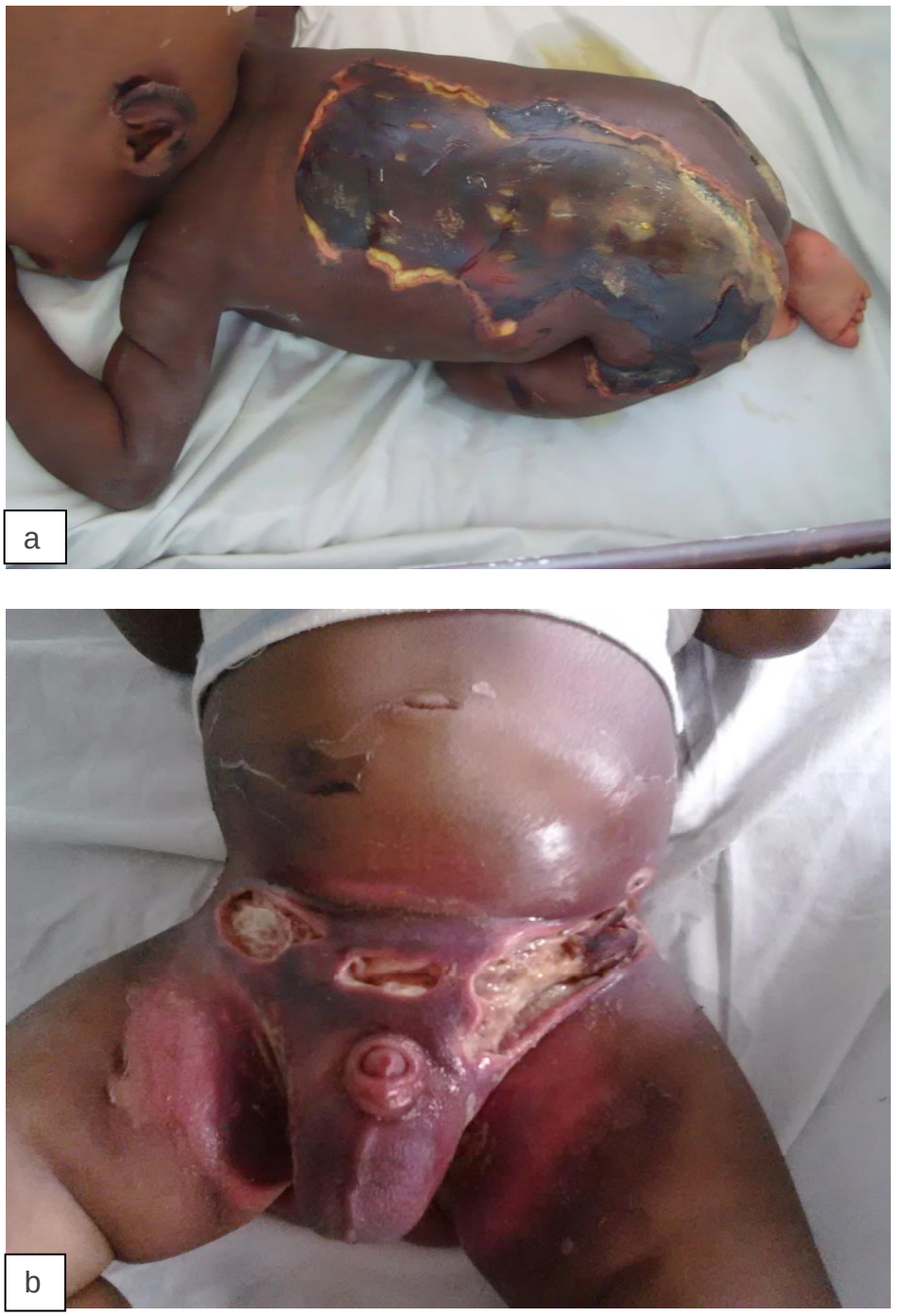


Figure 8a and b: Necrotizing fasciitis

Ecthyma Gangrenosum

Definition: Ecthyma gangrenosum is a cutaneous infection usually caused by *Pseudomonas aeruginosa.*

Aetiology: It is usually a manifestation of bacterial systemic infection with *P. aeruginosa* in immunosuppressed persons, including those with AIDS, diabetes mellitus and neutropenia.

Clinical presentation: Characteristically presents as tender pustules or haemorrhagic blisters with an erythematous edge that progress to form a central black eschar and ulcerate.

Epidemiology: Ecthyma gangrenosum is rare.

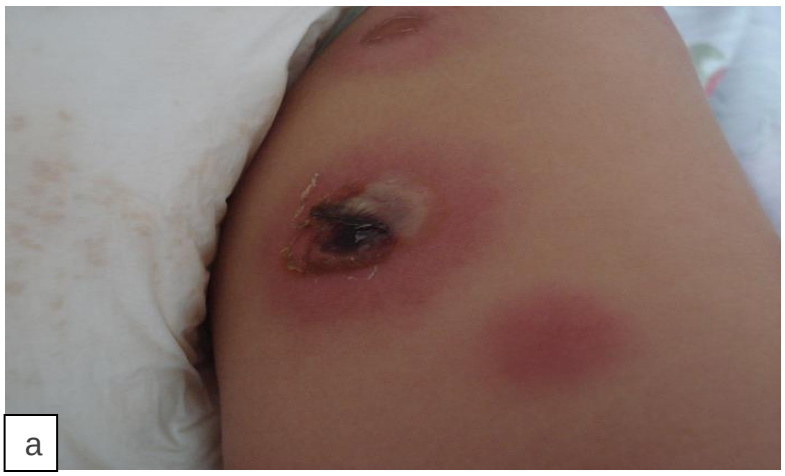
Diagnosis: Ecthyma gangrenosum is a clinical diagnosis and suspicion of the disease warrants a prompt tissue and blood cultures.

Prevention: Maintenance of personal hygiene and care of open wounds in immunosuppressed persons.

Treatment: On clinical suspicion, broad-spectrum empiric antibiotic therapy to include anti-pseudomonal coverage should be initiated. Options include aminoglycosides, fluoroquinolones e.g. ciprofloxacin or third-generation cephalosporins e.g. ceftazidime/ceftriazone. If the lesions fail to respond to antibiotics, surgical debridement may be required.

Further reading

1. Weiel JJ, Zhang AC, Smith JA et al. Clinicopathologic aspects of Ecthyma Gangrenosum in paediatric patients: A case series and review of the literature. J Clin Anat Pathol 2013; 1: 1-5
2. Fink M, Conrad D, Matthews M et al. Primary ecthyma gangrenosum as a presenting sign of leukaemia in a child. Dermatol Online J. 2012; 18(3):3.



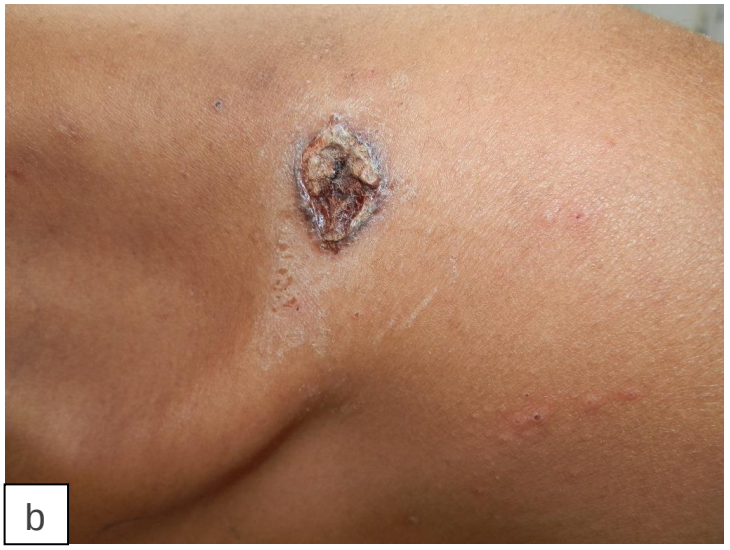


Figure 9a and b: Necrotic ulcers in ecthyma gangrenosum with an erythematous rim in (a) Differential diagnosis includes other lesions presenting with a black necrotic centre (eschar) – cutaneous anthrax, cutaneous aspergillosis, rickettsia and cutaneous leishmaniasis

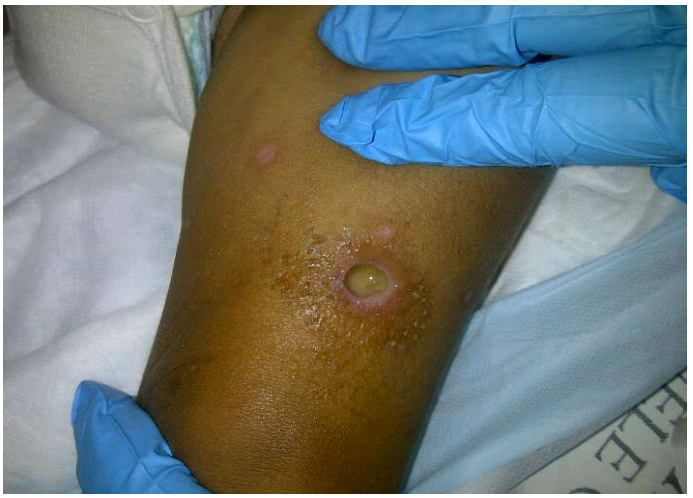


Figure 10: Ecthyma gangrenosum: showing a lesion at a late stage of evolution.

Table 1: Treatment options: Bacterial Infections

Bacterial Infections	**1st line therapy**		**Alternative therapy**
Impetigo	Topical therapy	Mupirocin	Fusidic acid
	Systematic antibiotics	Flucloxacillin, IV cloxacillin	Macrolides e.g. Erythromycin
Folliculitis	Topical therapy	Mupirocin	Macrolides
	Systematic antibiotics	Flucloxacillin	Erythromycin, Cephalexin
Furunculosis	As for folliculitis		
Necrotising Fasciiitis	IV penicillin G, gentamycin and clindamycin	Fasciotomy as required	
Ecthyma gangrenosum	Ciprofloxacin, ceftazidime		

Cutaneous Tuberculosis (TB)

Definition: This refers to either invasion of the skin and mucous membranes with *Mycobacterium tuberculosis* or a hypersensitivity reaction to the organism.

Aetiology: *M. tuberculosis* can infect the skin and the route of infection and immune status of the person influences clinical presentation. Tuberculids and erythema induratum are hypersensitivity reactions usually seen in people with good immunity.

Clinical Presentations

- Tuberculids – typical lesions are small, erythematous papules that become pustules and undergo central ulceration and heal spontaneously within weeks, leaving a varioliform scar. The lesions develop symmetrically over the extensor surfaces, particularly the knees, the elbows, and the dorsum of the hands and the feet, although widespread involvement may be present.
- Tuberculids are thought to be an exaggerated host immunologic response to the mycobacteria or its antigens in the blood stream. As many as 40% of the patients may have accompanying active TB.
- Scrofuloderma – refers to direct extension of TB from underlying lymph nodes, bones or joints into the skin. Usually seen as firm painless nodule and ulcerate and heal with scarring.
- Lupus vulgaris – chronic progressive direct infection of the skin presenting as reddish-brown plaques with a jelly-like consistency.
- TB verrucosa cutis – results from direct inoculation of TB into the skin of a person who was previously infected with the bacteria. Presents as brownish-red wart-like growths.
- BCGitis – presents often as fever and regional lymphadenopathy sometimes becoming suppurative. However, in immunosuppressed persons, systemic dissemination of the attenuated *Mycobacterium bovis* vaccine can occur.
- Cutaneous TB immune reconstitution inflammatory syndrome – on initiation of antiretroviral therapy in HIV-infected persons, there may be a paradoxical worsening of any of the above-mentioned clinical presentations of cutaneous TB.
- Miliary TB – widespread seeding of *Mycobacterium* tuberculosis into internal organs and the skin via haematogenous spread. Miliary TB is so named because of a millet-like appearance of the TB bacilli in the lung, as seen on a chest x-ray. On the skin miliary TB most often presents as vesiculopapules, the size of a pinhead that become necrotic.

Epidemiology: Cutaneous TB is rare.

Diagnosis: Cutaneous TB is confirmed by a skin biopsy that shows characteristic features and a tissue culture.

Prevention: Vaccination, early detection, treatment and completion of the course are the mainstays of disease transmission in general. However, the risk of transmission in cutaneous TB is minimal.

Treatment: Six months standard intensive treatment with rifampicin, isoniazid, pyrazinamide and ethambutol for 2 months followed by the continuation phase with rifampicin and isoniazid is effective for cutaneous TB. However, in instances of severe or complicated disease it may be extended to nine months.

Complications: Miliary TB has a high mortality, scrofuloderma may be associated with severe scarring and contractures and lupus vulgaris may result in squamous cell carcinomas.

Further reading

1. Barbagallo J, Tager P, Ingleton R al. Cutaneous tuberculosis: diagnosis and treatment. Am J Clin Dermatol. 2002;3(5):319-28.
2. Rezai MS, Khotaei G, Mamishi S et al. Disseminated Bacillus Calmette-Guerin infection after BCG vaccination J Trop Pediatr. 2008 Dec; 54(6):413-6.
3. Jordaan HF, Schneider JW, Schaaf HS et al. Papulonecrotic tuberculid in children. A report of eight patients. Am J Dermatopathol. 1996 18(2):172-85.
4. Jordaan HF, Schneider JW, Abdulla EA. Nodular tuberculid: a report of four patients. Pediatr Dermatol. 2000; 17(3):183-8.
5. Puri N. A clinical and histopathological profile of patients with cutaneous tuberculosis. Indian J Dermatol. 2011;56(5):550-2.

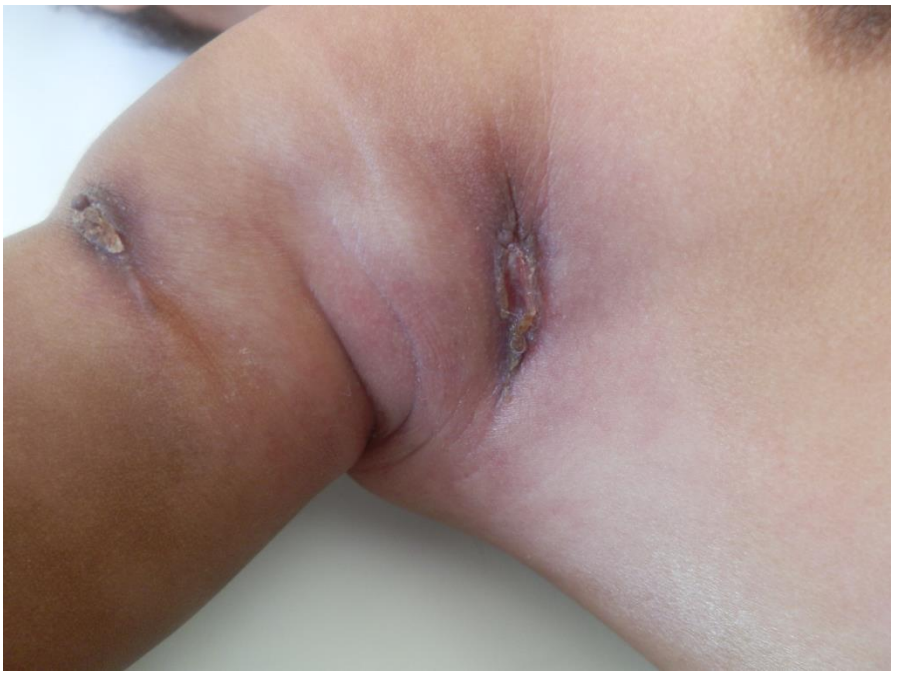


Figure 11: Scrofuloderma: Ulceration in the axilla and arm of an HIV-infected child with tuberculosis.

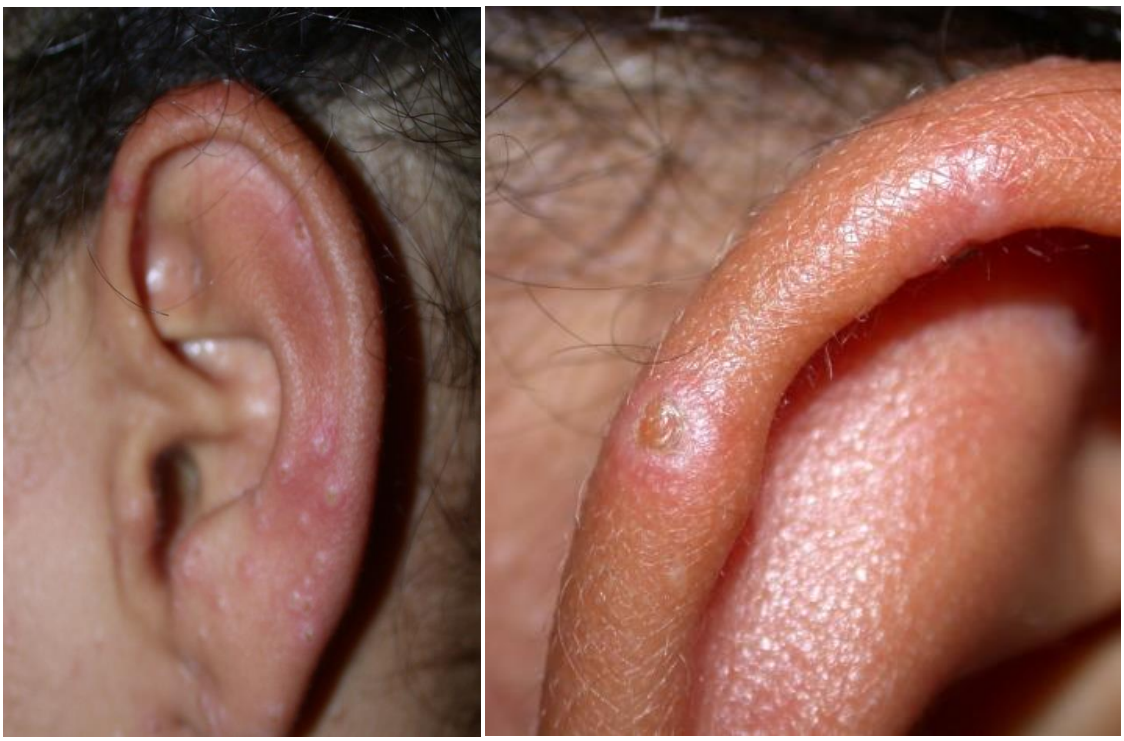


Figure 12: Papulonecrotic tuberculids on the ear of a child. Note the papules with central necrosis.

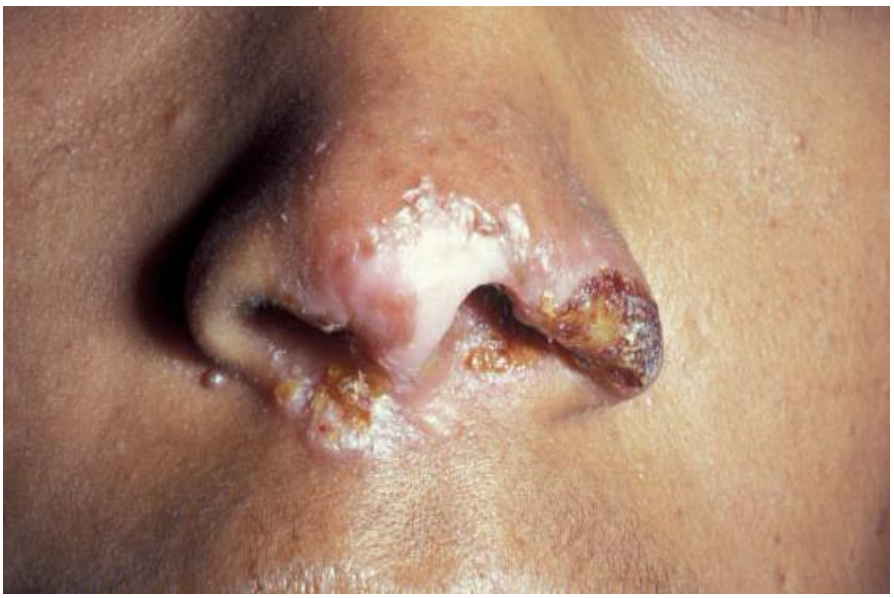


Figure 13: Lupus vulgaris on the nose of a patient with tuberculosis.

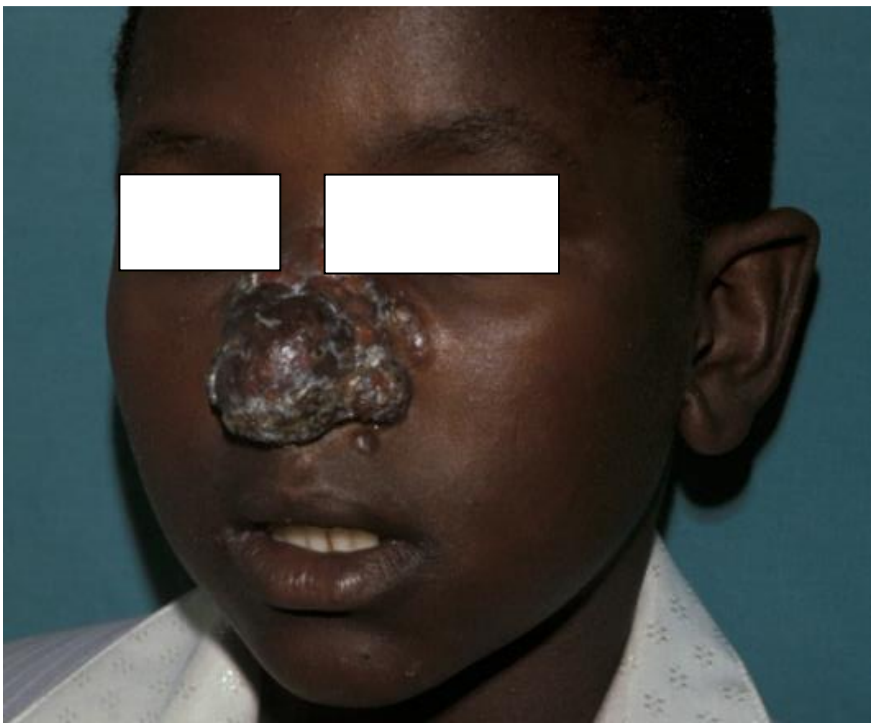


Figure 14: Large plaque and satellite nodules on the nose of a child with lupus vulgaris.

CHAPTER 2: VIRAL SKIN INFECTIONS

Herpes Simplex

Description: Herpes simplex viral (HSV) is a common, chronic or recurrent infection in the paediatric HIV population. The clinical presentation of HSV in HIV-infected patients is often atypical and standard therapy often ineffective. HSV infection should be suspected in any chronic vesicular or mucocutaneous ulceration disease and Tzank smear should be performed.

HSV usually affects both the buccal and genital mucosae, but in HIV can affect the skin.

Aetiology: Herpes simplex (HSV) type 1 causes oral lesions while type 2 affects genitalia. An infected mother can transmit the virus to her unborn child through exposure to infected maternal genital fluids.

Clinical presentation: HSV presents as orolabial painful blisters and/or punched out ulcers, which may be associated with fever, irritability and lymphadenopathy. In HIV, the ulcers are chronic and non-healing with rolled edges. A high index of suspicion is needed to make the diagnosis.

In neonates and immune-compromised individuals, it may present as disseminated disease and in this setting encephalitis is not uncommon.

Epidemiology: In any population and age group, HSV-1 is more common than HSV-2 and the prevalence of HSV-1 in non–high-risk populations increases in a linear fashion with age, with most initial infections occurring in childhood and adolescence. HSV-1 prevalence is > 40% in 15 year olds, before increasing to 60%–90% in adulthood. HSV-2 is prevalence is strongly associated with age, increasing from negligible levels in children < 12 years to as high as 80% amongst older higher risk populations.

Diagnosis: In uncomplicated cases, the diagnosis is mainly clinical, but a Tzanck smear, viral culture, PCR technique is helpful in atypical cases including CSF PCR or culture in suspected encephalitis.

Prevention: HSV is transmitted most commonly during delivery, but also can be transmitted in utero or through postnatal contact with the mother or other caretakers. Prevention is therefore crucial, some specialists recommend prophylactic acyclovir therapy, some recommend routine caesarean section and others recommend both. However, for those who have a history of recurrent genital HSV, a recent review of best evidence found insufficient data to support the use of prophylactic acyclovir. Contact with infected vesicles should be avoided.

Treatment: The drug of choice for treating localised HSV infection in infants and children is acyclovir. The recommended dose is 20 mg/kg/day in five divided doses Xu-10 days. Usually if the child <2 years: acyclovir 100 mg 5 times a day for 10 days or 200 mg three times a day for 10 days.

If child >2 years: acyclovir 200mg 5 times a day for 10 days or 400 mg three times a day for 10 days. In case of acyclovir resistance or where available: Foscarnet 120-200 mg in two to three divided doses can be used.

Although commonly prescribed by many physicians, topical antiviral medications such as acyclovir ointment are not recommended to treat most mucocutaneous HSV lesions because such therapy does not reduce the severity or duration of infections in immunocompetent hosts. Topical therapy can be used in immunocompromised patients to accelerate the healing of lesions.

Complications: Dissemination, concomitant infection with other pathogens including viruses, such as CMV, yeasts infection (Candida) or secondary bacteria may occur. Potential risk of developing HPV associated epithelial neoplasia exists.

Further reading

1. Mofenson LM, Brady MT, Danner SP et al. Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. MMWR Recomm Rep. 2009; 58(RR-11):1–248.
2. Smith KJ, Skelton HG III, Angritt. Histopathologic features of HIV associated skin disease. Dermatol Clin 1991; 9:551-8.
3. Weis H. Epidemiology of herpes simplex infection type 2 infection in the developing world. Herpes 2004; 11 Suppl 1: 24A-25A.
4. Chayavichitsilp P, Buckwalter JV, Krakowski AC et al. Herpes Simplex. Pediatrics in Review 30 (4), 2009: 119 -130 (doi: 10.1542/pir.30-4-119).
5. Workowski K, Berman S. Centers for Disease Control and Prevention. Diseases characterized by genital ulcers. Sexually transmitted diseases treatment guidelines 2006. MMWR Morbid Mortal Wkly Rep. 2006; 55RR-11):14–30.
6. Hollier L, Wendel G. Third trimester antiviral prophylaxis for preventing maternal genital herpes simplex virus (HSV) recurrences and neonatal infection. Cochrane Database Syst Rev. 2008;1: CD004946.

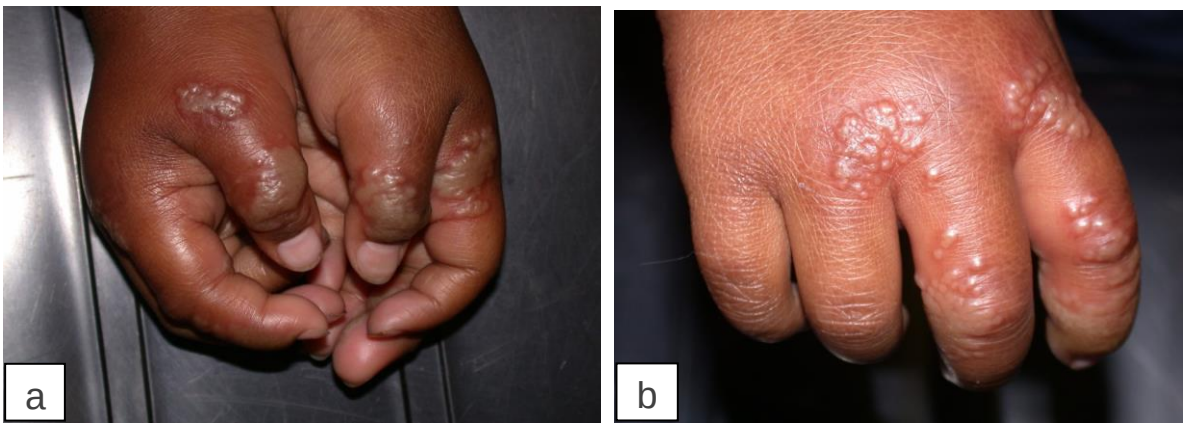


Figure 15a and b: Multiple grouped vesicles on the hand of a child with herpes simplex infection.

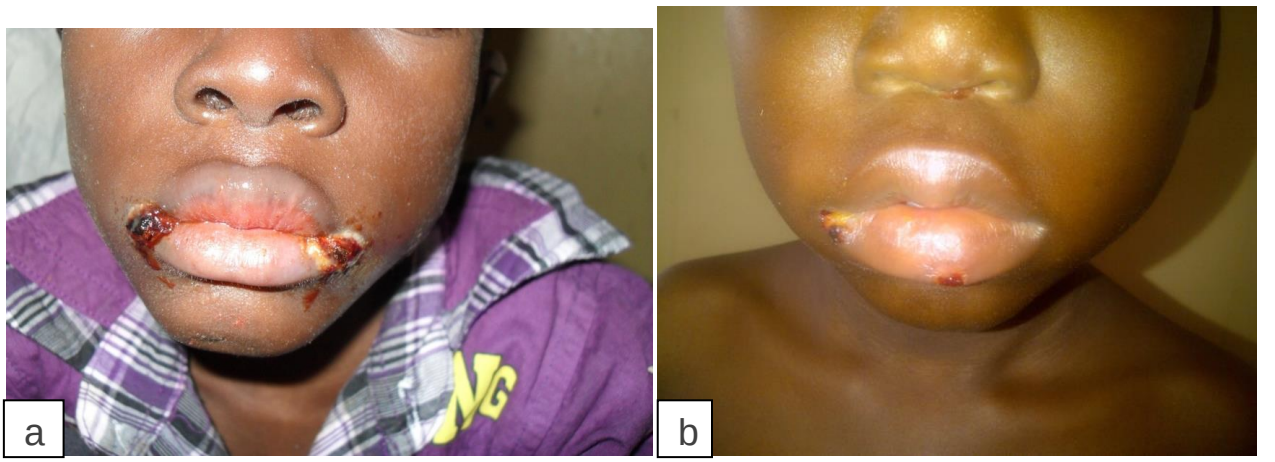


Figure 16a and b: Angular stomatitis in children with herpes simplex. Note the involvement of the columella in (b)

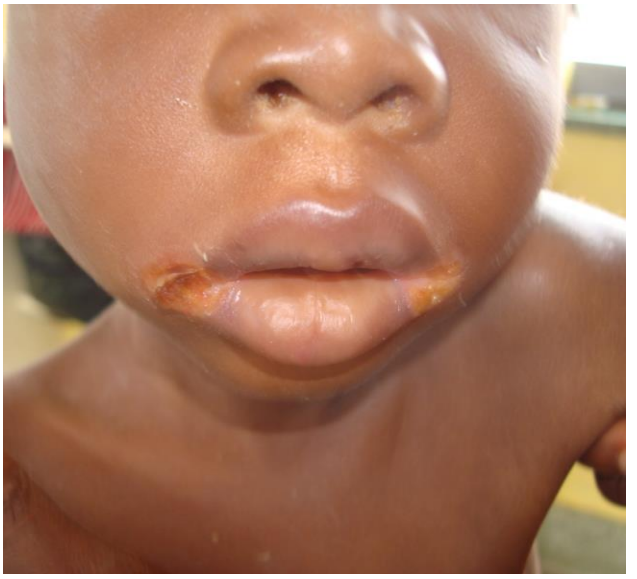


Figure 17: Herpes simplex lesions with angular stomatitis and possible secondary bacterial infection.

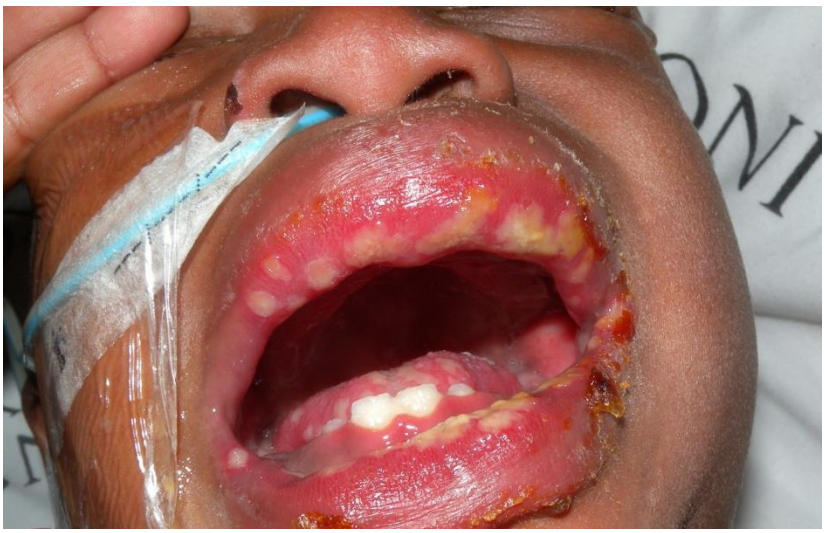


Figure 18: Herpes simplex in an immunocompromised child affecting the lips, angle of the mouth and the tongue

Eczema herpeticum

Patients with atopic dermatitis are susceptible to acute generalised infections with herpes simplex virus, referred to as eczema herpeticum. Eczema herpeticum can be caused by either type 1 or type 2 HSV. Eczema herpeticum in immunocompromised children such as those who have HIV, tend to have higher risks of dissemination and longer durations of outbreaks and are less responsive to therapy.

Eczema herpeticum presents as monomorphic eruptions of dome-shaped vesicles that may transform into pustules. The vesicles dry out within 2 to 3 weeks and may leave erosive pits. These "punched out" erosions can create a scalloped appearance at the periphery of the large denuded area.

Eczema herpeticum is a clinical diagnosis and can be confirmed by a Tzanck smear, performed by unroofing a vesicle and scraping the base of a lesion. On light microscopic examination, multinucleated giant cells are seen. HSV culture, PCR or a direct fluorescent antibody test are other confirmatory tests. When a secondary infection is suspected, a bacterial culture is obtained.

Prevention: Parents of children with moderate to severe eczema should be made aware of eczema herpeticum and advised to seek help early. Children with atopic eczema, especially those with a history of eczema herpeticum, should avoid close contact with relatives and friends with active herpes simplex.

Secondary bacterial infection with *S aureus* or ß-haemolytic streptococci may occur which may be indicated by yellow crusting. The secondary infection may be heralded by a high fever and other systemic symptoms. A more severe complication is periorbital eczema herpeticum that can result in keratoconjunctivitis with possible stromal scarring and subsequent blindness. Patients who have eye involvement require immediate ophthalmologic evaluation.

Treatment: Severe cases require acyclovir, as early as possible for 7 days and oral antibiotics if secondary bacterial infection is suspected. The underlying eczema should be treated to avoid recurrences. EH is not necessarily more common in HIV, but needs higher and longer doses of treatment.

Further reading

1. Peng WM, Jenneck C, Bussmann C et al. Risk factors of atopic dermatitis patients for eczema herpeticum. J Invest Dermatol 2007; 127: 1261–3.
2. Swart RN, Vermeer BJ, van Der Meer JW et al. Treatment of eczema herpeticum with acyclovir. Arch Dermatol 1983; 119: 13–6.
3. Jawitz JC, Hines HC, Moshell AN. Treatment of eczema herpeticum with systemic acyclovir. Arch Dermatol 1985; 121: 274–5.
4. Muelleman PJ, Doyle JA, House RF Jr. Eczema herpeticum treated with oral acyclovir. J Am Acad Dermatol 1986; 15: 716–7.
5. Latta RA, Baker DA. Treatment of recurrent eczema herpeticum in pregnancy with acyclovir. Infect Dis Obstet Gynecol 1996; 4: 239–42.

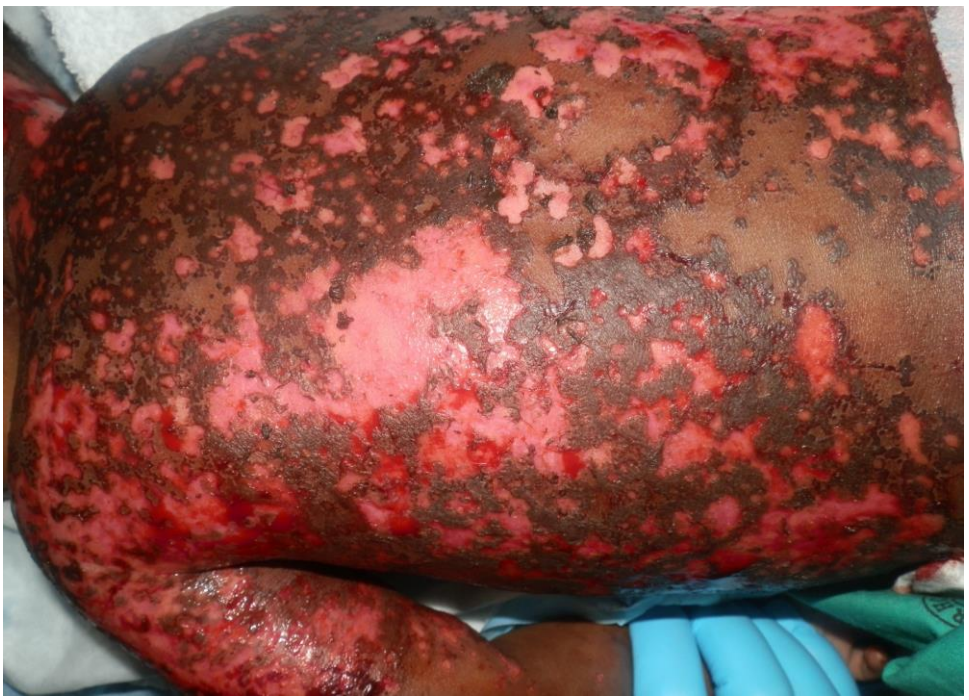


Figure 19: Eczema herpeticum. Shallow and punched out ulcers, widespread on trunk and face. Some ulcers have coalesced to form large haemorrhagic ulcers.

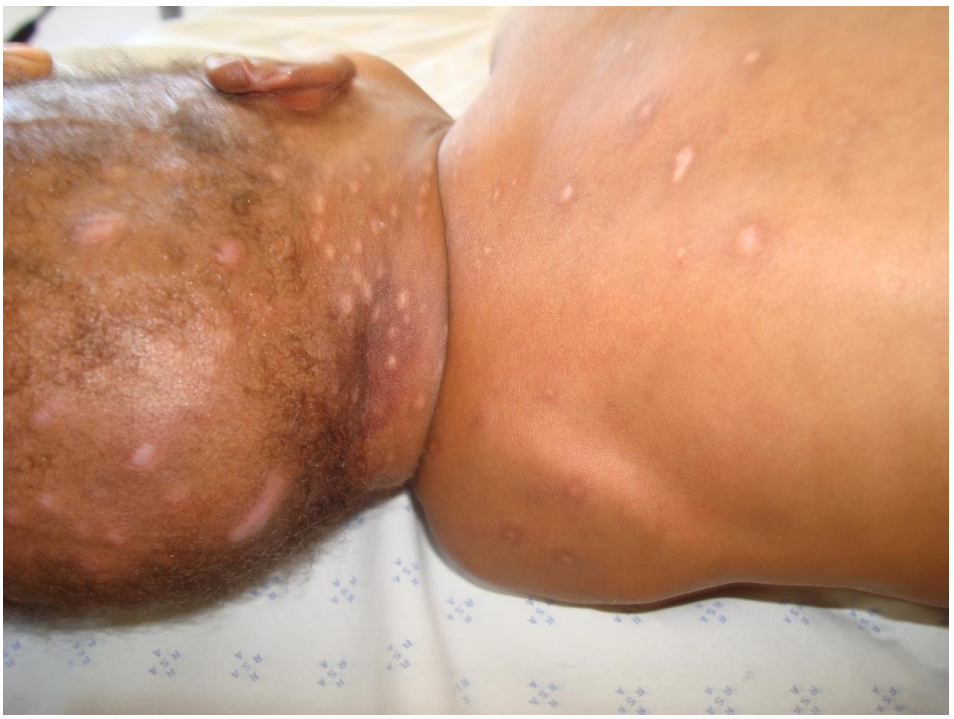


Figure 20: Eczema Herpeticum: Residual lesions in a 4 month old child treated 4 weeks earlier for eczema herpeticum.

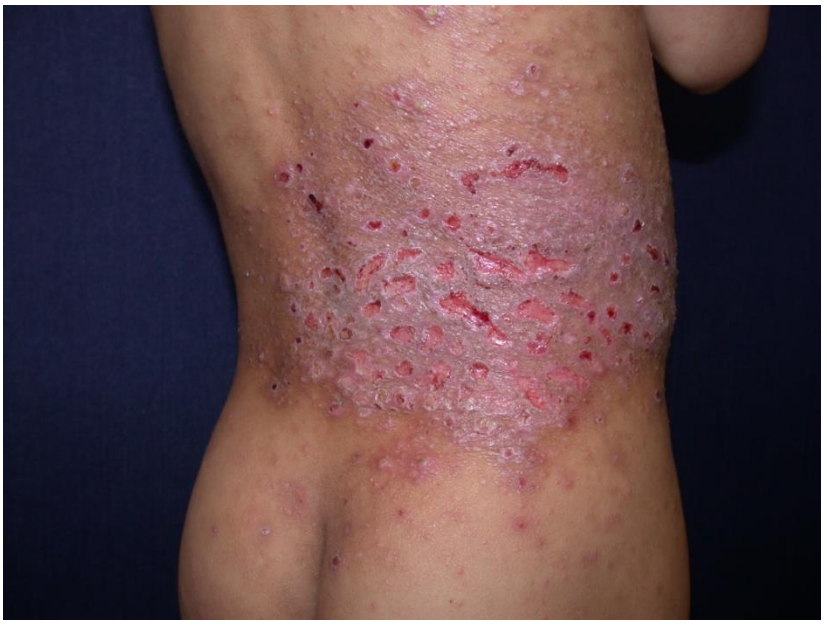


Figure 21: Punched out ulcers of eczema herpeticum confined to plaques of eczema in a child with atopic dermatitis.

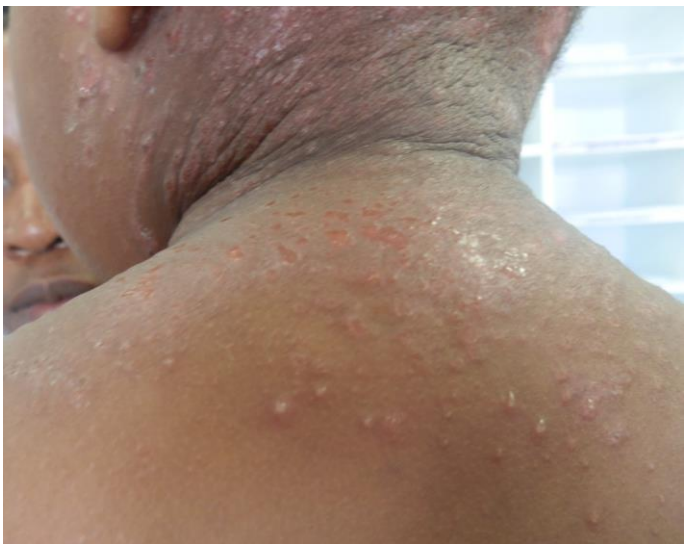


Figure 22: Eczema herpeticum. A combination of vesicles and shallow, punched out ulcers in the background of atopic eczema. Differential diagnosis to consider: Acute contact dermatitis.

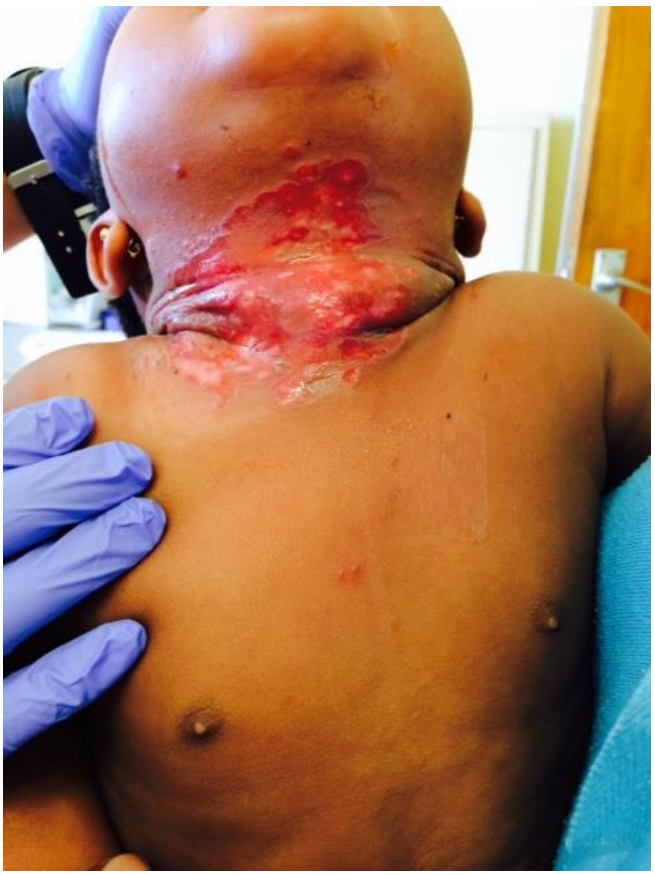


Figure 23: Severe confluent ulcers of eczema herpeticum on the neck of a child with atopic dermatitis

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Herpes Zoster (Shingles)

Herpes zoster is rare in immunocompetent children but an increased incidence is described in HIV-infected persons, sometimes as an early clinical sign of the development of AIDS.

Description: It is usually localized to a dermatome as a result of reactivation of the dormant virus in the sensory ganglion acquired during primary varicella or chicken pox infection. The word zoster means a girdle because it passes round the body like a girdle.

Aetiology: Is caused by a neurodermotropic virus called varicella zoster virus. It follows a clinical or sub clinical varicella (chicken pox) infection early in life or occasionally in utero. Predisposing factors include HIV infection, chronic steroid use, malignancies and diabetes mellitus.

Clinical presentation: The prodromal symptoms are hyperesthesia, paresthesias, burning dysesthesias or pruritus along the affected dermatome(s). The most common presenting features are pain and vesiculations Thoracic and cranial nerves are the most commonly involved. In most situations herpes zoster is confined to a single dermatome but can be multidermatomal or disseminated in HIV-infected children.

Epidemiology: It is distributed worldwide and is a common complication of HIV.

Diagnosis: Diagnosis is mainly clinical but in cases of uncertainty, Tzanck smear, viral culture, PCR is helpful.

Prevention: Varicella zoster vaccine in susceptible individuals.

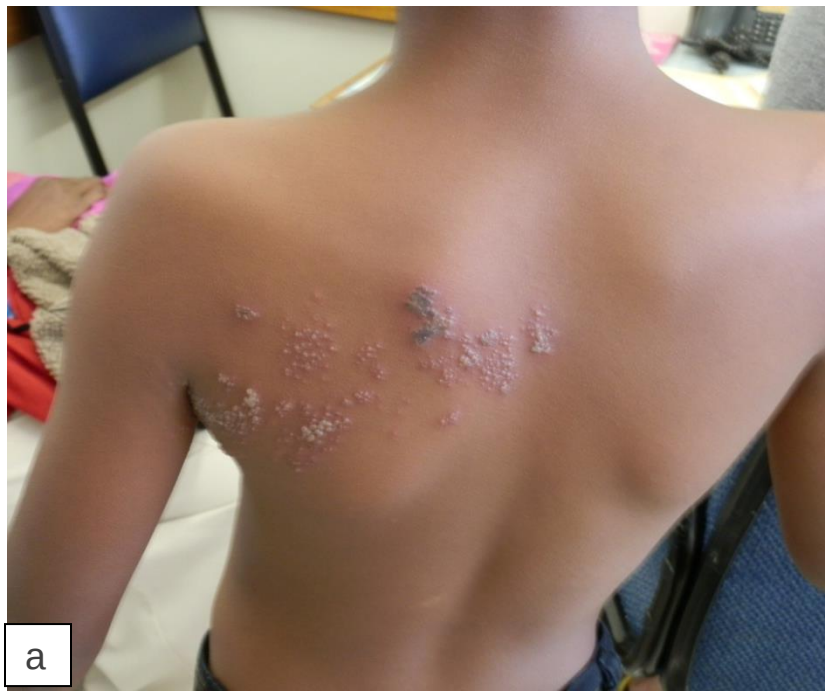
Treatment: Rest and analgesics are sufficient for mild attacks of zoster in the young. Soothing antiseptic applications may be helpful and secondary bacterial infections require antibiotics. Treatment of HZ is with antivirals: acyclovir 200mg five times a day for 7 days or IV acyclovir 5 mg/kg 8-hourly. In case of acyclovir resistance: Where available: Famciclovir and valacyclovir are other options. Foscarnet 120-200 mg in two to three divided doses, in case of acyclovir resistance or when available. The antiviral medications are most effective when started within 72 hours of onset of the rash. Opioids, tricyclic anti-depressants and anti-convulsants are useful in managing post-herpetic neuralgia.

Complications: Post-herpetic neuralgia, secondary bacterial infections. Recently, a vaccine has been developed for varicella zoster, which should reduce the population frequency of post-herpetic neuralgia. Encephalitis other main systemic complications are varicella pneumonia and hepatitis.

Further reading

1. Latheef EN, Pavithran K. Herpes zoster. A clinical study in 205 patients. Indian J Dermatol 2011; 56(5): 529–532.

2. Gil A, Gil R, Alvaro A, Martin MS, Gonzale A. Burden of herpes zoster requiring hospitalization in Spain during a seven-year period (1998–2004). BMC Infect Dis. 2009; 9: 55.
3. Sykes W. Origin of "zoster" in herpes zoster. Br Med J. 1902; 1(2154): 930.
4. Stankus SJ, Dlugopolski M, Packer D. Management of Herpes Zoster (Shingles) and Postherpetic Neuralgia. Am Fam Physician. 2000; 61(8):2437-2444
5. Ash S, Hewitt C. HIV-associated cutaneous disorders. Curr Opin Infect Dis 1994;7: 195-201.
6. Grossman M. Chronic hyperkeratotic herpes zoster and human immunodeficiency virus infection. J Am Acad Dermatol 1993;28:306-308.
7. Leibovitz E, Kaul A, Rigaud M, et al. Chronic varicella zoster in a child infected with human immunodeficiency virus: case report and review of the literature. Cutis 1992;49:27-31
8. Kimberlin DW, Whitley RJ. Varicella-zoster vaccine for the prevention of herpes zoster. N Engl J Med 2007; 356: 1338–43.



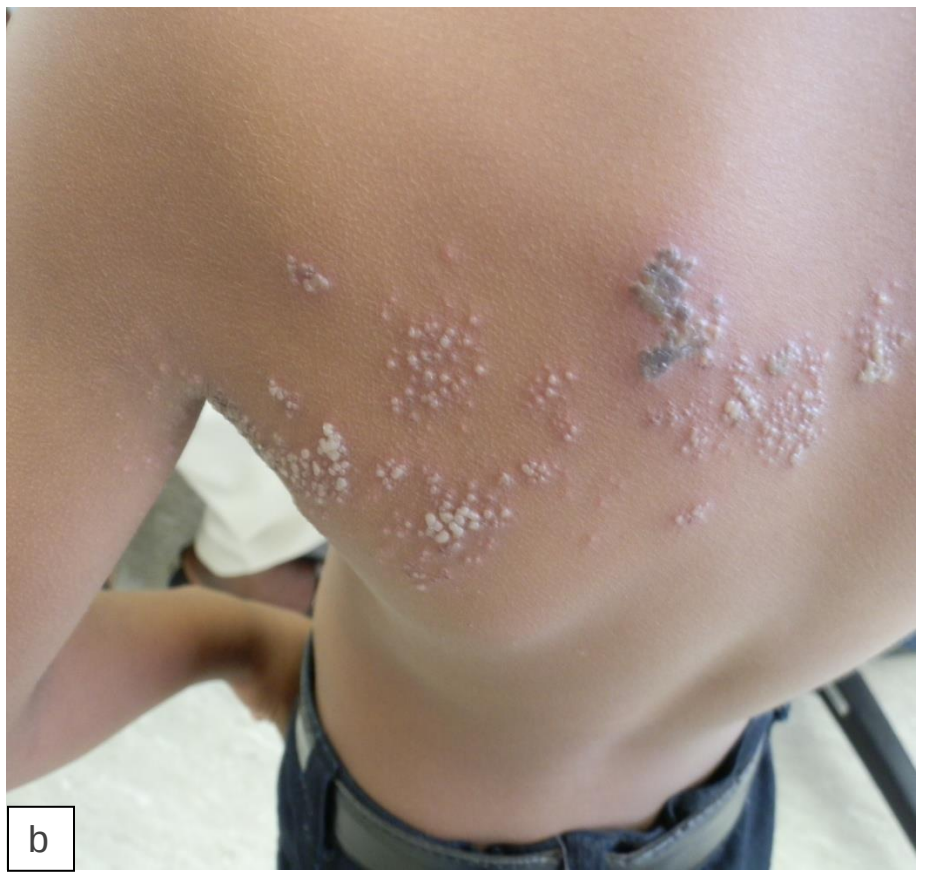


Figure 24a and b: Herpes zoster showing: grouped vesicles and pustules lesions with some crusting in T1/T2 dermatomal distribution.

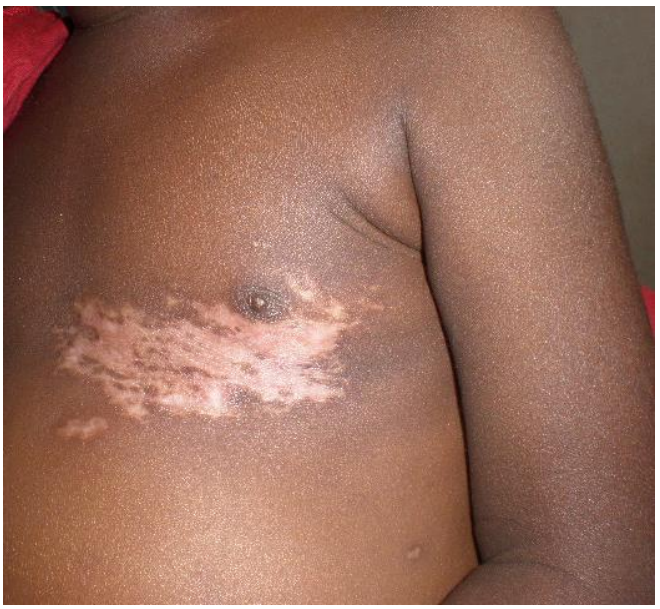


Figure 25: Healed Herpes zoster showing scarring and post-inflammatory hypopigmentation.

Viral Warts

The different morphological variants of warts are found in 5-30% of patients with HIV infection.

Plane Warts (Verruca Plana)

Description: These are flat warts (verruca plana)

Aetiology: Human papilloma virus (HPV) type 3 and, less often, types 10, 27, and 41 are the causative agents of verruca plana.

Clinical presentation: The warts are very slightly elevated above the level of surrounding skin and can be slightly hypo or hyperpigmented. Plane warts in HIV infection tend to be extensive and may be photodistributed.

Epidemiology: Plane warts are common and have no gender predilection. Prevalence of about 20% in HIV-infected children has been reported. Transmission can be either directly through person to person contact or indirectly through sharing of fomites.

Diagnosis: Diagnosis is mainly clinical. In cases of doubt PCR and histology are helpful.

Prevention: Healthy skin care and avoiding skin contact with an infected person.

Treatment: Response to treatment is usually unsatisfactory. Treatment options include salicylic or lactic acid in flexible colloidal preparations and 0.05% tretinoin creams. Initiation of ART does not seem to improve plane warts.

Complications: Potential risk of development of HPV associated epithelial neoplasia.

Further reading

1. Mankahla A, Mosam A. Common skin conditions in children with HIV/AIDS. Am J Clinc Dermato 2012; 13 (3): 153-166.
2. Lipke MM. An armamentarium of wart treatments. Clinical medicine and research 2006; 4 (4): 273-293.
3. Panya MF, Mgonda YM, Massawe AW. The pattern of mucocutaneous disorders in HIV – infected children attending care and treatment centres in Dar es Salaam, Tanzania. BMC Public Health. 2009; 9: 234.
4. Berger TG, Greene I. Bacterial, viral, fungal and parasitic infections in HIV disease and AIDS. Dermatol Clin 1991; 9: 465–92.
5. Barbosa P. Plantar verrucae and HIV infection. Clin Podiatr Med Surg 1998; 15: 317–27.
6. Anonymous. Clinicians should check women with HPV for HIV. Aids Alert 1999; 14: 39–41.

7. Lowe S, Ferrand RA, Morris-Jones R et al. Skin disease among human immunodeficiency virus infected adolescents in Zimbabwe: a strong indicator of underlying HIV infection. Pediatric Infect Dis J 2010; 29(4): 356-51.

Epidermodysplasia verruciformis

Description: Epidermodysplasia verruciformis (EV) is an inherited clinical variant of verruca plana in which there is widespread and persistent infection with HPV. Patients frequently harbor multiple HPV subtypes. Subtypes 5 and 8 are associated with squamous cell carcinomas. The other subtypes are 14, 17, 20 and 47.

Clinical presentation: A characteristic combination of plane warts, pityriasis versicolor-like lesions and reddish plaques.

Complication: Malignant transformation occurs in 20 - 40% of patients and onset is usually in the 20s. However metastatic disease is rare.

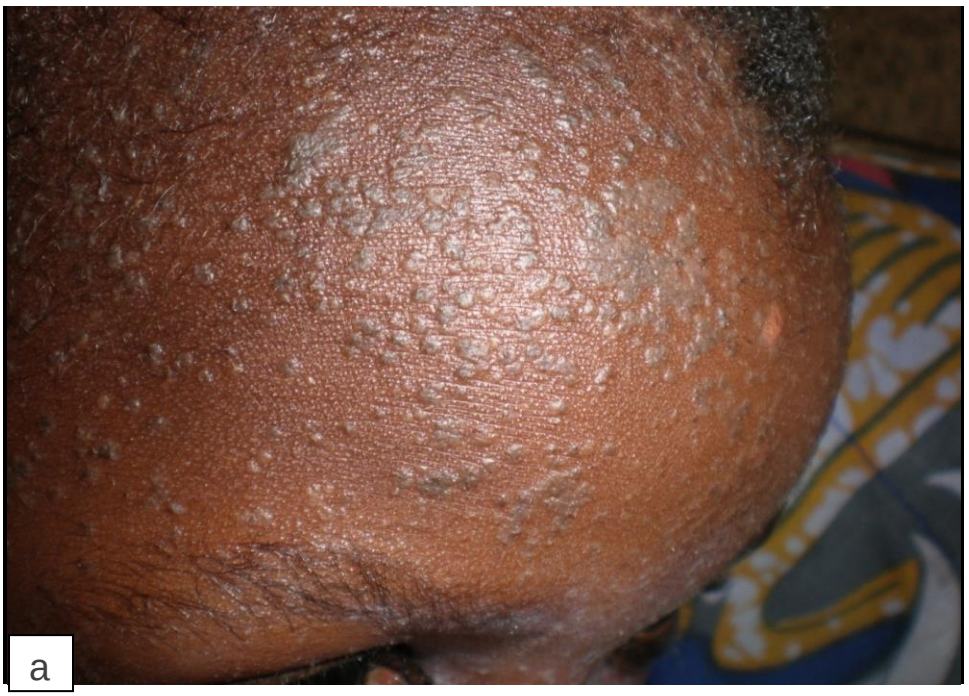
Prevention: Avoidance of excessive sun exposure, with diligent use of effective sunscreen.

Treatment: Patients should be observed for the development of squamous cell carcinomas and premalignant lesions, which should be excised or locally ablated. Oral retinoids have been used but their long-term effectiveness is uncertain.

First-line option: etretinate, starting dose of 1 mg/kg/day, but the effect is dose dependent and relapse occurs if the drug is stopped.

Second-line option: The combination of etretinate plus IFN-α may also produce a useful clinical effect.

Other options include oral isotretinoin, which has been shown to improve the clinical appearance of the benign lesions. Occasional but inconsistent benefits have been reported with topical imiquimod, topical vitamin D analogues, topical immunotherapy with squaric acid dibutylester and oral cimetidine.



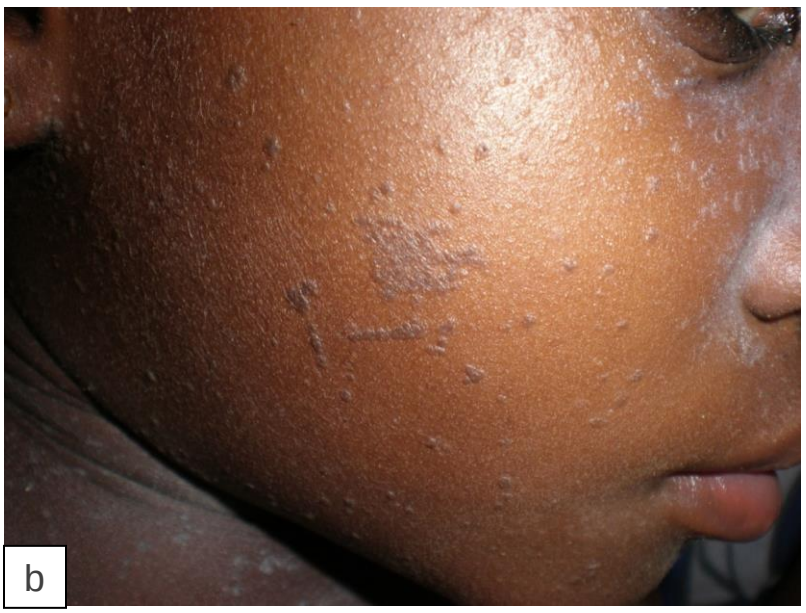


Figure 26a and b: Hyperpigmented flat warts on the face of a child. Note the linear arrangement on the cheek following lines of trauma, a phenomenon called koebnerization or isomorphic response.

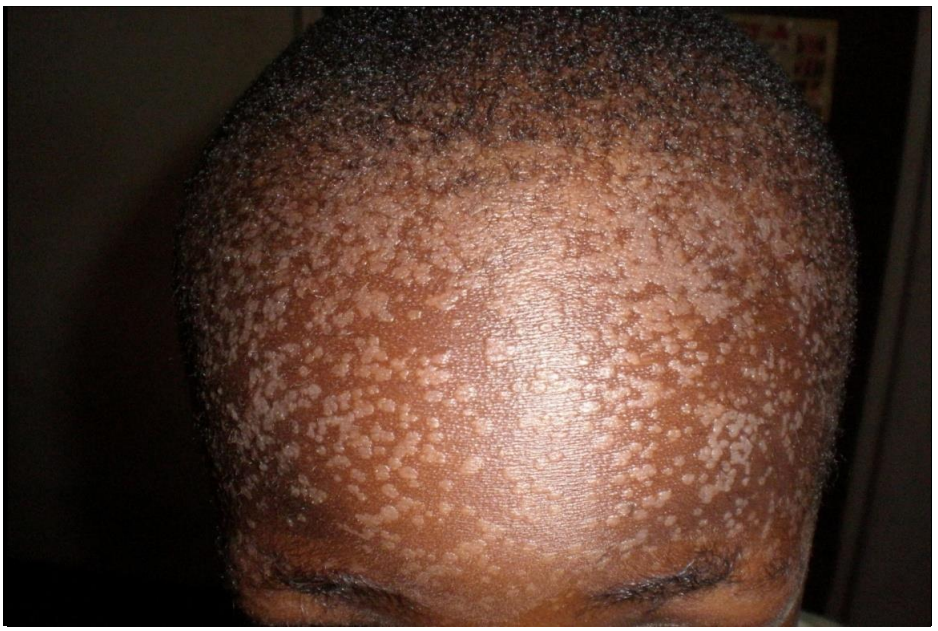


Figure 27: Flat hypopigmented plagues on the forehead of a child with epidermodysplasia verruciformis. The lesion was initially misdiagnosed as tinea versicolor.

Palmoplantar and common warts

Clinical Presentation: Verrucous papules on palms and soles. Common warts can be verrucous, mosaic or filiform. Periungual involvement common.

Epidemiology: HIV-infected children are more susceptible and the warts tend to be more extensive and recalcitrant.

Diagnosis: The diagnosis is based upon clinical appearance. Paring of overlying hyperkeratotic debris usually reveals thrombosed capillaries. This helps to differentiate warts from calluses. In cases of doubt PCR and histology are helpful.

Prevention: Advice on simple measures to limit the spread of the infection by avoiding physical contact with the warts and cleaning of fomites may be advised.

Treatment: Treatment options include salicylic acid, cantharidin, topical 5-fluorouracil, cryotherapy, paring, cautery or CO_2 laser.

Further reading

1. Johnston J, King CM, Shanks S, Khademi S, Nelson J, Yu J, Barbosa P. Prevalence of plantar verrucae in patients with human immunodeficiency virus infection during the post-highly active antiretroviral therapy era. J Am Podiatr Med Assoc. 2011 Jan-Feb;101(1):35-40.
2. Barbosa P. Plantar verrucae and HIV infection. Clin Podiatr Med Surg 1998; 15:317.
3. Sterling JC, Gibbs S, Haque Hussain SS, et al. British Association of Dermatologists' guidelines for the management of cutaneous warts 2014. Br J Dermatol 2014; 171:696-712.

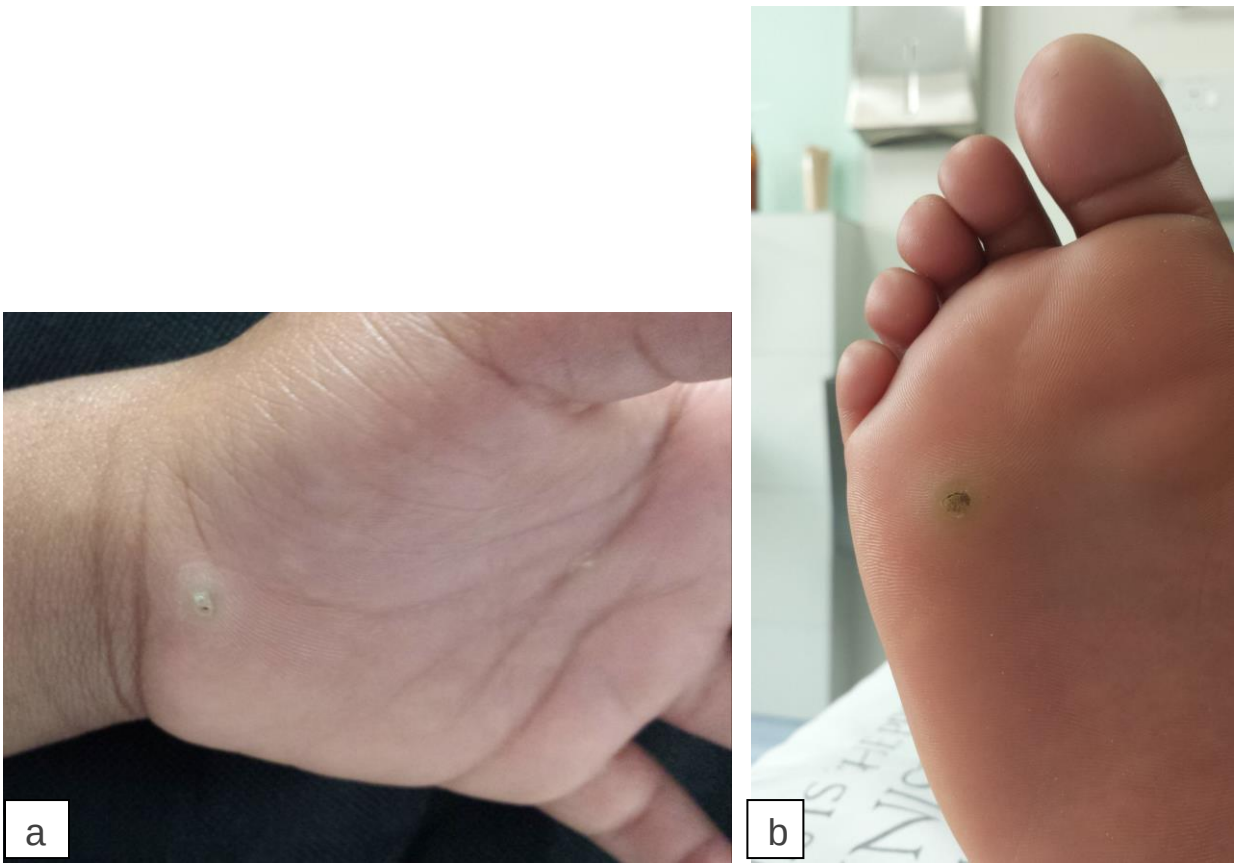


Figure 28a and b: Palmar and plantar warts on the sole and palm of a child.

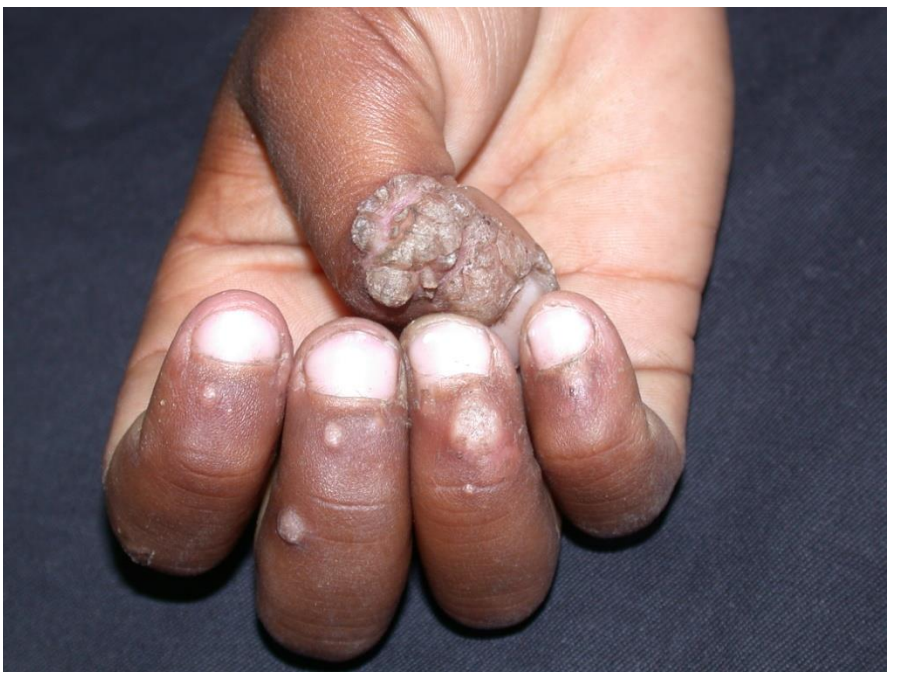


Figure 29: Common warts presenting as multiple papules on distal end of fingers, together with a much larger hyperkeratotic, verrucous plaque on the distal end of the left thumb.

Oral warts (Heck's Disease)

Clinical Presentation: Whitish or pale papules with a smooth or roughened surface. Can affect any part of the oral cavity.

Epidemiology: HIV-infected children are more susceptible to oral warts, which are rare in immunocompetent persons. In the era of ART, the prevalence of oral warts is increasing estimated to be between 1.6 – 2.6%.

Diagnosis: Diagnosis is mainly clinical. In cases of doubt PCR and histology are helpful. Human papilloma virus types 13 and 32 are the most commonly implicated.

Prevention: Avoid biting warts in other areas of the body.

Treatment: Treatment options include surgery, cautery or CO_2 laser. Topical imiquimod 5% cream has been successfully used.

Complications: Potential risk of development of HPV associated epithelial neoplasia.

Further reading

1. King MD, Reznik DA, O'Daniels CM, Larsen NM, Osterholt D, Blumberg HM. Human papillomavirus-associated oral warts among human immunodeficiency virus-seropositive patients in the era of highly active antiretroviral therapy: an emerging infection. Clin Infect Dis. 2002 Mar 1;34(5):641-8.
2. Greenspan, D., et al., Effect of highly active antiretroviral therapy on frequency of oral warts. The Lancet, 2001. 357(9266): p. 1411-1412.

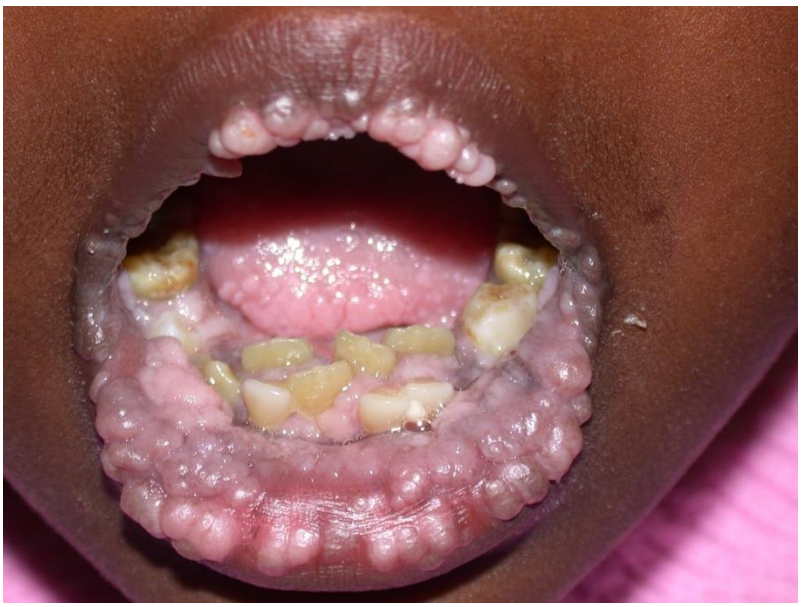


Figure 30: Warts - longstanding oral lesions in an HIV-infected child affecting alignment of teeth.

Genital Warts and Perianal Warts

Description: Warts on the genital and perianal area have variable clinical presentations.

Aetiology: At least 40 subtypes of human papilloma virus (HPV) have been shown to cause genital warts. Of these subtypes 16 and 18 are considered to be high risk as they are associated with development of squamous cell carcinomas,

Clinical presentation: anogenital warts (condylomata acuminata) may present as flat, dome-shaped, cauliflower-shaped, or pedunculated lesions.

Epidemiology: Anogenital warts are common sexually transmitted disease estimated to occur in 1% of sexually active adults. In young children, they may be an indication of sexual abuse.

Diagnosis: Diagnosis of anogenital warts is mainly clinical and the diagnosis can be confirmed by histology or PCR. The latter is used for subtyping to rule out high risk subtypes.

Prevention: Advice on simple measures to limit the spread of the infection by avoiding physical contact with the warts and cleaning of fomites may be advised. HPV vaccines are effective for prevention of HPV-associated malignancies.

Treatment: Not all warts need treatment as many give little inconvenience and will resolve spontaneously. Where treatment is needed first-line options include 20% podophyllin, cryotherapy and salicylic acid. Second-line options include imiquimod. Spontaneous remission has been reported in 20-30 of infected patients.

Complications: Potential risk of developing HPV associated epithelial neoplasia exists. Genital warts in children may be a manifestation of child abuse.

Further reading

1. Mankahla A, Mosam A. Common skin conditions in children with HIV/AIDS. Am J Clinc Dermato 2012; 13 (3): 153-166.
2. Lipke MM. An armamentarium of wart treatments. Clinical medicine and research 2006; 4 (4): 273-293.
3. Panya MF, Mgonda YM, Massawe AW. The pattern of mucocutaneous disorders in HIV – infected children attending care and treatment centres in Dar es Salaam, Tanzania. BMC Public Health. 2009; 9: 234.
4. Yanofsky VR, Patel RV, Goldenberg G. Genital warts: a comprehensive review. J Clin Aesthet Dermatol. 2012; 5(6): 25–36.

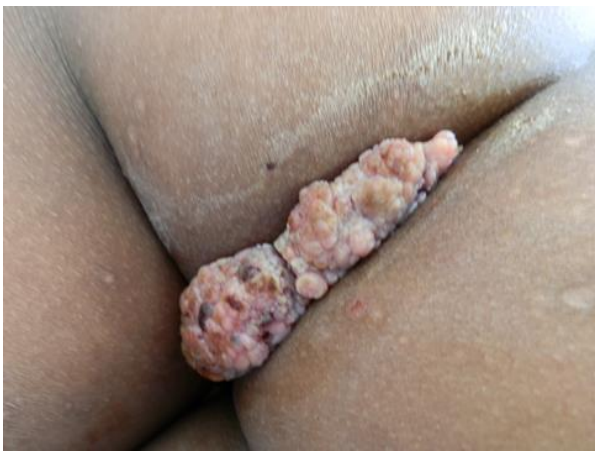


Figure 31: Perineal warts

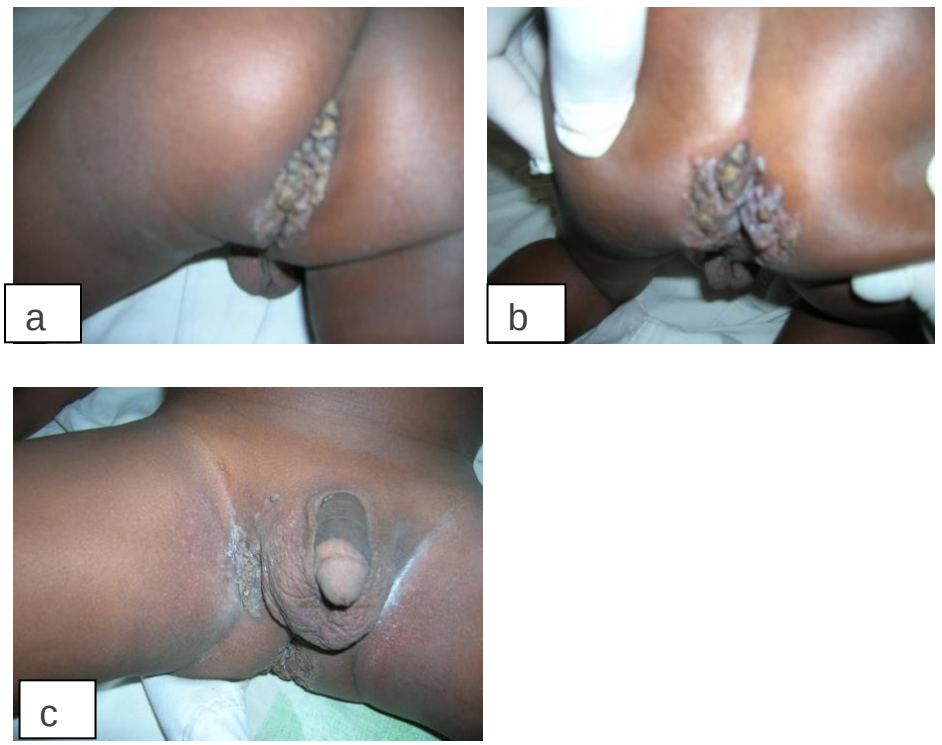


Figure 32a, b and c: Perianal and perineal warts in a 2-year-old boy. The mother also had perineal warts.

Measles (Rubeola)

Description: A contagious disease caused by measles virus with characteristic rash that starts from the face and spreads to the extremities.

Aetiology: Measles is caused by the measles virus. Lack of immunization is a risk factor although disease has been recorded among immunized infants. Vitamin A deficiency state has been associated with severe disease.

Clinical presentation: High grade fever is usually the first sign of measles at about 10 to 12 days after exposure to the virus, and lasts four to seven days. Other symptoms in the initial stage are catarrh, cough, red and watery eyes, and small white spots inside the cheeks (Koplik's spots). Koplik's spots are pathognomonic for measles but last for less than 24 hours. A maculopapular rash follows, usually on the face and upper neck after several days and then spreads to reach the hands and feet. The rash lasts for five to six days, and then fades. On average, the rash occurs 14 days after exposure to the virus (range 7 – 18 days).

Epidemiology: The incidence in Africa is estimated to be as high as 17. 2 cases per 100,000 population. There is a higher incidence of contracting measles in HIV-infected children. In addition, there is an increased case fatality. Outbreaks of the disease still occur in parts of Africa. The virus is spread by close contact with infected nasal or throat secretions.

Diagnosis: Detailed history, including immunization history and a thorough physical examination for characteristic features should be done. Demonstration of measles IgM antibodies (where available) confirms the diagnosis.

Prevention: Routine measles vaccination for children (at 9 months of age) combined with mass immunization campaigns in countries with high case and death rates. The World Health Organization recommends two vaccinations at 6 and 9 months for HIV exposed and infected children. The vaccine is safe, effective and inexpensive. It may be given in combination with rubella and/or mumps vaccines in countries where these illnesses are problems. It is equally effective in the single or combined form.

Treatment: There is no effective anti-viral treatment. Supportive care is the mainstay and should ensure good nutrition, adequate fluid intake and treatment of dehydration. Antibiotics should be prescribed to treat secondary pneumonia and bacterial infections of the eye and ear. Two doses of vitamin A supplements, given 24 hours apart is recommended for all children diagnosed with measles in developing countries. Vitamin A supplements have been shown to reduce the number of deaths from measles by 50%.

Complications: Blindness, encephalitis, diarrhoea, otitis media, lower respiratory infections such as pneumonia

Further reading

1. Nilsson A, Chiodi F. Measles Outbreak in Africa—Is There a Link to the HIV-1 Epidemic? PLoS Pathog. 2011; 7(2): e1001241.
2. WHO.2013. Measles fact sheet. Available from: http://www.who.int/mediacentre/factsheets/fs286/en/.

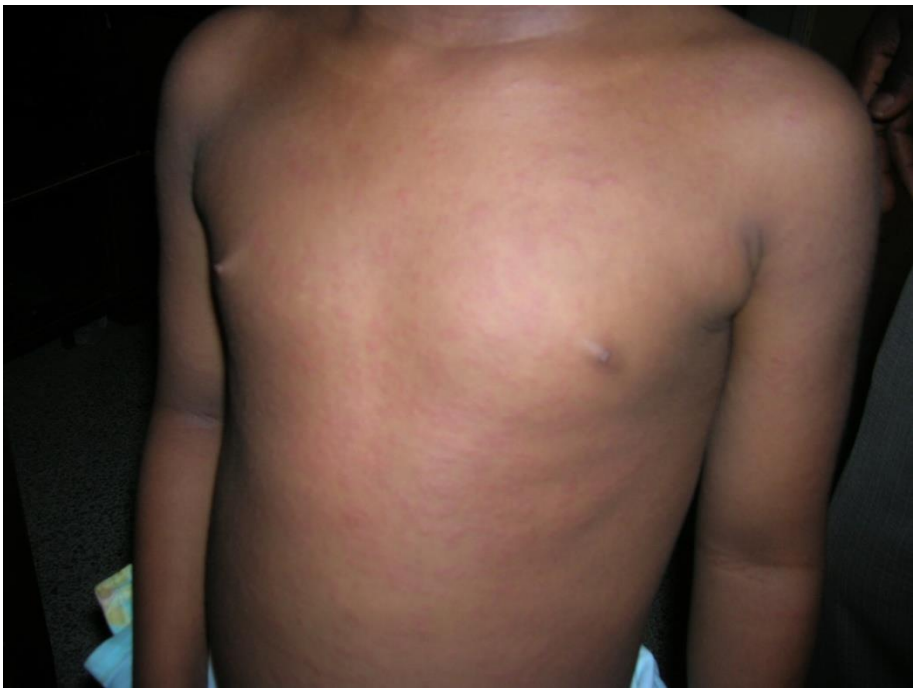


Figure 33: Measles: fresh maculopapular lesions.

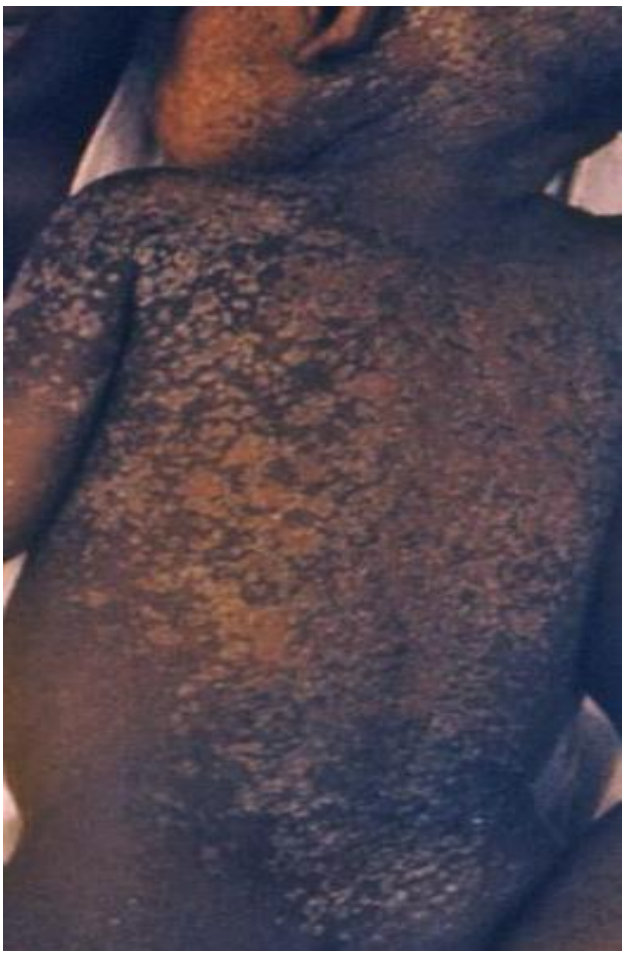


Figure 34: Measles: desquamating rash

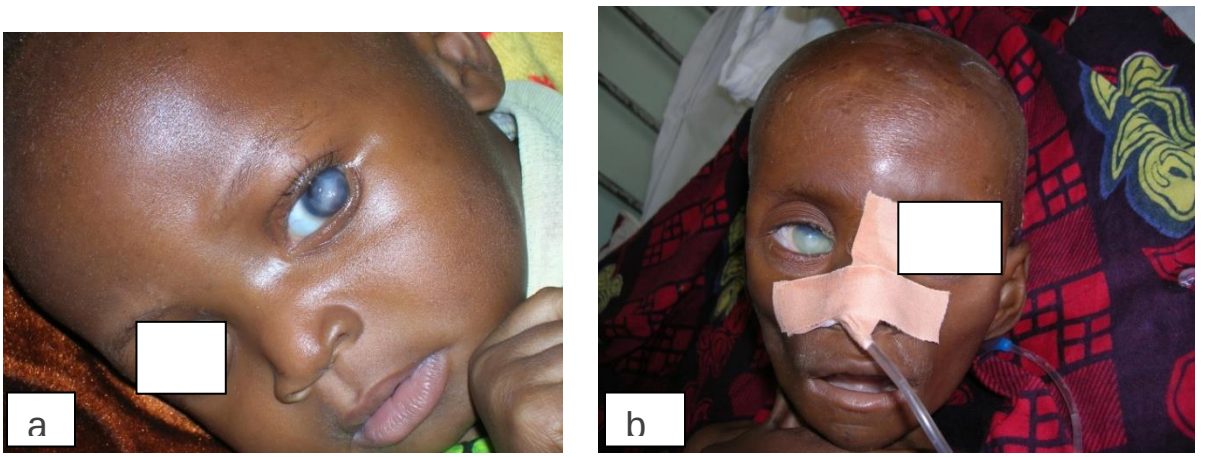


Figure 35a and b: Measles complication in two children: a. keratitis b. panophthalmitis

Molluscum Contagiosum

Description: Molluscum contagiosum (MC) is a common viral skin infection of the skin.

Aetiology: MC is caused by poxvirus – a DNA virus from the Poxviridae family.

Clinical presentation: Usually present as small pearly, dome shaped, small, discrete lesions with central umbilication. In HIV-infected individuals, atypical varieties such as large or non-umbilicated lesions are found. Individual papules may coalesce to form the agminate variety. Lesions tend to be recalcitrant and resistant to treatment.

Epidemiology: MC is seen in 10-20% of AIDS patients. Transmission is by autoinoculation and physical contact.

Diagnosis: mainly a clinical diagnosis but a skin biopsy staining of the curdy material with Giemsa and demonstration of eosinophilic molluscum bodies can be helpful in atypical cases.

Prevention: Avoidance of close contact with infected persons.

Treatment: Infection is usually self-limiting and spontaneously resolves after 18-24 months in mild cases and therefore no treatment may be necessary. If problematic and extensive the most commonly used therapeutic options include 5% salicylic acid/lactic acid preparations, trichloroacetic acid, curettage, cautery and cryotherapy. Less commonly imiquimod cream, tretinoin cream, cantharidin and benzyl peroxide are used with variable success. Large lesions can be removed surgically. Treatments may cause scarring and leave marks long term. HAART improves outcome in HIV-infected children and should be considered in eligible patients.

Complications: Infected and inflamed MC can cause disfigurement and scarring.

Further reading

1. Chularojanamontri L, Tuchinda P, Kulthanan K et al. Generalized molluscum contagiosum in an HIV patient treated with diphencyprone. J Dermatol Case Rep. 2010; 4(4): 60–62.
2. Dhar S, Jain S, Verma G, Tanwar R. Disseminated and atypical molluscum contagiosum in an AIDS patient. Indian J Dermatol Venereol Leprol. 1996; 62:331–2.
3. Sen S, Goswami BK, Karjyi N et al. Disfiguring molluscum contagiosum in an HIV positive patient responding to antiretroviral therapy. Indian J Dermatol. 2009; 54(2): 180–182.
4. Theiler M, Kempf W, Kerl K et al. Disseminated molluscum contagiosum in a HIV-positive child. Improvement after therapy with 5% imiquimod. J Dermatol Case Rep. 2011; 5(2): 19–23.
5. Hogan MT. Cutaneous infestations associated with HIV/AIDS. Dermatol Clin 2006; 24:473-95.

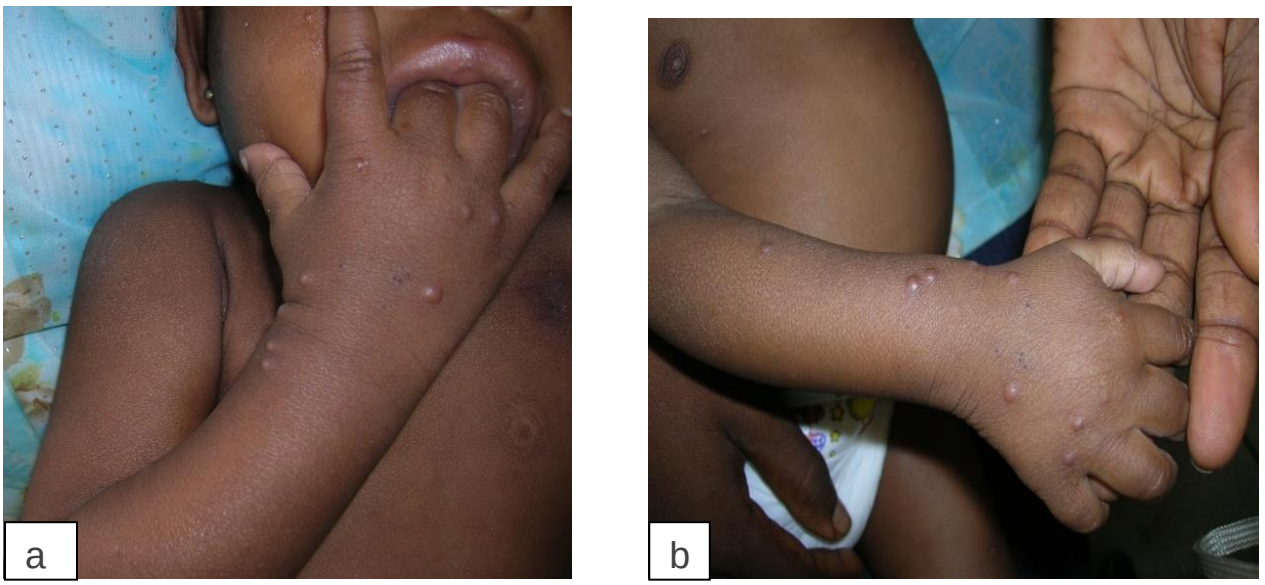


Figure 36a and b: Molluscum contagiosum in HIV- 12 month old girl, the lesion involved the extremities and the face (not shown). A differential diagnosis is papular urticaria.

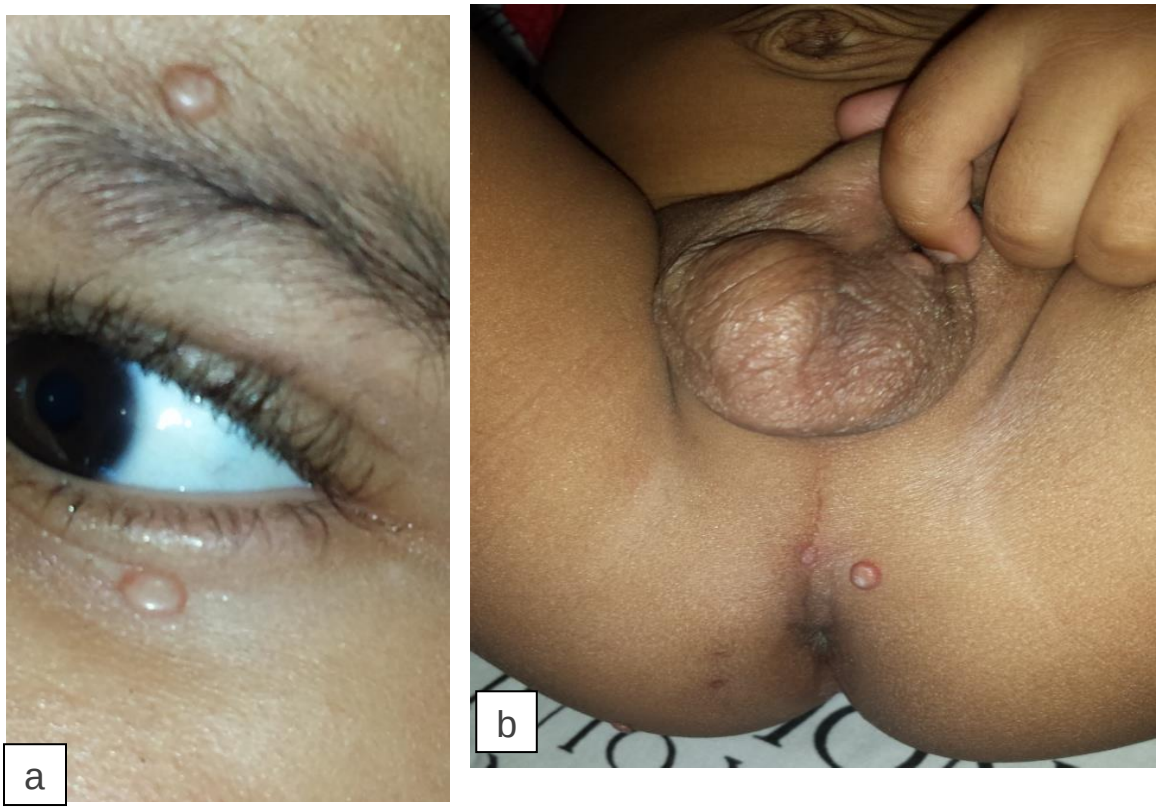


Figure 37a and b: Molluscum contagiosum appearing below the eyelid and peri-anal regions 3 months after commencing ART in an 8-month-old child.

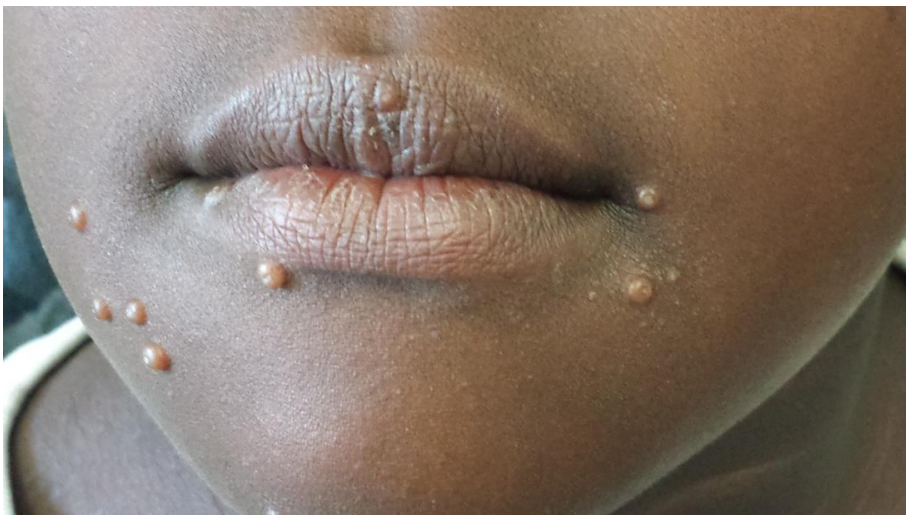


Figure 38: Multiple mollusca in the perilabial region in a 6-year-old girl several years after antiretroviral therapy was started and she had achieved complete viral suppression.

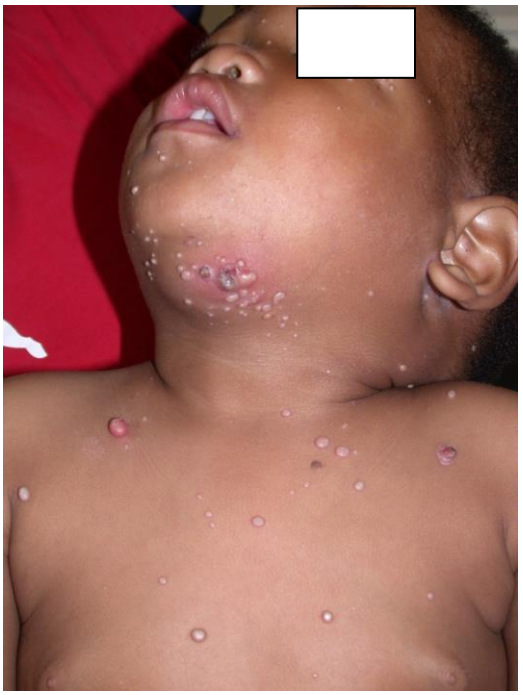


Figure 39: Multiple molluscum lesions on the face, neck and upper chest in an HIV-infected child. Lesions are of different sizes and are at different stages of evolution. Secondary infection and inflammation are common.

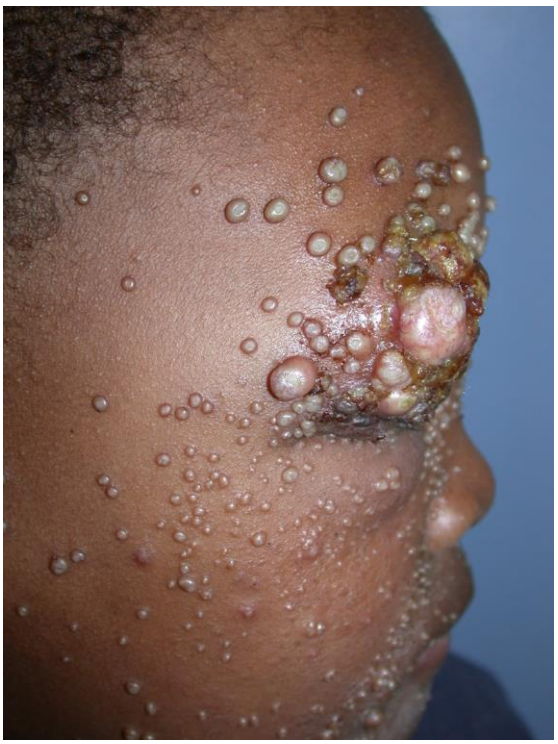


Figure 40: Extensive molluscum in an HIV-infected child on the face involving the eyelid. Note the giant molluscum.

Table 2: Treatment options: Viral infections

Infection	First-line treatment	Alternative treatment	Where available
HSV	Acyclovir	Valacyclovir Famciclovir	Foscarnet
Eczema Herpeticum	Acyclovir	Valacyclovir Famciclovir	Foscarnet
Herpes Zoster	Acyclovir	Valacyclovir Famciclovir	Foscarnet
Verruca Plana	Salicylic/lactic acid	0.05% tretinoin creams	
EDV	Oral cimetidine	Isotretinoin etretinate plus IFN-α	-Imiquimod -Vitamin D analogue -Squaric acid dibutylester
Genital Warts	20% Podophyllin	Imiquimod	
Molluscum contagiosum	5% salicylic Acid/lactic acid benzoyl benzoate	-Trichloroacetic acid -Liquid nitrogen -Tretinoin cream	Curettage Cautery Imiquimod cream Cantharadin
Measles	Vitamin A supplements	Antibiotics as required	

EDV- Epidermodysplasia verruciformis

CHAPTER 3: FUNGAL SKIN INFECTIONS

Superficial Fungal Infection

Dermatophytosis

Description: Dermatophyte infections are common in HIV-infected children. They include: tinea capitis, tinea corporis, tinea unguium and tinea pedis.

Tinea

Aetiology: These infections are caused by fungi called dermatophytes, which produce an enzyme called keratinase to break down keratin.

Clinical presentation: Depends on part of the body affected. In the skin, it presents as "rings" (ring worm), with raised edges and clearing at the centre of the lesions, alopecia in the scalp (tinea capitis), may present with scaly feet and/or macerated web spaces (tinea pedis) or may involve the nails leading to the destruction and discoloration of the nails (tinea unguium).

Epidemiology: Common around the world. Specific fungal aetiology varies from one geographical region to another.

Diagnosis: Is mainly clinical but a simple potassium hydroxide (KOH) preparation may be helpful. A KOH mount can be easily prepared by gently scraping the infected skin or blister roof with a sterile scalpel blade onto a glass slide with 1 to 2 drops of 10% KOH. The sample is then examined under the microscope for the presence of hyphae. Alternatively, specimen can be sent for fungal culture for identification of the causative organism and Under Wood's lamp (UV) colonies will fluoresce.

Prevention: Changing footwear frequently, drying feet well after bathing (especially between toes), refraining from sharing articles of clothing, and appropriately treating friends and family members of affected patients, can be very helpful in minimizing risks of exposure and reinfection.

Treatment: The treatment of dermatophyte infections usually involves the use of oral terbinafine, fluconazole, itraconazole, griseofulvin or one of several well-tried topical preparations.

A commonly used oral antifungal of choice is griseofulvin 10-20 mg/kg for at least 6 weeks for skin and hair infection, 6 weeks for tinea capitis and in severe hair, skin and scalp infections, up to 3 months.

Generally, topical therapies are used for localized or mild infections, oral antifungals for the more extensive infections. There is a variety of topical antifungal agents, including clotrimazole, econazole,

oxiconazole, miconazole, terbinafine, and naftifine applied to the affected areas twice daily for 2 to 4 weeks.

For nail infections, longer therapy with oral agents is usually necessary. However, children respond better to topical therapy than adults because of a thinner nail plate and potentially faster nail growth rate.

Complications: Secondary bacterial infection and ID reaction (autoeczematisation as a hypersensitivity reaction to the fungus).

Further reading

1. Jain A, Jain S, Rawat S. Emerging fungal infections among children: A review on its clinical manifestations, diagnosis, and prevention. J Pharm Bioallied Sci. 2010; 2(4): 314–320.
2. Rich P, Houpt KR, LaMarca A et al. Safety and efficacy of short-duration oral terbinafine for the treatment of tinea corporis or tinea cruris in subjects with HIV infection or diabetes. Cutis 2001; 68: 15–22.
3. Friedlander SF, Chan YC, Chan YH, Eichenfield LF. Onychomycosis does not always require systemic treatment for cure: a trial using topical therapy. Pediatr Dermatol. 2013 May-Jun;30(3):316-22.

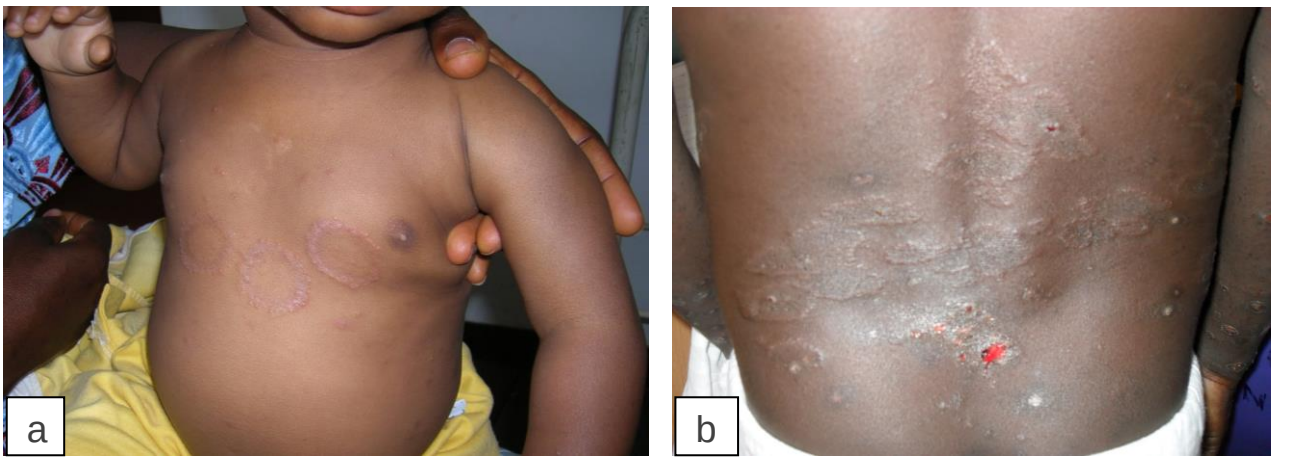


Figure 41a and b: Tinea corporis lesions on the trunk. Well demarcated lesions with raised edge and central clearing.

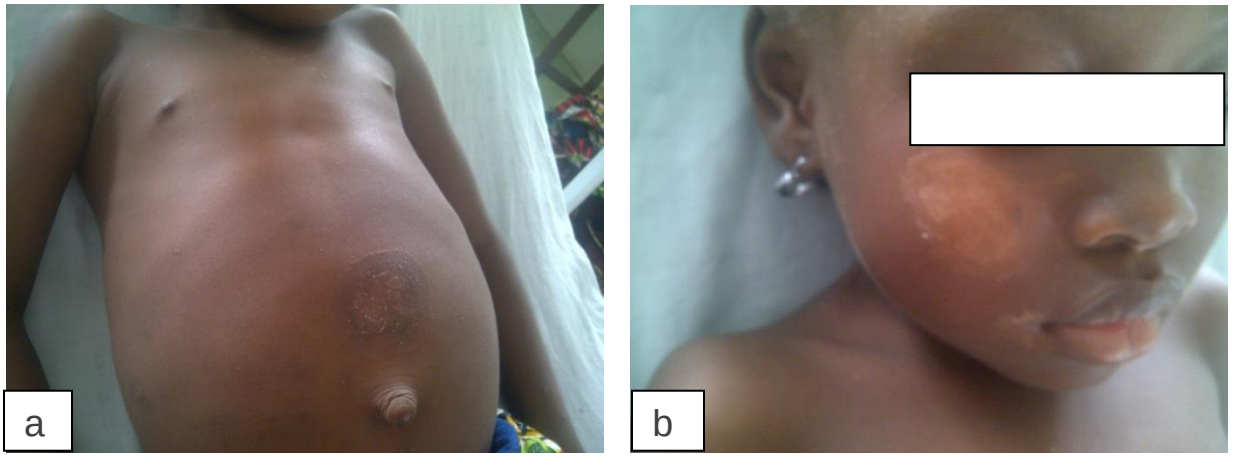


Figure 42 a and b: Tinea corporis on the anterior abdominal wall and right cheek. Note the ring shaped scaly lesion with central area of clearance.

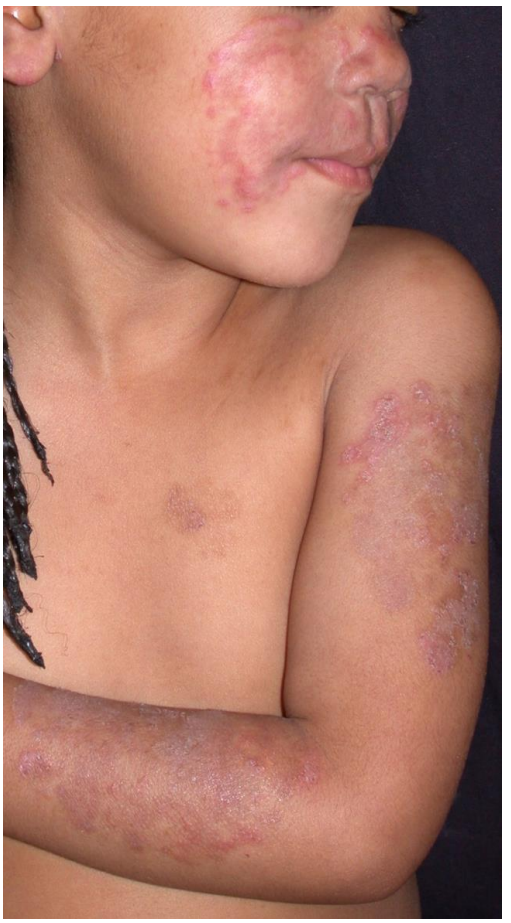


Figure 43: Annular plaques of tinea faciale and corporis on a child. Note multiple rings.

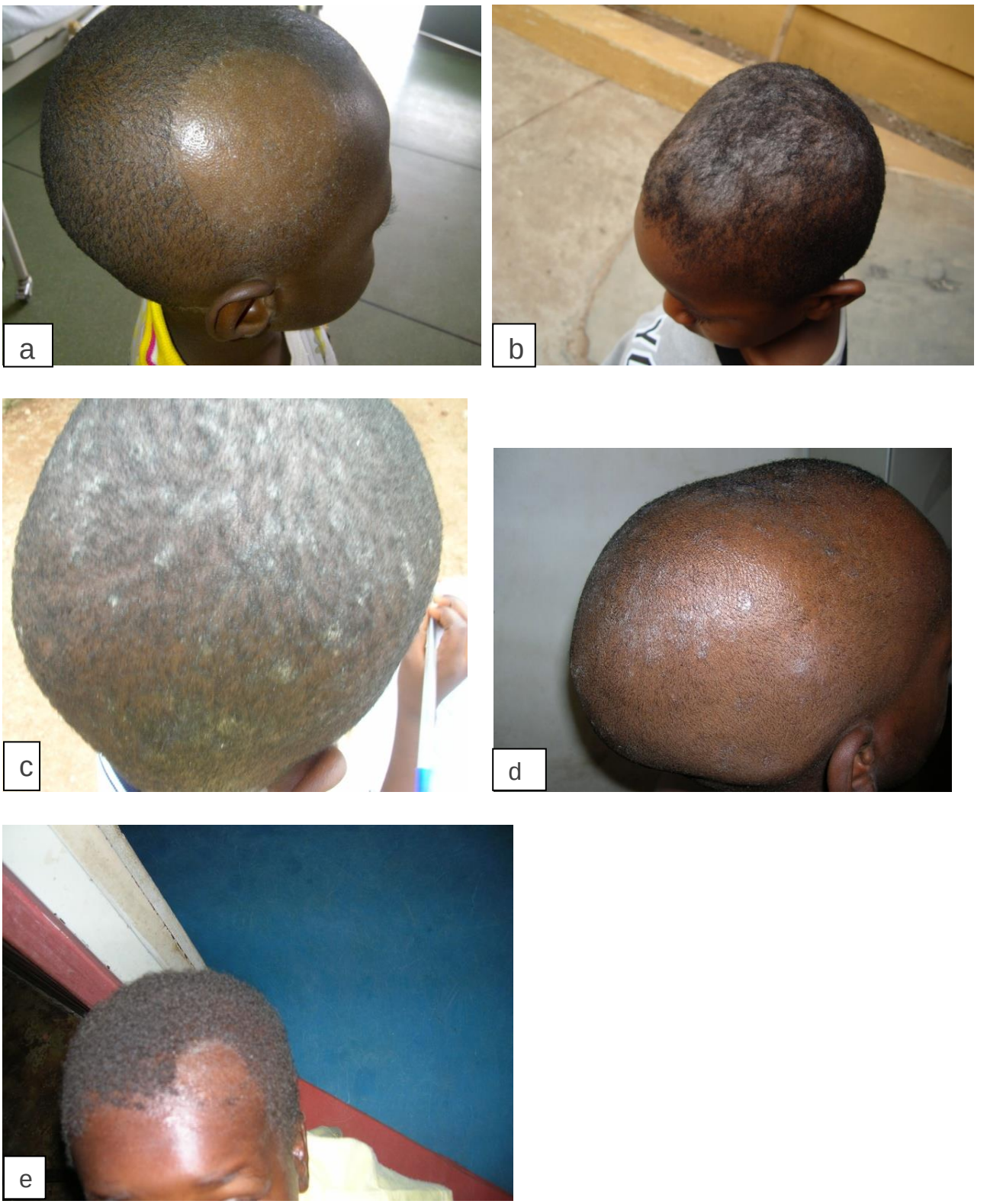


Figure 44 a, b, c, d and e: Variants of tinea capitis on the scalp of 5 children.

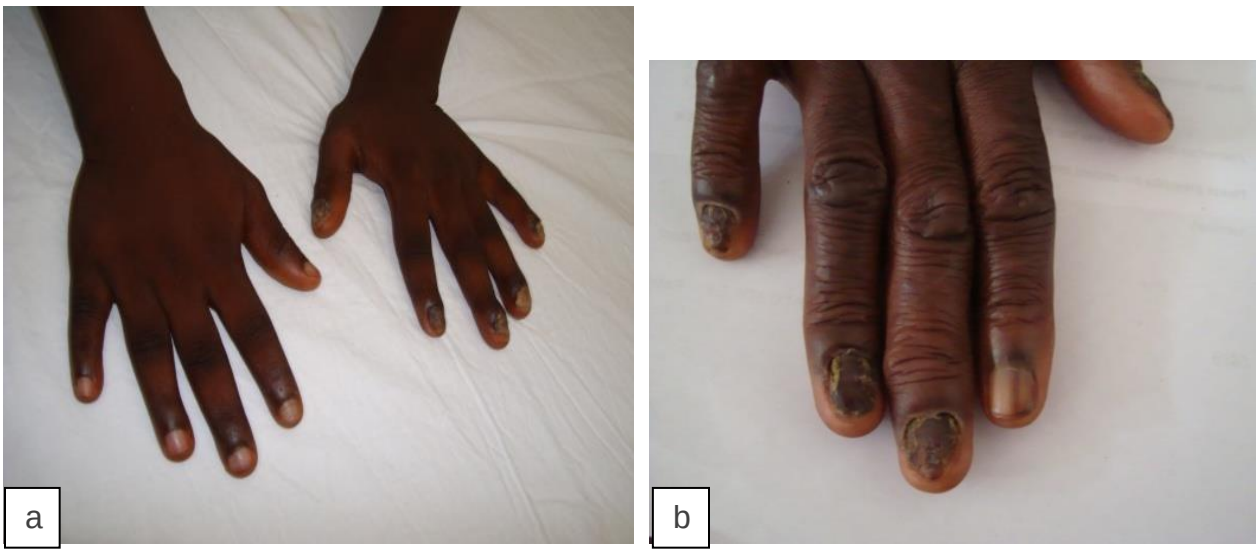


Figure 45 a and b: Tinea unguium in a 5-year-old boy (left) and in his mother (right); both presenting in the ART clinic.

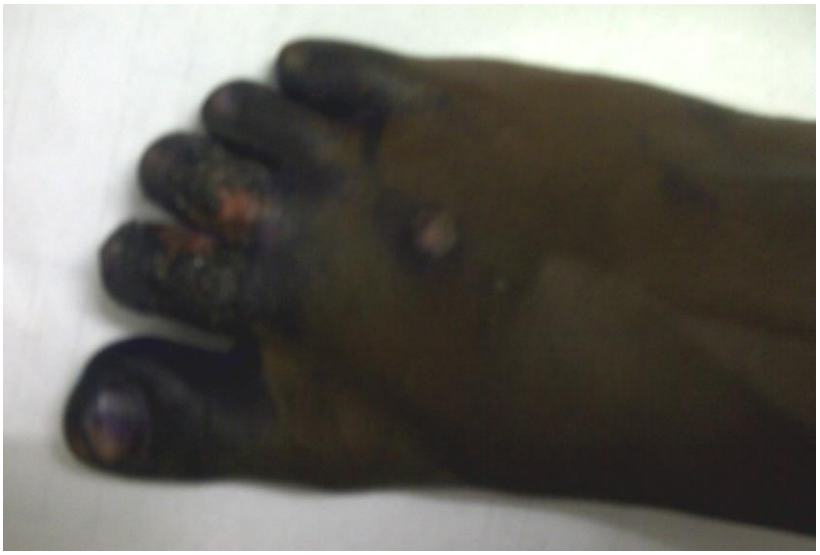


Figure 46: Tinea pedis. Gentian violet applied on the lesion.

Inflammatory Tinea

Tinea infections results in diverse clinical features, ranging from the carrier-state to severe tinea corporis with heavy inflammation.

Although the clinical features of tinea may be similar to those seen in adults with erythema and scaling, signs of dermatophyte infection in children may be nonspecific and mimic other conditions, such as psoriasis, atopic dermatitis, contact dermatitis, dyshidrotic eczema, juvenile plantar dermatosis, impetigo, herpetic infection, and cellulitis. Vesicles and bullae may also be more common in children with inflammatory tinea, mimicking bacterial or herpetic cellulitis.

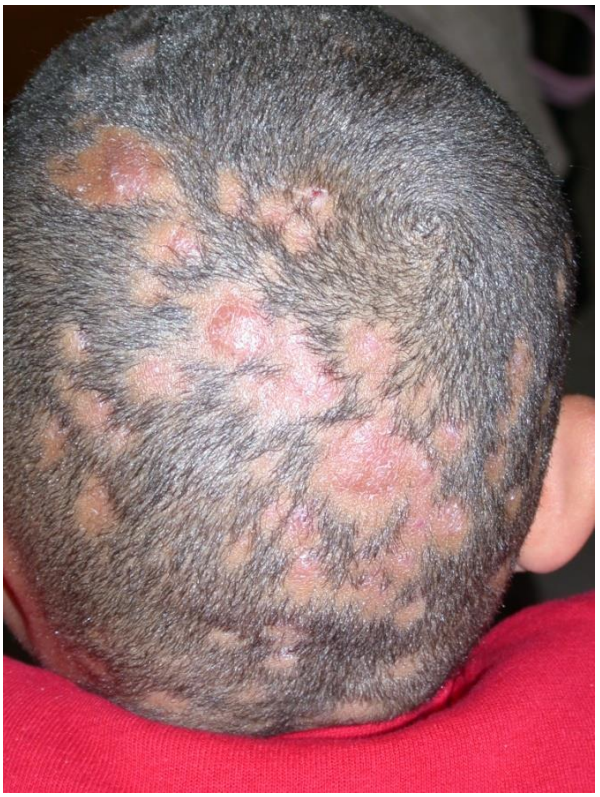


Figure 47: Inflammatory tinea capitis. Note the boggy masses associated with alopecia and scarring.

Pityriasis Versicolor (Tinea Versicolor)

Description: A mild, chronic infection of the skin caused by *Malassezia* yeast.

Aetiology: Is caused by the fungi *Malassezia* and the infection is milder and more superficial than the dermatophyte infections. Isolated species of *Malassezia* in patients include *M. globosa, M. sympodialis, M. furfur, M. obtusa,* and *M. restricta.*

Clinical presentation: The primary lesion is a sharply demarcated macule, sometimes slightly erythematous, but characterized essentially by fine, discrete or confluent branny scale that can be hyperpigmented or hypopigmented mainly on the upper trunk. The scale can be accentuated by stretching the lesions, making them scalier.

Epidemiology: Affects adolescents and adults. Prevalence of tinea versicolor is as high as 40% has been reported in the tropics. Climatic and local environmental factors account for variation in the prevalence seen in different geographical regions.

Diagnosis: This is mainly clinical but potassium hydroxide direct microscopy or visualization of the scaly lesions under Wood's lamp (UV), which shows the typical yellow fluorescence.

Differential diagnoses: Vitiligo and chloasma are normally distinguishable by their complete absence of scaling. Differential diagnoses include: seborrheic dermatitis, pityriasis rosea, secondary syphilis, pinta and tinea corporis.

Treatment: Selenium sulphide in a detergent base, available as shampoo or lotion in 1% or 2.5% concentrations (Selsun® shampoo Blue, Head & shoulders), applied to all the affected areas and left for 10 minutes before washing off or left overnight. In ordinary cases that settle spontaneously or as a result of treatment, the residual depigmentation may remain for many months without any scaling.

Other options include the topical azole antifungals (clotrimazole and ketoconazole). Terbinafine 1% cream is also effective. For widespread lesions topical ketoconazole, 2-3 applications may suffice.

For prophylaxis, selenium sulphide may be applied overnight once a month. Alternatives include 20% sodium hyposulphite solution, and 50:50 propylene glycol in water used long-term as suppressive therapy to prevent relapse.

Oral ketoconazole and itraconazole are also very effective especially when combined with topical antimycotics. Ketoconazole is not recommended in children <10 years. Fluconazole as a single 6 mg/kg dose may also be adequate but some patients may require longer periods of therapy. Itraconazole is active against pityriasis versicolor in a dose of 5 mg/kg usually given over 5 days.

Complications: In ordinary cases that settle spontaneously or as a result of treatment, the residual depigmentation may remain for many months without any scaling. Disfigurement of the affected areas and deep invasive infections may occur in untreated cases.

Further reading

1. Jain A, Jain S, Rawat S. Emerging fungal infections among children: A review on its clinical manifestations, diagnosis, and prevention. J Pharm Bioallied Sci. 2010; 2(4): 314–320.
2. Chaudhary R, Singh S, Banerjee T, Tilak R. Prevalence of different Malassezia species in pityriasis versicolor in central India. Indian J Dermatol Venereol Leprol. 2010;76(2):159-64.
3. Sunenshine PJ, Schwartz RA, Janniger CK. Tinea versicolor. International Journal of Dermatology 1998; 37 (9): 648-655.
4. Borelli D, Jacobs PH, Nall L. Tinea versicolor: epidemiologic, clinical, and therapeutic aspects. J Am Acad Dermatol. 1991; 25:300-305.
5. Shah A, Koticha A, Ubale M, Wanjare S, Mehta P, Khopkar U. Identification and speciation of Malassezia in patients clinically suspected of having pityriasis versicolor. Indian J Dermatol 2013;58: 239.

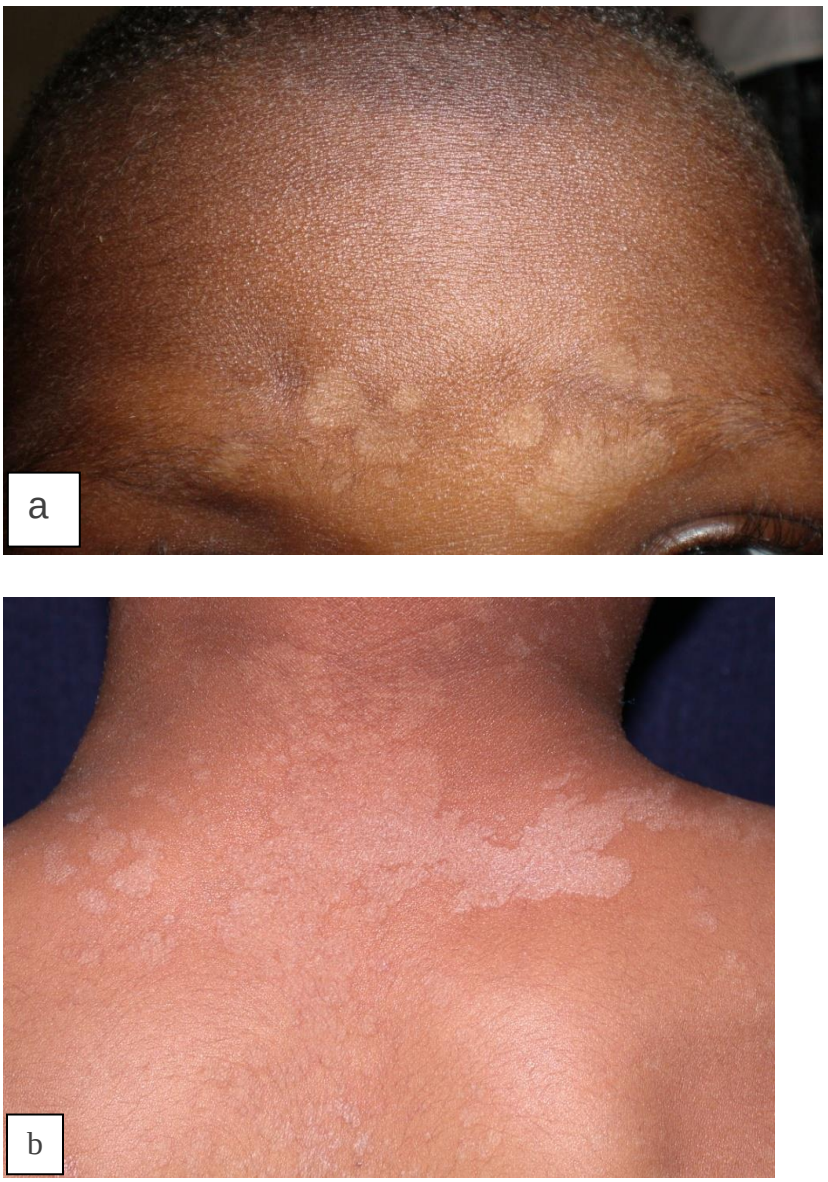


Figure 48a and b: Sharply demarcated macules with fine branny scaling on the forehead and back of children with tinea versicolor. Note the increased scaling after stretching the skin in (b).

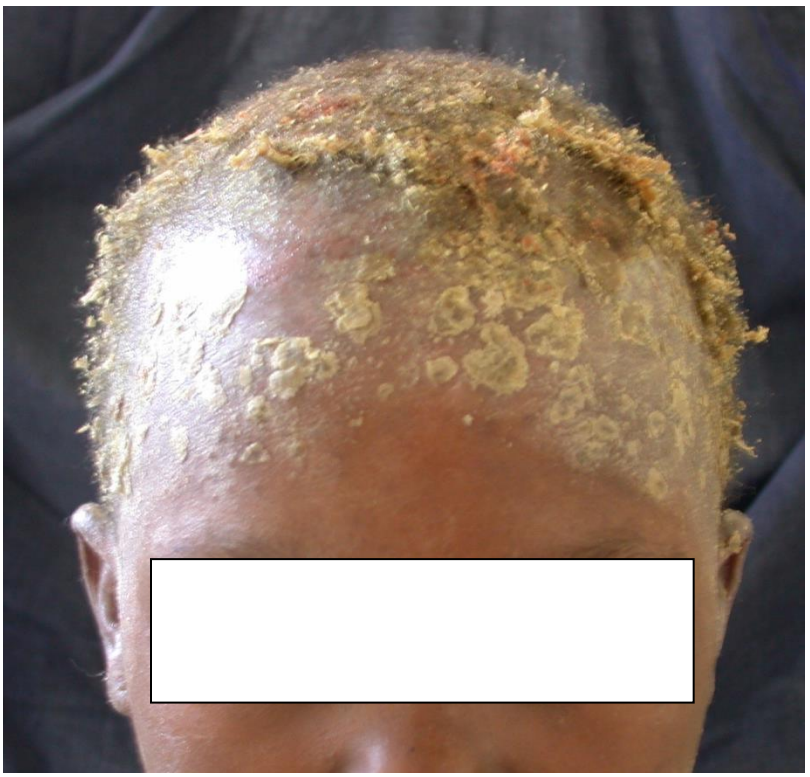


Figure 49: Pityriasis amiantacea, used sometimes to describe a severe form of seborrheic dermatitis.

Candidiasis

Description: Candidiasis is the most common opportunistic infection seen in HIV-infected children. It can affect the oral cavity, the oesophagus and the peri-anal region.

Aetiology: *Candida albicans* is the yeast responsible or candidiasis.

Clinical presentation: Oral candidiasis (thrush) occurs on the surface of the tongue, palate and buccal mucosa as white patches (plaques). This can be distinguished from milk curds by scraping the surface of the plaque, which results in erythema and point bleeds. Pseudomembranous candidiasis manifests as creamy white-to-yellow oral plaques. Atrophic candidiasis manifests as distinct areas of erythema with the loss of tongue papillae if the tongue is affected. Hyperplastic candidiasis (with both erythematous and white mucosal coloration symmetrically distributed) and angular cheilitis are other clinical variants of candidiasis.

Oral thrush can be seen in neonates and in patients receiving prolonged antibiotics and systemic steroids. Oesophageal candidiasis presents with dysphagia, odynophagia and retrosternal pain. Diaper rash due to candidiasis is usually red with a clearly defined border and consists of small red spots close to the large patches (satellite lesion). Diaper rash lasting for 3 days or longer may be candidiasis. *Candida albicans* is one of the causes of onychomycosis. In severely immunocompromised children the organism can cause candidemia or invasive candidiasis.

Epidemiology: Candida albicans is the most common cause of mucosal and oesophageal candidiasis. Oral thrush and diaper dermatitis occur among 50%-85% of HIV-infected children.

Diagnosis: Candidiasis is a clinical diagnosis which can be confirmed by a potassium hydroxide preparation and culture. Cobblestoning appearance on barium swallow may be seen in oesophageal candidiasis.

Prevention: In the mouth, for instance, this involves frequent toilet in the seriously ill, and denture hygiene in other patients, whereas in *Candida* infections affecting the skin, careful drying of affected sites is important.

Treatment: In many cases, topical antifungal therapy alone is sufficient to control the disease. Effective topicals include clotrimazole, nystatin and amphotericin B. Systemic therapy with fluconazole, itraconazole or amphotericin B is indicated in oesophageal disease. In addition, oral antifungals are used to prevent systemic candidiasis in severely immunocompromised patients. Clotrimazole troches or lozenges are used at 50mg 5 times a day while fluconazole and itraconazole dosing are 3-12mg/kg/day and 5mg/kg/day respectively.

Children with severe oral involvement due to diffuse and persistent candidiasis resistant to conventional treatment also tend to have feeding difficulties that may be related to oesophageal involvement. In these cases, the only effective therapy is intravenous fluconazole or amphotericin B.

Complications: Haematogenous dissemination of disease and invasive candidiasis can occur, resulting in candidemia, meningitis, endocarditis, renal disease, endophthalmitis, and hepatosplenic disease.

Further reading

1. Álvaro-Meca A, Jensen J, Micheloud D et al. Rate of candidiasis among HIV-infected children in Spain in the era of highly active antiretroviral therapy (1997–2008). BMC Infect Dis. 2013; 13: 115.
2. Oladokun RE, Okoje VN, Osinusi K et al. Oral Lesions and their association with CD4 Count and Viral Load in HIV Positive Nigerian Children. Oral Health Dent Manag. 2013; 12(4):200-4.
3. Mofenson LM, Brady MT, Danner SP et al. Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. MMWR Recomm Rep. 2009; 58 (RR-11):1–248.4. JS Greenspan, D Greenspan. The epidemiology of the oral lesions of HIV infection in the developed world. Oral Diseases 2002; 8 (S2), 34–39 doi:10.1034/j.1601-0825.2002.00009.x).

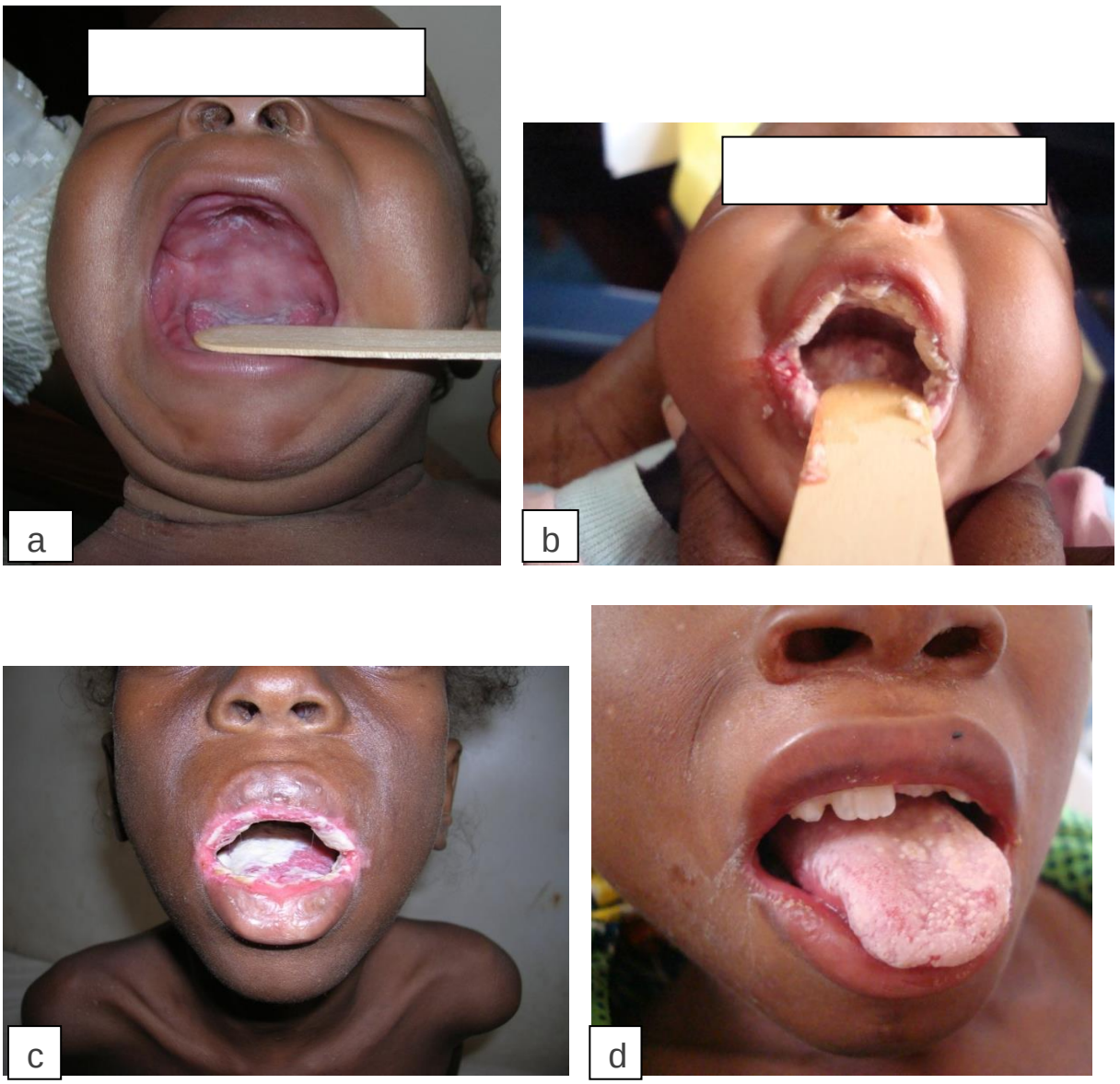


Figure 50a, b, c, and d: Oral candida in immunosuppressed children. Affecting the tongue and palate in (a), severe form in (b) and (c) and pseudomembranous variant in (d).

Anogenital Candidiasis

C. albicans is commonly isolated from the moist skin of the buttocks and genitalia of the infant but is more prevalent where the skin is affected by napkin rash. Satellite lesions may be seen.

Diagnosis: moistened swab or a scraping may be taken to discover whether or not *Candida* is present on the affected skin. If *Candida* is present, a trial of anti-candida therapy is indicated.

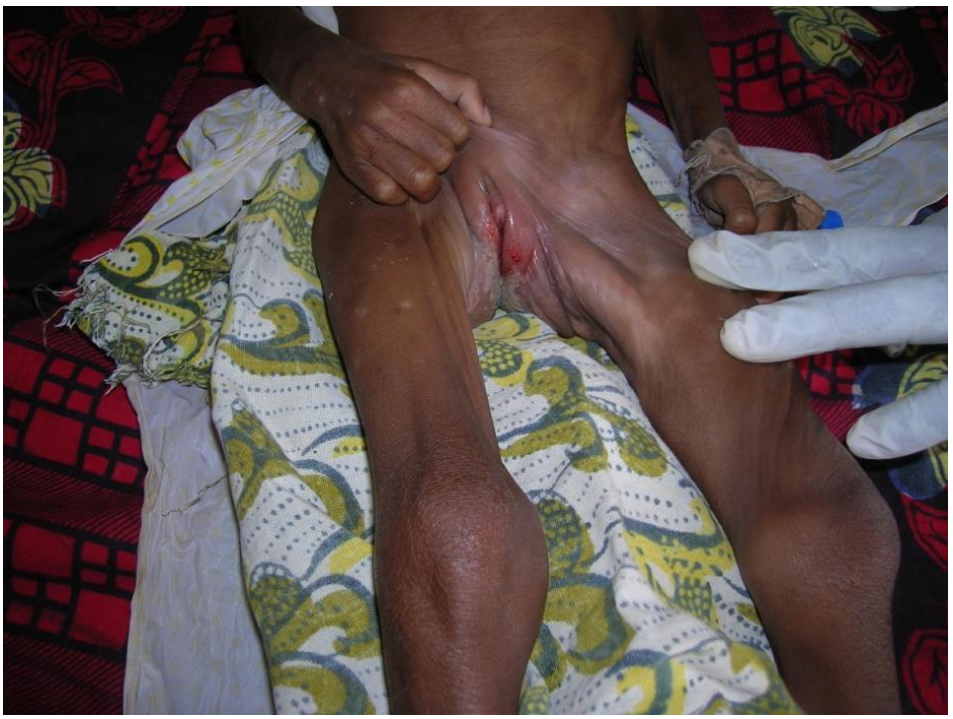


Figure 51: 2-year-old girl with severe pruritus vulva from vaginal candidiasis

Deep Fungal Infections

Histoplasmosis

Description:

Aetiology: Histoplasmosis is a fungal infection caused by the dimorphic fungus Histoplasma capsulatum.

Clinical presentation: Histoplasmosis is mainly inhaled and usually presents as a disseminated disease. Localized infections are rare. Skin may be the most frequent site of localised infection.

The cutaneous lesions of histoplasmosis are polymorphous and include papules, plaques, which may be crusted, erosions, ulcers, exanthems, nodules, acneiform eruptions, exanthems, molluscum-like lesions, acneiform folliculitis, psoriasiform eruptions, panniculitis, hyperkeratotic plaques, vasculitic lesions, erythema multiforme-like lesions, exfoliative dermatitis, abscesses and cellulitis. Oral ulcers and erosions are the most common manifestation of disseminated disease. There may be associated systemic symptoms including fever, lymphadenopathy, hepatosplenomegaly, lung disease and pancytopenia.

Diagnosis: Chest X-rays, tissue biopsies for histology and culture aid diagnosis. *Histoplasma capsulatum* can be identified on skin biopsy by the Gomori methenamine silver stain however culture of the organism is the gold standard.

Treatment: In addition to ART, infected patients benefit from systemic antifungal treatment with itraconazole or amphotericin B with long-term prophylaxis. For disseminated infection, the preferred approach is to give IV amphotericin for 4 weeks followed by itraconazole prophylaxis.

Further reading

1. Chang P, Rodas C. Skin lesions in histoplasmosis. Clin Dermatol 2012 ; 30(6):592-8.
2. Johnson RA. HIV disease: mucocutaneous fungal infections in HIV disease. Clin Dermatol 2000; 18: 411–22.
3. Imenez-Acosta FJ, Vicandim B, Viguer JM et al. Diagnostic value of cutaneous cytology in opportunistic fungal infections of patients with acquired immuno- deficiency syndrome. J Am Acad Dermatol 1988; 18: 383–4.
4. Penneys NS. Skin manifestations of AIDS. London: Martin Dunitz, 1990.
5. Casariego Z, Kelly GR, Perez H et al. Disseminated histoplasmosis with orofacial involvement in HIV-1-infected patients with AIDS: manifestation and treatment. Oral Dis 1997; 3: 184–7.
6. Ramdial P, Mosam A, Dlova NC et al. Disseminated cutaneous histoplasmosis in patients infected with human immunodeficiency virus. J Cutan Pathol 2002; 29: 215–25.

7. Antinori S, Magni C, Nebuloni M et al. Histoplasmosis among human immuno- deficiency virus-infected people in Europe: report of 4 cases and review of the literature. Medicine (Baltimore) 2006; 85: 22–36.
8. Casotti JA, Motta TQ, Ferreira CU et a. Disseminated histoplasmosis in HIV positive patients in Espirito Santo state, Brazil: a clinical-laboratory study of 12 cases (1999–2001). Braz J Infect Dis 2006; 10: 327–30.
9. Cunha VS, Zampese MS, Aquino VR et al. Mucocutaneous manifestations of disseminated histoplasmosis in patients with acquired immunodeficiency syndrome: particular aspects in a Latin-American population. Clin Exp Dermatol 2007; 32: 25.

Figure 52: Multiple lesions seen in the face of this child with histoplasmosis based on histopathology. Note nodules with hyperkeratotic centres, some of which seem umbilicated.

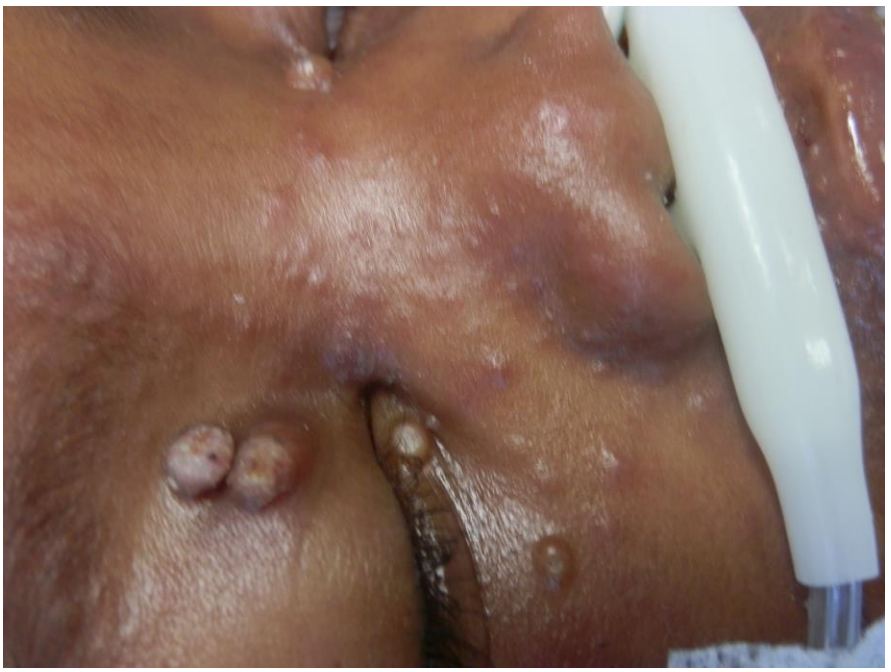


Figure 53: Close up photograph showing the same lesions as described above. Numerous erythematous papules widespread on the trunk of the same child as above with histoplasmosis, together with scarring from previous lesions.

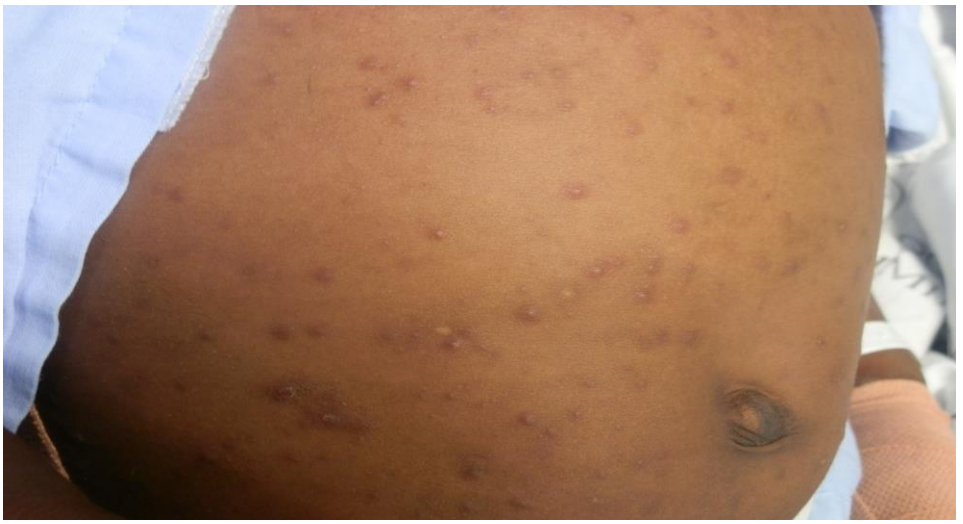


Figure 54: Numerous erythematous papules widespread on the trunk of the same child as above with histoplasmosis, together with scarring from previous lesions.

Figures 52 – 54 above emphasize the polymorphous nature of histoplasmosis lesion.

Cryptococcal Infection

Aetiology: Cryptococcosis is caused by *Cryptococcus neoformans.*

Clinical presentation: Brain, lung and skin are sites of predilection. In the skin, it presents as jelly-like necrotizing papules and nodules that resemble molluscum contagiosum. Acneiform, tumourous (warty) and papulopustular variants of the disease have been documented.

Epidemiology: Before the advent of ART, was estimated to affect 5-10% of persons with AIDS in the US and UK, and 30-40% in Africa.

Diagnosis: For systemic disease, serology, blood culture, urine culture and lumber culture should be done. Cutaneous disease can be confirmed by skin biopsy with special stains for the cryptococcal capsule and culture or Tzanck smear.

Treatment: Intravenous amphotericin B and oral fluconazole (see cryptoccocal infection in Part 2 of the atlas). Secondary prophylaxis is with fluconazole.

Further reading

1. Ricchi E, Manfredi R, Scarani P et al. Cutaneous cryptococcosis and AIDS. J Am Acad Dermatol 1991; 25: 335–6.
2. Blauvelt A, Kerdel FA. Cutaneous cryptococcosis mimicking Kaposi's sarcoma as the initial manifestation of disseminated disease. Int J Dermatol 1992; 31: 279- 280.
3. Coker LR, Swain R, Morris R, McCall CO. Disseminated cryptococcosis presenting as pseudofolliculitis in an AIDS patient. Cutis 2000; 66: 207–10.
4. Jimenez-Acosta FJ, Vicandim B, Viguer JM et al. Diagnostic value of cutaneous cytology in opportunistic fungal infections of patients with acquired immuno- deficiency syndrome. J Am Acad Dermatol 1988; 18: 383 - 384.
5. 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/.

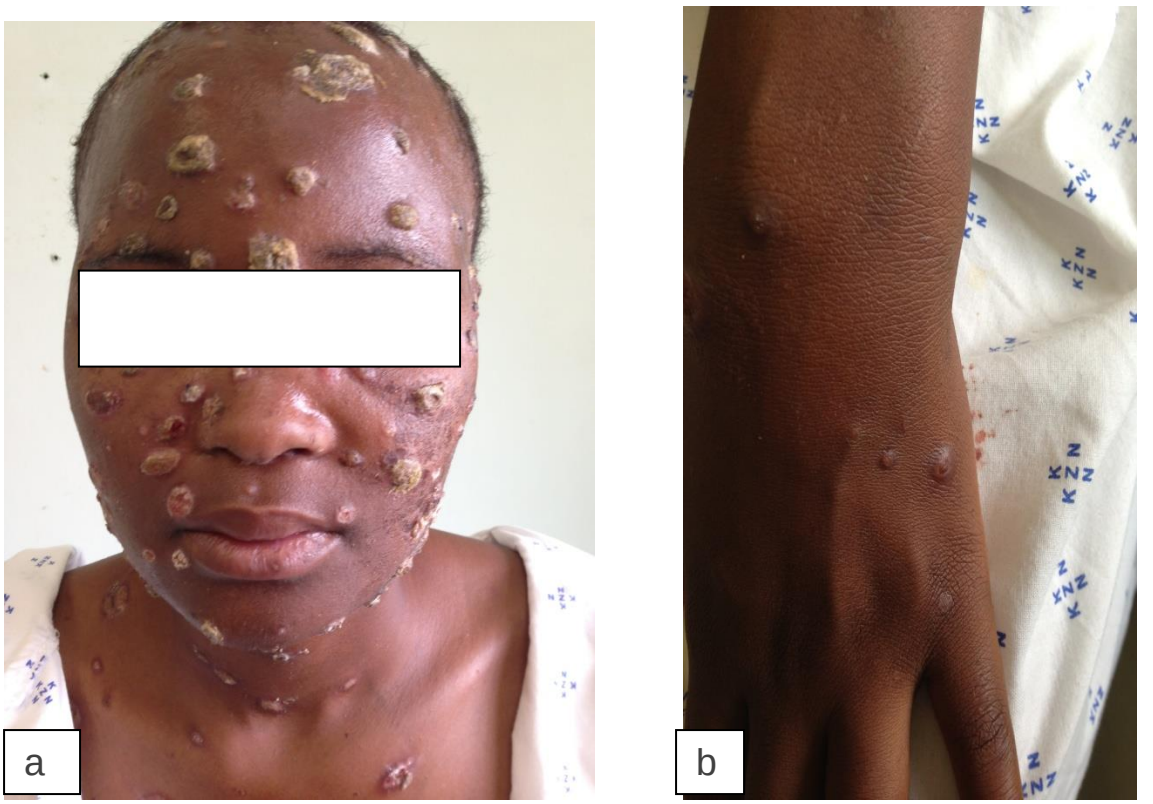


Figure 55a and b: Cutaneous cryptococcosis (Courtesy of Prof. Anisa Mosam. Dermatology Department, University of Kwazulu Natal).

Emergomyces Africanus (Formerly Emmonsia) Infection

A recent report of cases of a new species of dimorphic fungus pathogenic to humans, especially in human immunodeficiency virus-infected was made in South Africa adults, most of whom presented with lung and skin lesions. A case of disseminated emmonsiosis has also been reported in an HIV-infected child. The child had severe immunosuppression (CD4+ T cell count 0.012 x 10^9/L). The DNA sequence was identical to the disseminated disease caused by the novel organism. Many of these cases of emergomycosis had initially been diagnosed as histoplasmosis.

Aetiology: Causative organism: closely related to Emmonsia pasteuriana now called Emergomyces africanus.

Treatment: Amphotericin B given for 6 weeks, in addition to initiation of ART.

Further reading

1. Kenyon C, Bonorchis K, Corcoran C, et al. A dimorphic fungus causing disseminated infection in South Africa. N Engl J Med 2013; 369 (15): 1416–1424.
2. Lochan H, Naicker P, Ryan A et al. A case of disseminated emmonsiosis in an HIV-infected child. Southern African HIV Clinician Society Conference; 24-27 Sept 2014.
3. Schwartz IS, Govender NP, Corcoran C, Dlamini S, Prozesky H, Burton R, Mendelson M, Taljaard J, Lehloenya R, Calligaro G, Colebunders R, Kenyon C. Clinical Characteristics, Diagnosis, Management, and Outcomes of Disseminated Emmonsiosis: A Retrospective Case Series. Clin Infect Dis. 2015 Sep 15;61(6):1004-12.

Sporotrichosis

Background: A deep fungal infections more common in adults affected with HIV than children. In immunocompetent individuals, infection generally results from cutaneous inoculation by trauma it may present as a disease of the skin and draining lymphatics. Sporotrichosis associated with HIV may in addition occur as pulmonary infection following spore inhalation and may be haematogenously spread from pulmonary infection to the skin and joints.

Aetiology: The agent, *Sporothrix schenckii*, a dimorphic fungus found in soil and in animal faeces, is responsible for most infections.

Epidemiology: Sporotrichosis is relatively uncommon even though it shares a worldwide distribution. In some parts of the world, the condition follows cat scratch or contact with the affected animal's wound.

Diagnosis: Tissue biopsy and fungal culture are the mainstay of diagnosis. Blood culture samples, bronchoalveolar lavage or CSF for microscopic examination may be helpful.

Clinical: On the skin, sporotrichosis presents as suppurating nodules that progress onto ulcers at the point of inoculation and progress proximally along lymphatic vessels. In disseminated disease the skin lesions are widespread.

Other organs can be affected in visceral disease including the CNS, joints, spleen, bone marrow, pneumonia, meningitis and eyes

Treatment: Amphotericin B at a dose of 0.7mg/kg per day for 3 to 4 weeks. Potassium iodide, normally used for infected patients is not recommended for HIV/AIDS patients. Other options include itraconazole and fluconazole.

Further reading

1. Carvalho MT, de Castro AP, Werner BB et al. Disseminated cutaneous sporotrichosis in a patient with AIDS: report of a case. Rev Soc Bras Med Trop, 35 (2002) 655–659S.
2. Hardman, I. Stephenson, D.R. Jenkins, M.J. Wiselka, E.M. Johnson. Disseminated Sporothrix schenckii in a patient with AIDS. J Infect. 2005; 51(3):e73-7.
3. Edwards C, Reuther WL, Greer DL. Disseminated osteoarticular sporotrichosis: treatment in a patient with acquired immunodeficiency syndrome. South Med J, 93 (2000), 803–806.
4. Rocha MM, Dassin T, Lira R et al. Sporotrichosis in patient with AIDS. Rev Iberoam Micol, 18 (2001), 133–136.
5. Kauffman CA, Hajjeh R, Chapman SW. Practice guidelines for the management of patients with sporotrichosis. For the Mycoses Study Group. Infectious Diseases Society of America. Clin Infect Dis, 30 (2000), 684–687.

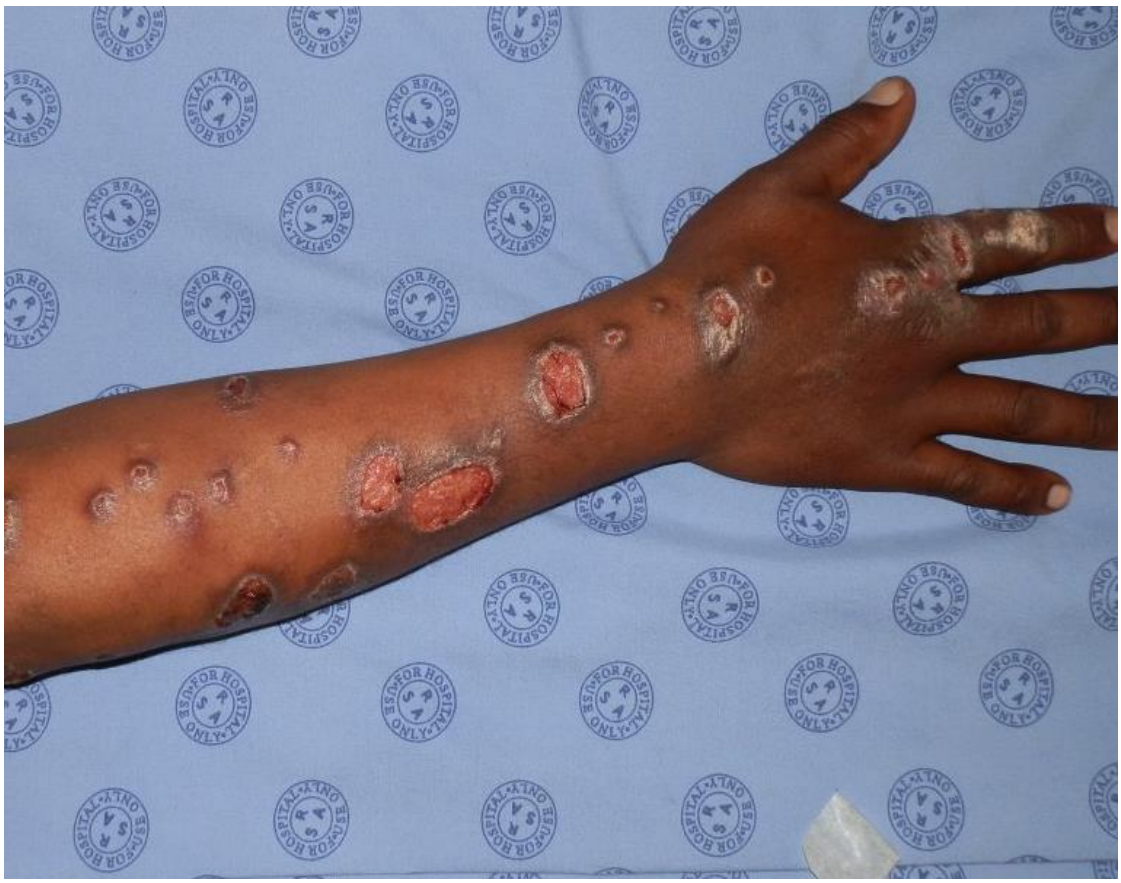


Figure 56: Sporotrichosis on the arm of an HIV-infected child. Note the predominantly linear "sporotrichoid spread" along the lymphatics.

Table 3: Fungal Infections – Treatment options

Condition	First line	Second line	Where available/ indicated
Superficial fungal infections			
Tinea Corporis	Topical agents: including clotrimazole, econazole, oxiconazole, miconazole, terbinafine, naftifine	Oral griseofulvin	Terbinafine, itraconazole, fluconazole
Tinea Capitis	Oral Griseofulvin 10mg/kg daily x 6 weeks	Fluconazole-6mg/kg once weekly for 6 weeks	Oral terbinafine, itraconazole
Candidiasis	Topical clotrimazole, nystatin	Clotrimazole troches	Severe infection - systemic agents: fluconazole, itraconazole, amphotericin B
Pityriasis versicolor	-20% sodium hyposulphite solution -2.5% selenium sulphide in a detergent base (Selsun® shampoo)	Ketoconazole shampoo, terbinafine 1% cream	Oral ketoconazole, itraconazole
Deep fungal infections			
Histoplasmosis	Oral itraconazole	Amphotericin B	
Cryptococcosis	Amphotericin B + Fluconazole	Fluconazole only	
Sporotrichosis	Amphotericin B	Itraconazole	Fluconazole

CHAPTER 4: SKIN INFESTATIONS

Scabies

Description: The clinical presentations of scabies include papular, nodular, bullous and crusted scabies.

Aetiology: Scabies is caused by a mite (*Sarcoptes scabiei var homini*) and has an incubation period of about three weeks.

Clinical presentation: Presents with Itching (severe at nights), characteristic burrow in the interdigital web spaces, papules, blisters, nodules, and eczematous changes. The skin lesions commonly involve web spaces, flexor surface of wrists, axillae, umbilicus, waist, feet, and ankles. In HIV-infected children it can affect the face, scalp and nail folds. Crusted or Norwegian scabies is mainly seen in immunosuppressed individuals such as patients with HIV/AIDS. It is highly contagious and may be the source of epidemics.

Epidemiology: An estimated 300 million cases per year occur worldwide. It is associated with overcrowding and poor sanitary conditions. Epidemics can occur among children in institutional care. Mode of transmission is mainly through direct contact.

Diagnosis: Clinical diagnosis can be made but definitive diagnosis is made by microscopic identification of mites, eggs, or mite faeces (scybala) from skin scrapings.

Prevention: Personal hygiene. Prompt diagnosis and effective treatment. Avoid close contact with infected persons or contaminated fomites.

Treatment: Treat the whole body and all contacts with scabicides. Where available, the commonly used scabicide is benzyl benzoate. If benzyl benzoate is not tolerated, sulphur ointment is used. For children <6months of age: 5% sulphur ointment twice daily for 3 days; 6 months – 2 years of age: ¼ strength benzyl benzoate as a single application; 2 – 12years of age: ½ strength benzyl benzoate as a single application and >12 years of age: full strength benzyl benzoate as a single application. Permethrin and ivermectin are alternative therapy: 200mcg/kg in two divided doses given 2 weeks apart. In crusted scabies oral ivermectin is best combined with a topical scabicide. It is useful to remember that the scabies mite can only live about 72 hours without human contact, but once on a person, the mites can live up to two months.

Tetmosol soap is added to wash the body, clothes and linen.

Complications: Secondary bacterial infection can occur.

Further reading

1. Gilmore SJ. Control Strategies for Endemic Childhood Scabies. PLoS One. 2011; 6(1): e15990.
2. Fernández-Sánchez M, Saeb-Lima M, Barrera CA et al. Crusted scabies-associated immune reconstitution inflammatory syndrome. BMC Infect Dis. 2012; 12: 323.
3. Orkin M. Scabies: what is new? Curr Probl Dermatol 1995;22:105–111.
4. Karthikeyan K. Treatment of scabies: newer perspectives. Postgrad Med J 2005; 81:7–11.
5. Hogan MT. Cutaneous infestations associated with HIV/AIDS. Dermatol Clin 2006; 24:473-95.
6. Gershon AA, Mervin M, Larussa P, et al. Varicella zoster viral infection in children with underlying human immunodeficiency viral infection. J Infect Dis 1997; 176: 1496-500.

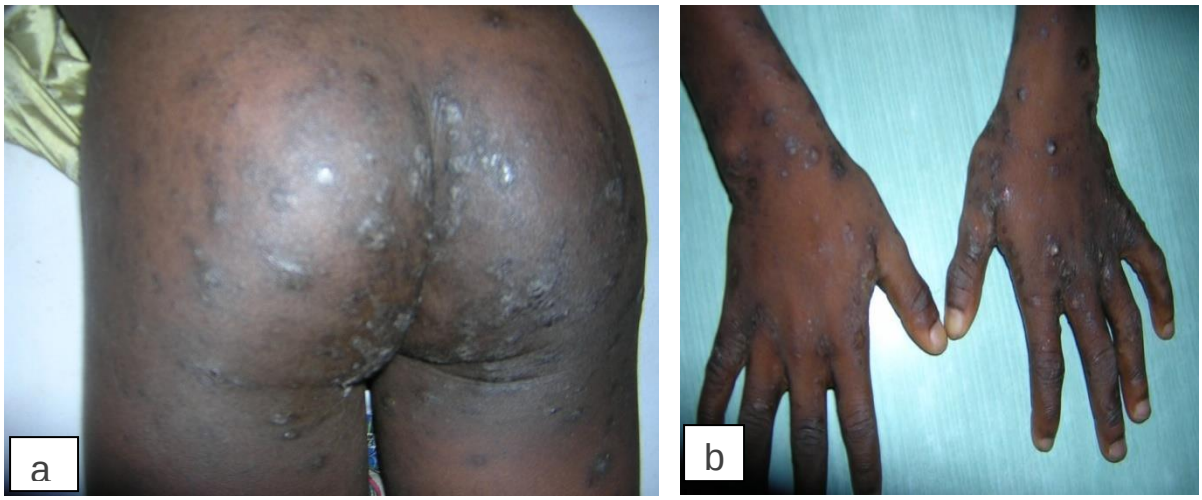


Figure 57: Scabies on buttock and hands, note web spaces involvement.

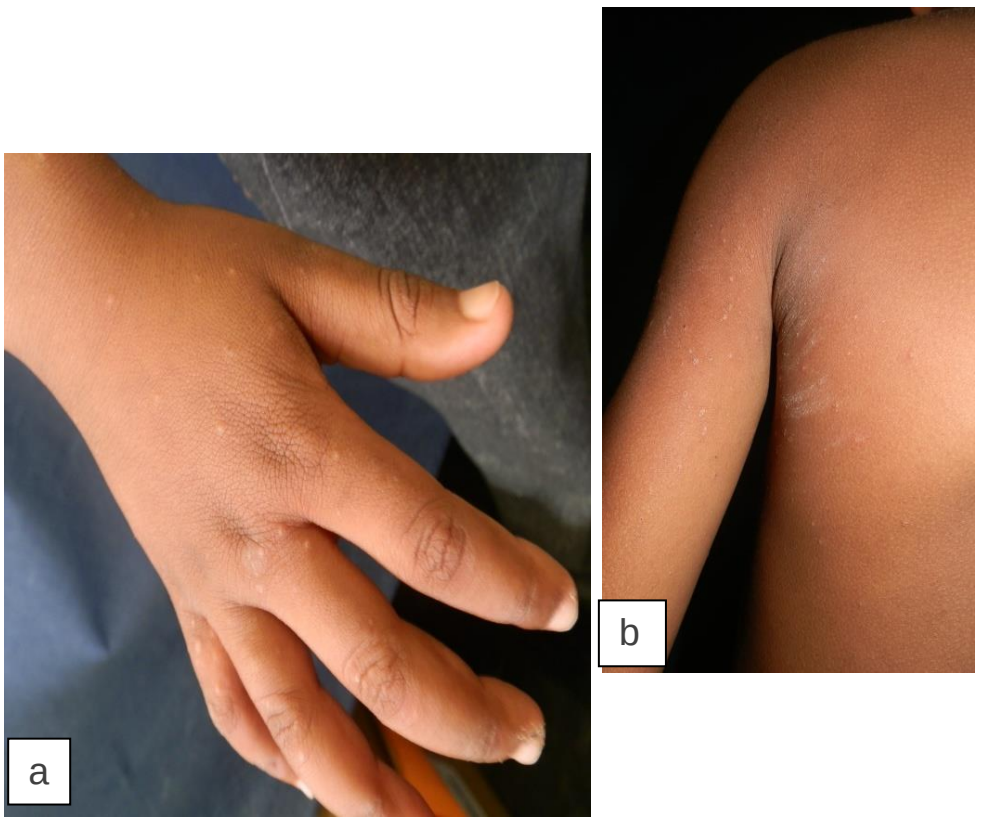


Figure 58a and b: Scabies: Note the interdigital distribution.

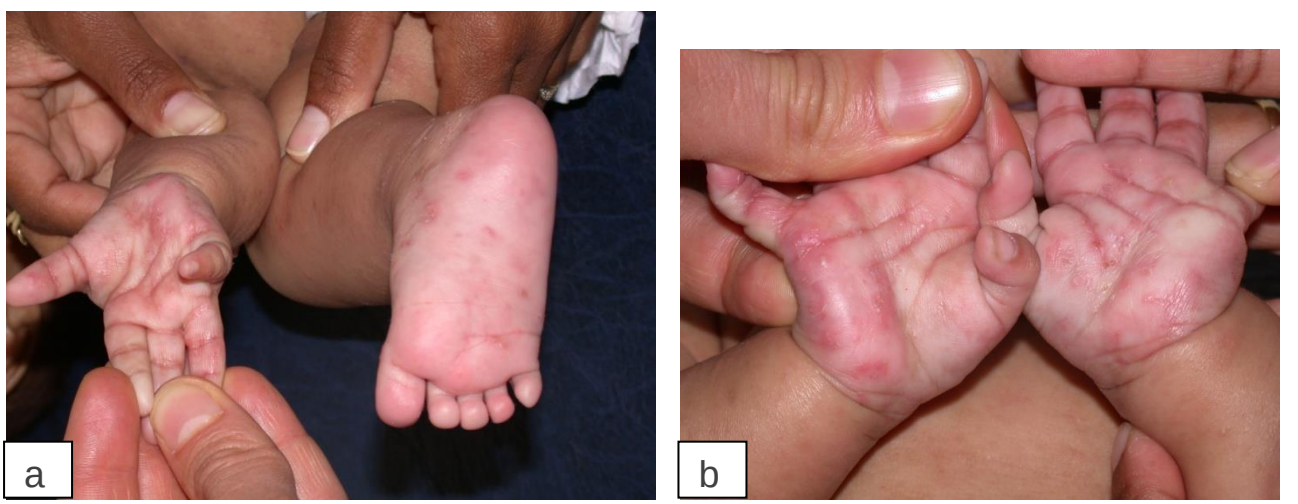


Figure 59a and b: Scabies on the sole and palms of an infant.

Pediculosis

Description: Pediculosis is infestation of the hairy parts of the body by lice.

Aetiology: Head lice are caused by *Pediculus humanus capitis* while pediculosis pubis causes infestation of the public area.

Clinical presentation: Itching on the affected area 3-4 weeks after infestation.

Epidemiology: A common parasitic infection in children and most prevalence in children between 3 and 11 years old. It is rare in African children due to the texture of their hair. There is no seasonal variation or relationship with the level of hygiene.

Diagnosis: Pediculosis is diagnosed by identifying live lice on the affected area.

Prevention: Health education. Avoid physical contact with infested persons and their materials such as beddings, clothing and comb.

Treatment: There is no modality that assures destruction of the eggs and hatched lice after a single treatment. Options include physical methods (wet combing), topical pediculicides (pyrethrins, pyrethroids pyrethrins, and lindane). Treatment should be repeated after an interval of 7-10 days. All other contacts should also be treated.

Complications: Secondary bacterial infections.

Further reading

1. Smith CH, Goldman RD. An incurable itch: head lice. Canadian Family Physician 2012; 58: 839-841.
2. Leone P. Scabies and pediculosis pubis: an update of treatment regimens and general review. Clin Infect Dis. 2007; 44: S153-S159.

Figure 60a and b: Pediculosis capitis in a) and lice in b).

Myiasis

Description: Myiasis manifests as boil-like lesions, usually on exposed areas of the body such as the trunk, thigh and buttocks.

Aetiology: The lesions are caused by infestation of the skin by developing larvae (maggots) of the tumbu fly (*Cordylobia anthropophaga*). The female fly lays its eggs on dry, sandy soil or on damp clothing hung out to dry. The eggs hatch in 1 to 3 days and penetrate the skin.

Epidemiology: The tumbu fly is prevalent in sub-Saharan Africa, thriving in the warm and humid environment. Myiasis occurs more commonly in children and during the raining season.

Clinical presentation: Lesions can be painful, pruritic, and tender, and patients often have the sense of something moving under the skin. There may also be fever or swollen glands. In ophthalmomyiasis, there may be severe eye irritation, redness, foreign body sensation, pain, lacrimation, and swelling of the eyelids.

Diagnosis: Each lesion has a central punctum from which serosanguinous fluid may be discharged and the movement of the larva may be noticed by the patient. The tip of the larva may protrude from the punctum. Diagnosis is typically made by identification of the larvae. Ultrasonography may be useful in establishing the diagnosis and in determining the size of the larvae. Biopsies are not usually necessary.

Treatment: A non-invasive mode of management is to occlude and suffocate the larva by application of petroleum jelly or liquid paraffin over the central punctum. This makes the larvae to emerge spontaneously head-first over the course of several hours, at which time, tweezers (or forceps) aid in the removal.

Prevention: Clothing should be hot-ironed and dried appropriately to remove any residual eggs in areas endemic to tumbu flies.

Further reading

1. Francesconi F, Lupi O. Myiasis. Clin Microbiol Rev. 2012;25(1):79-105. doi: 10.1128/CMR.00010-11.
2. Blechman AB, Wilson BB. Myiasis. http://emedicine.medscape.com/article/1491170-overview.

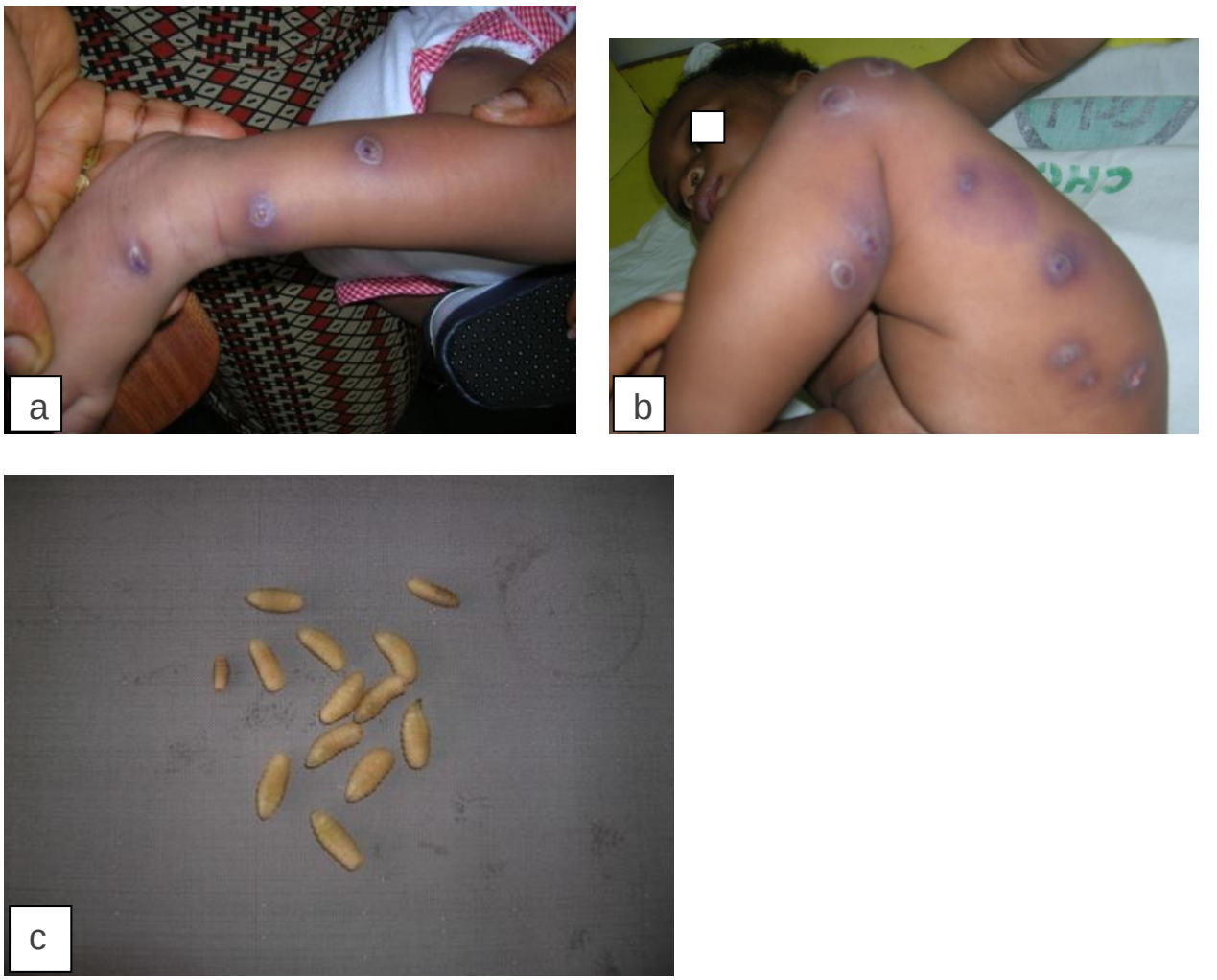


Figure 61a, b and c: Myiasis involving the lower limbs in a 6-month-old girl seen in the clinic (a), (b). The larvae (c) were expressed from the lesions.

Table 4: Parasitic infections – Treatment options

Condition	Treatment1	Treatment2	Treatment3
Scabies	Benzyl benzoate	Ivermectin	Permethrin
Pediculosis	Physical methods (wet combing)	Choice of pyrethrins, pyrethroids, lindane	Oral antihelminthics and antibiotics
Myaisis	Petroleum jelly or liquid paraffin over the central punctum		

CHAPTER 5: INFLAMMATORY SKIN CONDITIONS

The most common conditions in this group are seborrheic dermatitis, xerosis and papular eruptions.

Moisturisers and emollients may be useful in certain conditions discussed in this section. They help sooth and hydrate the skin and include oil instilled in the baths (e.g. liquid paraffin) and creams (e.g. Cetomacrogol cream). Lotions and ointments (emulsifying ointment or humectants such as 5-10% Urea contained in emulsifying ointment) are also available to be applied directly to the skin but are reserved for applications to very dry skin.

Topical corticosteroids (applied to the skin as cream or ointment) used as anti-inflammatory agents are subdivided into seven groups, with group one being the most potent and group seven the least potent *(WHO model prescribing information- Drugs used in skin diseases. Geneva, World Health Organization, 1997).*

Group 1: Super high potency e.g. clobetasol propionate 0.05%.

Group 2: High potency e.g. betamethasone diproprionate 0.05%.

Group 3: Upper-mid potency e.g. mometasone furoate 0.1% ointment.

Group 4: Mid potency e.g. mometasone furoate 0.1% cream.

Group 5: Lower-mid potency e.g. betamethasone valerate 0.1%.

Group 6: Mild potency e.g. fluocinolone acetonide 0.01%.

Group 7: Least potent e.g. hydrocortisone 1%.

Papular Urticaria

Definition: Recurrent and often chronic hypersensitivity reaction to insect bites.

Aetiology: The reaction results from mosquito, flea, bedbug and other insect bites in hypersensitized children.

Epidemiology: Papular urticaria is predominantly a disease of children although it also occurs in non-local adults. It is thought to affect adults who have not been desensitized by previous recurrent bites by the same insects. It is a self-limiting condition and the children tend to outgrow the disease.

Clinical presentation: It presents as intensely pruritic papules that may be surrounded by a wheal. In severe cases blisters may form. The lesions tend to occur in groups or clusters in exposed and covered parts of the body. Scratching may result in excoriation and dyspigmentation. In recurrent cases, the lesions are usually in different stages of evolution.

Diagnosis: Papular urticaria is a clinical diagnosis. A skin biopsy is helpful in supporting the diagnosis in difficult cases.

Prevention: Insect repellents and insecticides help prevent insect bites

Treatment: This is mainly symptomatic and topical steroids (e.g. 1% Hydrocortisone cream) and antihistamines (e.g. Chlorpheniramine) are helpful**.**

Complications: secondary bacterial infections

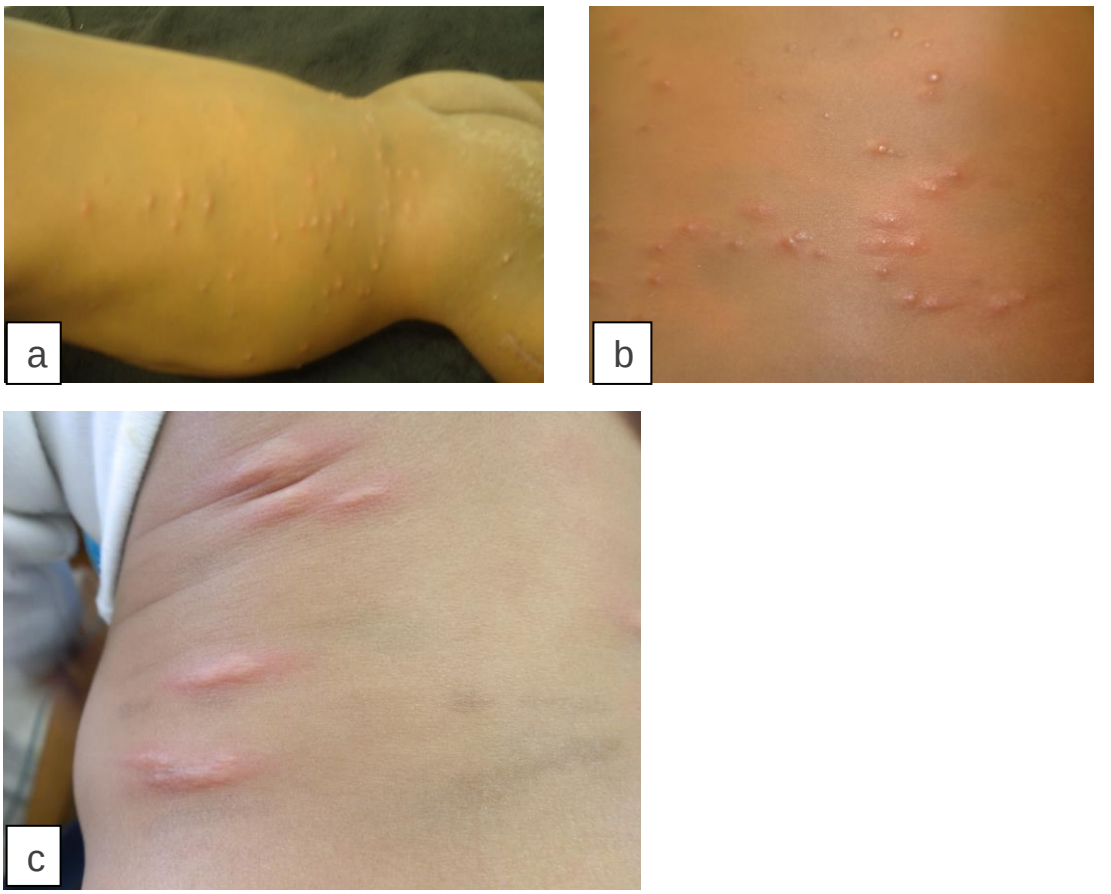


Figure 62a, b and c: Papular urticaria. Note the urticarial plaques in (a), (b) and blisters in (c).

Papular Pruritic Eruption of HIV (PPE)

HIV-related pruritic papular eruption (PPE) and eosinophilic folliculitis (EF) are poorly differentiated and are confused in their diagnosis.

Description: Papular pruritic eruptions (PPE) are a common dermatological manifestation of HIV and may often be the may often be the first sign of HIV which could be useful in diagnosing the infection. PPE is a sign of advanced degree of immunosuppression, occurring at low CD4 T-cell counts. The severity of PPE increases as CD4 counts decrease.

PPE has a clinical overlap with eosinophilic folliculitis (EF) of HIV.

Epidemiology: PPE prevalence varies between 10 and 60% depending on geographical area. It is common in Africa and Asia.

Aetiopathogenesis: PPE is postulated to be due to altered and exaggerated immune response to arthropod antigens as a result of the increased involvement of exposed or uncovered skin. It is associated with eosinophilia and elevated IgE.

Clinical presentation: PPE presents as chronic waxing and waning, intensely pruritic papules and symmetric involving predominantly the extremities and trunk, though facial involvement can also occur. The mucous membranes, palms and soles are spared. Extensive excoriation with subsequent scarring and post-inflammatory hyperpigmentation from scratching and infection can be disfiguring and stigmatizing.

Diagnosis: Skin biopsy is helpful to diagnose both EF and PPE. PPE histology shows a wedge-shaped, moderately dense, superficial and deep perivascular and interstitial lymphocytic and eosinophilic infiltrate; the epidermis is hyperplastic and there may be a spongiotic punctum.

Differential diagnosis: Differential diagnosis of both PPE and EF include nodular prurigo, prebullous pemphigoid, scabies, papulonecrotic tuberculid, drug eruption, photodermatitis, secondary syphilis, onchodermatitis and eosinophilic, pityrosporum, bacterial and acneiform folliculitis.

Treatment: It is a strong clinical indication for initiating ART. Initiation of ART has been shown to dramatically decrease the severity of PPE-HIV, often with lesions disappearing and not returning. Treatment of PPE is similar to that of eosinophilic folliculitis. Topical steroids, antihistamines, phototherapy and pentoxifylline (oxpentifylline) have been claimed to be efficacious.

Eosinophilic folliculitis (EF)

EF is common among HIV-infected children. It is a marker of CD4 decline. The cause of EF is unknown. It is thought to be a result of immune dysregulation to a variety of agents such as

Pityrosporum ovale, or the follicular mite *Demodex folliculorum*, an autoimmune reaction to the sebocyte, or a component of sebum.

Clinical presentation: EF has characteristic morphology and distribution, resembling insect bites. EF presents as a centripetal (face and trunk) eruption of pruritic, erythematous, perifollicular papules and pustules. Patients with eosinophilic folliculitis may be subclinically photosensitive. It manifests as discrete erythematous papules, or papules surmounted by a tiny pustule concentrated on the face, neck, upper trunk and proximal part of the upper limbs. It is usually itchy and may be difficult to differentiate from papular pruritic eruption.

Diagnosis: Skin biopsy for EF characteristically shows degranulating eosinophils and mast cells in a perifollicular distribution. Blood tests may be useful in EF as there may be a peripheral eosinophilia.

Treatment: For EF institution of ART is critical. The first line of treatment is topical steroids, emollients, and oral antihistamines. Phototherapy is the most successful treatment modality but other treatments that have been tried including topical disodium cromoglycate, topical tacrolimus, oral antibiotics (erythromycin, tetracyclines, co-trimoxazole), oral itraconazole (for its anti-eosinophilic effect), oral dapsone, oral indomethacin, oral isotretinoin and oral metronidazole with antipruritic agents.

Prevention: The lesions can be reduced by covering the extremities to reduce exposure to insect bites.

Complications: Secondary bacterial infections.

Further reading

1. Afonso JP, Tomimori J, Michalany NS et al. Pruritic papular eruption and eosinophilic folliculitis associated with human immunodeficiency virus (HIV) infection: a histopathological and immunohistochemical comparative study. J Am Acad Dermatol. 2012; 67(2):269-75.
2. Ramos H, Pagliari C, Takakura CF et al. Pruritic papular eruptions associated with HIV-aetiopathogenesis evaluated by clinical, immunohistochemical, and ultrastructural analysis. J Dermatol. 2005;32:549-56.
3. Castelnuovo B, Byakwaga H, Menten J et al. Can response of a pruritic papular eruption to antiretroviral therapy be used as a clinical parameter to monitor virological outcome? AIDS. 2008;22: 269-73.
4. Mgonda YM, Chale PNF. The burden of co-existing dermatological disorders and their tendency of being overlooked among patients admitted to Muhimbili National Hospital in Dar es Salaam, Tanzania. BMC Dermatol. 2011; 11: 8.
5. Lakshmi SJ, Rao GR, Ramalakshmi S et al. Pruritic papular eruptions of HIV: A clinicopathologic and therapeutic study. Indian J Dermatol Venereol Leprol. 2008; 74:501–3.
6. Resneck JS, Van Beek M, Furmanski L et al. Etiology of Pruritic Papular Eruption with HIV Infection in Uganda. JAMA. 2004; 292: 2614–21.

7. Naswa S, Khambati R, Marfatia RS. Pruritic papular eruptions as presenting illness of HIV. Indian J Sex Transm Dis. 2011; 32(2): 118–120.
8. Singh F, Rudikoff D. HIV-associated pruritus: etiology and management. Am J Clin Dermatol 2003; 4 (3): 177-188.
9. Fearfield LA, Rowe A, Francis N, et al. Itchy folliculitis and human immunodeficiency virus infection: clinicopathological and immunological features, pathogenesis and treatment. Br J Dermatol 1999; 141: 3-11.
10. Guidelines on the Treatment of Skin and Oral HIV-Associated Conditions in Children and Adults. Geneva: World Health Organization; 2014. 6, Evidence and recommendations on papular pruritic eruption. Available from: https://www.ncbi.nlm.nih.gov/books/NBK305405.

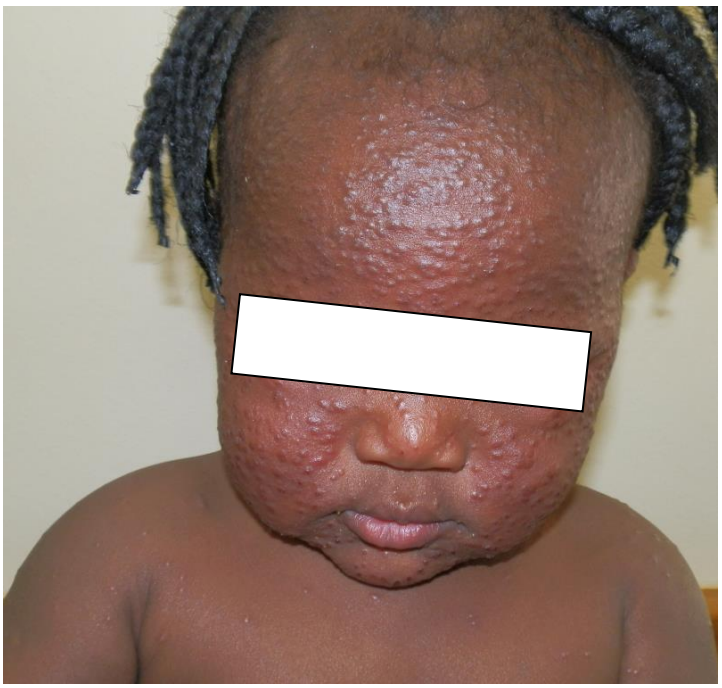


Figure 63: Eosinophilic folliculitis – multiple monomorphous papules of on the face of an HIV-infected child.

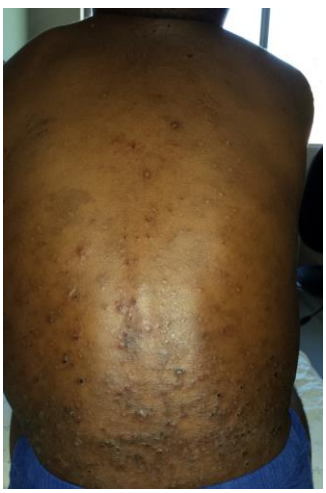


Figure 64: Papular pruritic eruptions (PPE) presenting with widespread papules, excoriations, some with crusted centres concentrated on the lower back.

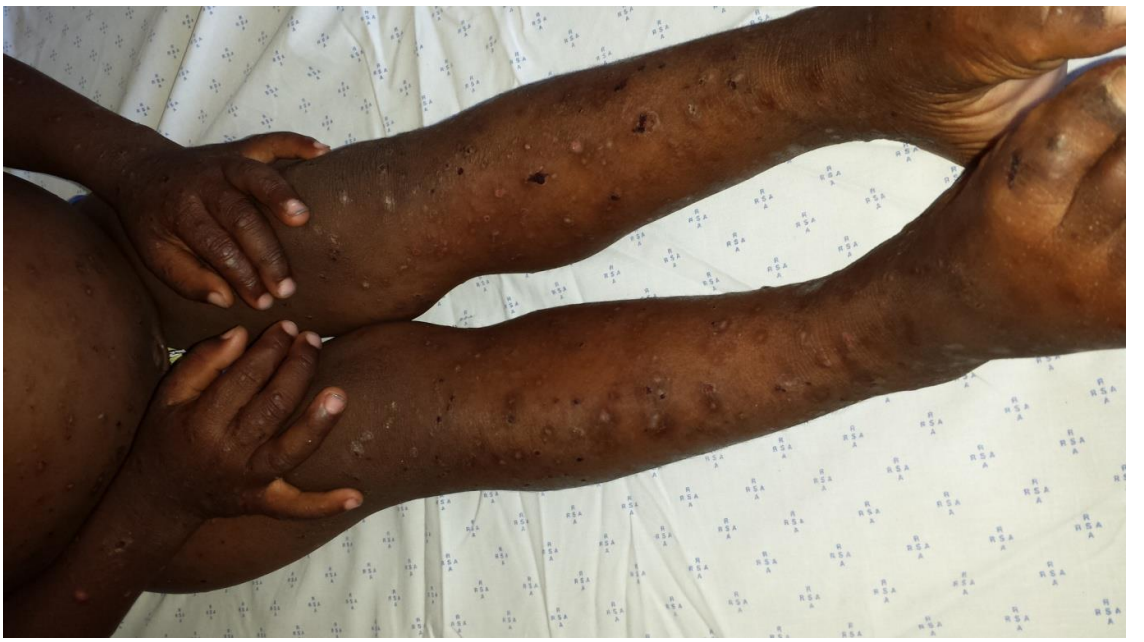


Figure 65: PPE- Widespread excoriated papules on the lower abdomen, dorsum of the hands and lower limbs.

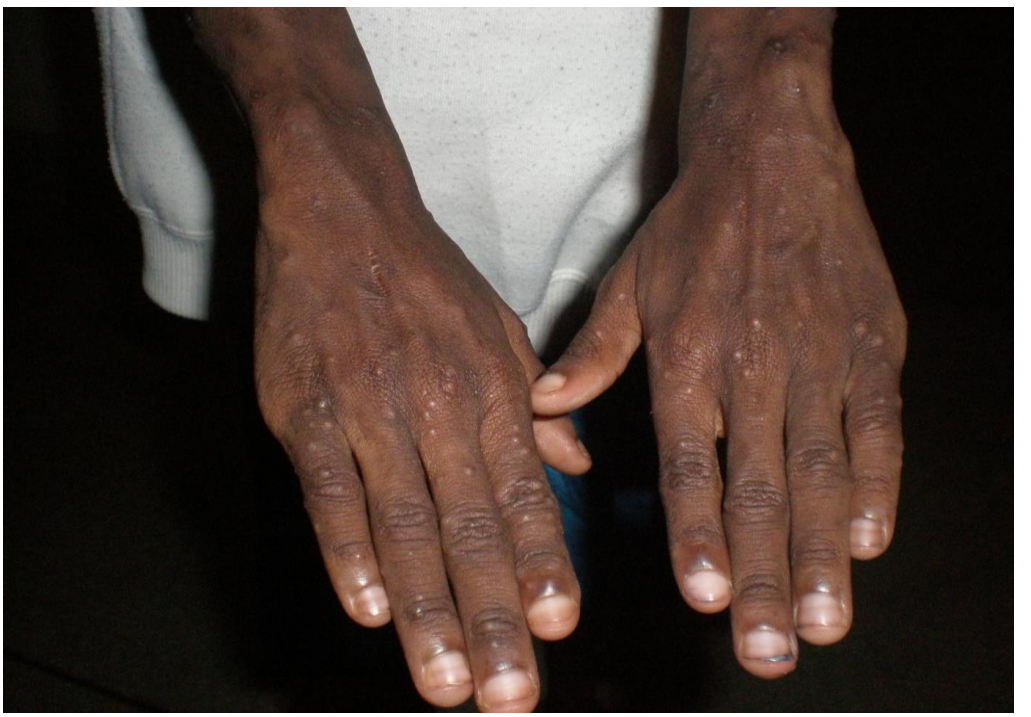


Figure 66: PPE in an HIV-infected adolescent: There were excoriated, erythematous, urticarial papules on the hand and trunk of this patient before initiation of ART.

Sebborrheic Dermatitis

Description: An inflammatory condition that is characterized by chronic and recurrent erythema and greasy scale in areas with terminal hairs and large sebaceous glands. There are two types: infantile and adult types.

Aetiology: The disease is thought to be related to overgrowth or abnormal or exaggerated immune response to *Malassezia* species (*Pityrosporum* yeasts). Sebaceous gland secretion, presence of *Malassezia* yeast, and the host immune response combine to play role in the pathogenesis of this skin condition.

Clinical presentation: Erythema, greasy scale, may also appear as macules or plaques with dry white or crusts or moist oily scale.

Epidemiology: Seborrheic dermatitis is the most common inflammatory dermatoses in HIV-infected children. The infantile type is self-limiting within the first few months of life while the adult type appears around the time of puberty. It affects the scalp, face (nasolabial folds and eyebrows), chest and body folds. The prevalence among HIV-infected individuals is about 40% and as high as 80% among AIDS patients.

Diagnosis: It is a clinical diagnosis, but fungal infection should be excluded with a negative potassium hydroxide test. Histologically, the lesions of seborrheic dermatitis in patients without HIV-1 are those of eczema; however, with chronicity tend to resemble those of psoriasis. Thus, in longstanding cases it may be difficult to differentiate seborrheic dermatitis from psoriasis, both clinically and histologically.

Treatment: Treatment options include topical steroids, antifungals and emollients. The scalp can be treated by washing daily with shampoos containing selenium sulphide, ketoconazole, zinc pyrithione, salicylic acid or coal tar.

Crusts or scales can be removed by overnight application of salicylic acid in water-soluble bases such as aqueous cream. Corticosteroid scalp applications or creams, with or without 2% precipitated sulphur, may alleviate erythema and itching.

For the face, low-potency corticosteroids such as 1% hydrocortisone are usually sufficient. These may be mixed with 2% precipitated sulphur or with an imidazole, as in some proprietary compounds. For the flexures, imidazole and hydrocortisone mixtures are best.

Treatment of the trunk usually requires potent topical corticosteroids. Oral itraconazole, which has activity against *Malassezia*, may be used at a dose of 100 mg for up to 3 weeks, and may result in long-term remission in some patients. Lithium succinate 5% cream with or without hydrocortisone has been useful in some cases.

Complications: Secondary infection with bacteria (*staphylococcus aureus*) or viruses (HSV-1).

Further reading

1. Gary G. Optimizing treatment approaches in seborrheic dermatitis. J Clin Aesthet Dermatol. 2013; 6(2): 44–49.
2. Filiberto Cedeno-Laurent F, Gómez-Flores M, Mendez N et al. New insights into HIV-1-primary skin disorders. J Int AIDS Soc. 2011; 14: 5.
3. Mathes BM, Douglass MC. Seborrheic dermatitis in patients with acquired immunodeficiency syndrome. J Am Acad Dermatol. 1985;14:947–951. doi: 10.1016/S0190-9622(85)70243-5.
4. Froschl M, Land HG, Landthaler M. Seborrheic dermatitis and atopic eczema in human immunodeficiency virus infection. Semin Dermatol. 1990; 14:230–232.
5. Ackerman AB. Histopathologic differentiation of eczematous dermatitides from psoriasis and seborrheic dermatitis. Cutis. 1977; 14:619–623.
6. East-Innis A. Management of common dermatological manifestations of HIV infection. Postgraduate doctor. Available from: http://www.postgraduatedoctor.com/.
7. Stefanki C, Alexander J, Stratigos JD. Skin manifestation of HIV in children. Clin Dermatol 2002; 20; 74-86.

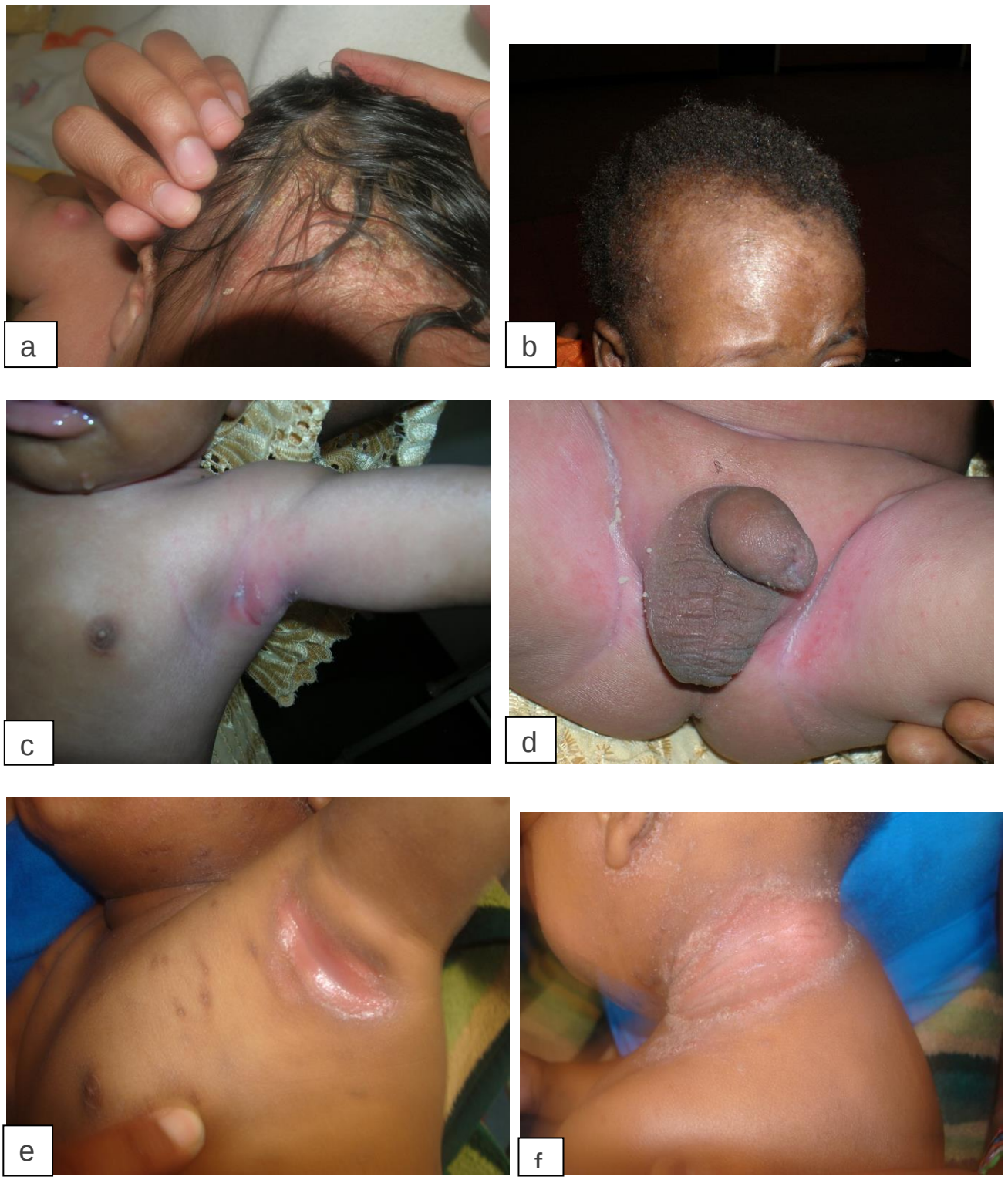


Figure 67a, b, c, d, e and f: Seborrheic dermatitis in young children affecting the scalp, neck, perineum and axilla.

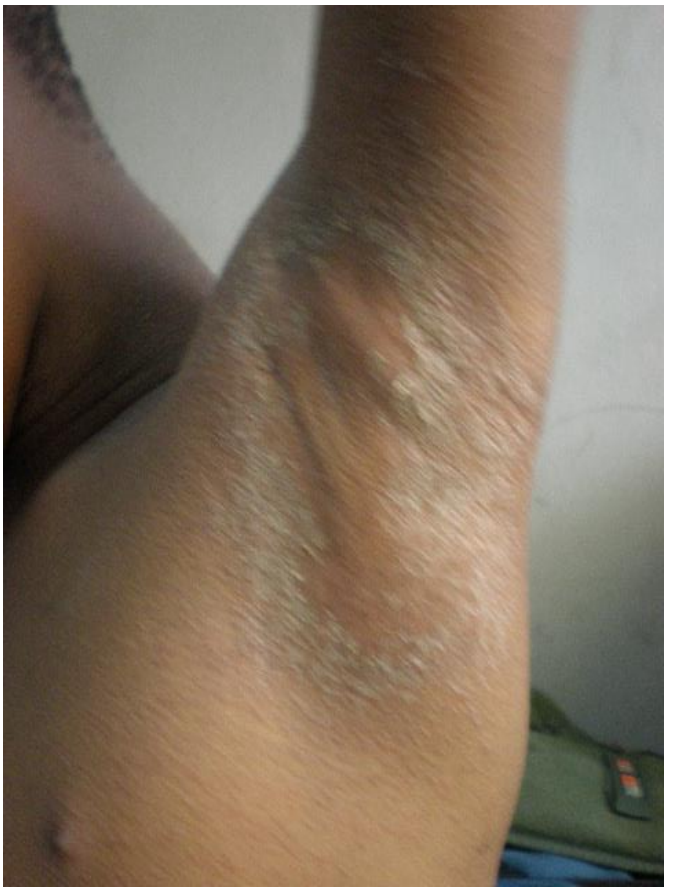


Figure 68: Seborrheic dermatitis in the axilla of an older child. Note the central exudation, scaling at the periphery.

Atopic Dermatitis

Description: A chronic skin condition characterized by xerosis, pruritus, and inflammation.

Aetiology: Unclear but "hygiene hypothesis" and the "keratinocyte apoptosis hypothesis" have been proposed. Interactions among genetic, environmental, skin barrier, immune factors, and stress are documented. Symptoms may be exacerbated by allergic reaction to several triggers.

Clinical presentation: Dryness of skin, itch, typical distribution all in a background of positive family history.

Epidemiology: Common among HIV-infected children. The risk of atopic dermatitis was increased by 30% in one study.

Diagnosis: Atopic dermatitis is a clinical diagnosis.

Prevention: There are no specific preventative measures but as in non-infected persons, avoidance of triggers, ensuring that the skin is always well moisturized is helpful.

Treatment: Avoid triggers. Use emollients, steroids and topical immune response modifiers such as tacrolimus.

Complications: Secondary bacterial infections.

Further reading

1. Gary G. Optimizing treatment approaches in seborrheic dermatitis. J Clin Aesthet Dermatol. 2013; 6(2): 44–49.
2. Ahuja A, Land K, Barnes CJ. Atopic dermatitis. South Med J. 2003 Nov; 96(11):1068-72.
3. Pastar Z, Lipozencić J, Ljubojević S. Etiopathogenesis of atopic dermatitis--an overview. Acta Dermatovenerol Croat. 2005;13(1):54-62.
4. Cedeno-Laurent F, Gómez-Flores M, Mendez N et al. New insights into HIV-1-primary skin disorders. Journal of the International AIDS Society 2011, 14:5. doi:10.1186/1758-2652-14-5.
5. Siberry GK, Leister E, Jacobson D. Increased risk of asthma and atopic dermatitis in perinatally HIV-infected children and adolescents. Clin Immunol. 2012; 142 (2): 201 -208.

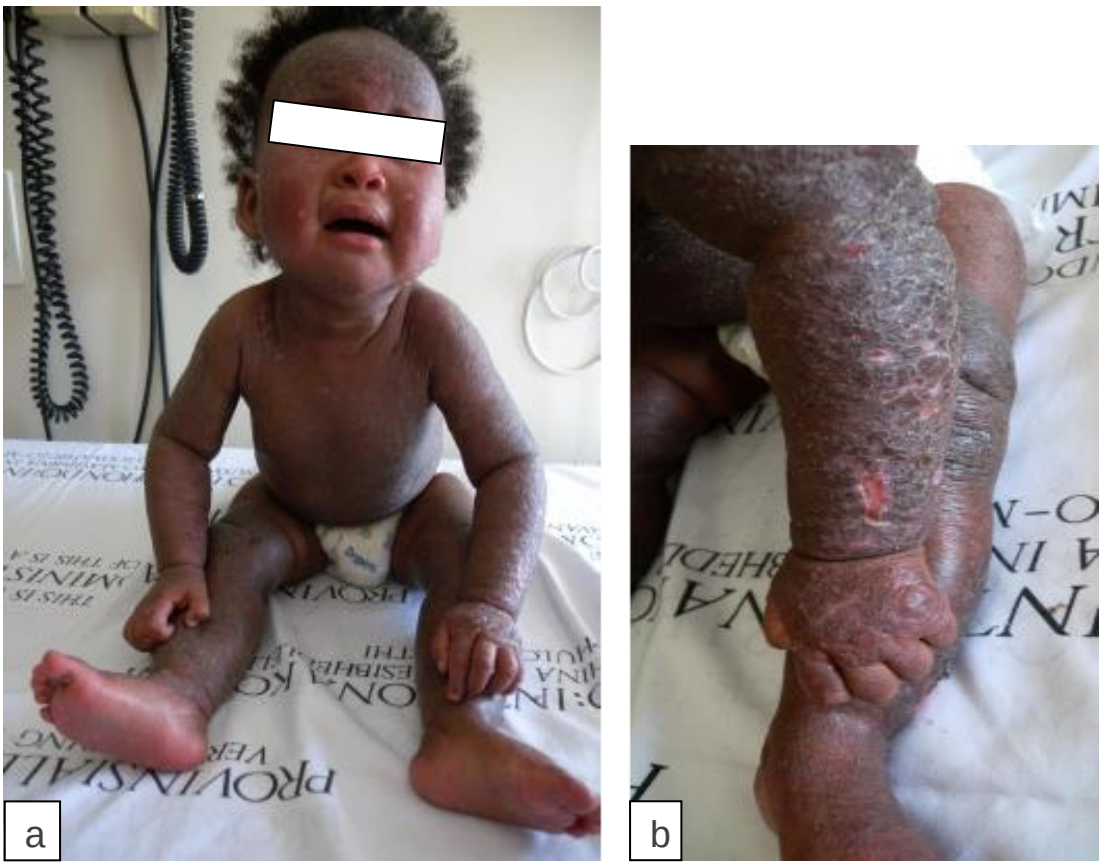


Figure 69 a and b: a)Severe atopic eczema presenting with extensive disease (erythroderma), and lichenification and excoriations. b) Close up shot highlighting the lesion on the limbs.

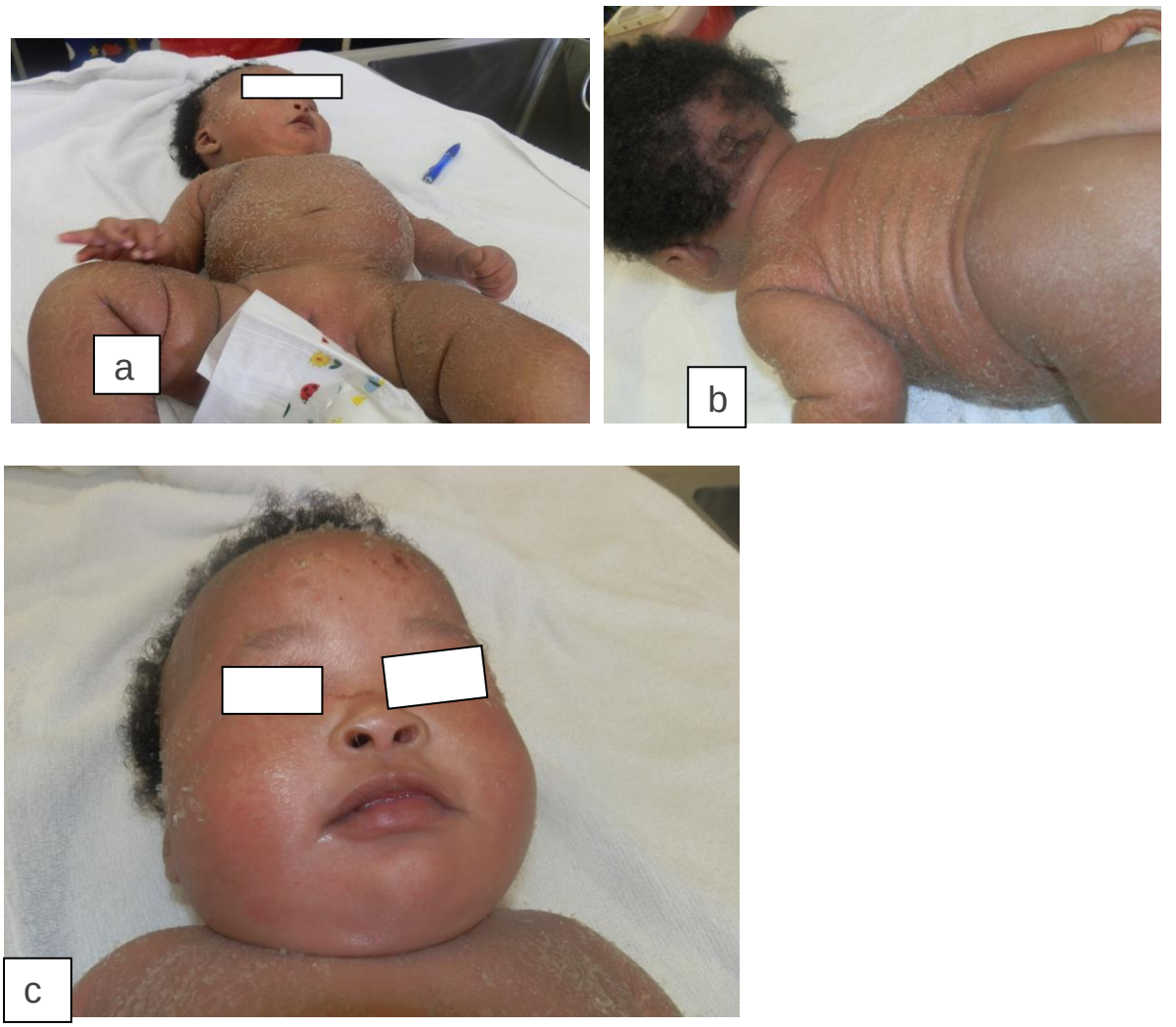


Figure 70a and b: Atopic dermatitis – Erythrodermic but less severe with mild scaling exfoliative dermatitis. c. Focus on face and upper chest wall. Note that the centre is face is spared in keeping with typical feature of atopic dermatitis.

Diaper Dermatitis (Contact Irritant Napkin Dermatitis)

Diaper dermatitis (DD) is the most common dermatitis found in infancy. DD was found to be one of the clinical markers of HIV infection in infants in an endemic area. Diaper dermatitis occurs when skin is exposed to prolonged wetness resulting in breakdown of the stratum corneum, the outer protective layer of the skin. Prolonged contact with urine and faeces is associated with irritant diaper dermatitis. Faecal proteases and lipases are the major irritants.

DD causes discomfort and predisposes infants to secondary infection including *Candida albicans*. It has also been found to be one of the clinical markers of HIV infection in infants in an endemic area.

Irritant contact diaper dermatitis is characterized by patches of erythema and scaling, mainly on the convex surfaces of buttocks, thighs, lower portion of abdomen, pubic region, labia majora, and scrotum

Diagnosis: Diagnosis of primary irritant diaper dermatitis is clinical. Mycological analysis to determine the contamination by Candida is indicated when there is intense erythema, satellite pustules or slow resolution of the disease.

Prevention: The key element of care in irritant contact diaper dermatitis is prevention. Frequent diaper changes are also important in preventing diaper dermatitis.

Treatment: Medical treatment of primary irritant diaper dermatitis consists of simple measures applied according to the severity and type of dermatitis.

Barrier creams made of zinc oxide, titanium dioxide and starch or creams with dexpanthenol may be used to avoid excessive humidity in the diaper area, minimize transepidermal loss of water and reduce skin permeability. These products may help prevent the contact of faeces with the already damaged skin, because they get adhered to the epidermis and are not easily removed with water.

Topical corticosteroids such as hydrocortisone may be applied if erythema persists. If dermatitis does not improve or there is marked erythema and pustules, Candida infection should be suspected and topical antifungals like clotrimazole commenced.

Further reading

1. Visscher MO. Recent advances in diaper dermatitis: etiology and treatment. Pediatr Health 2009; 3: 81-98.
2. Fernandes JD, Machado MC, Oliveira ZN. Clinical presentation and treatment of diaper dermatitis--part II.An Bras Dermatol. 2009; 84:47-54.
3. Jaspan HB, Myer L, Madhi SA et al. Utility of clinical parameters to identify HIV infection in infants below ten weeks of age in South Africa: a prospective cohort study. BMC Pediatr. 2011;11:104.

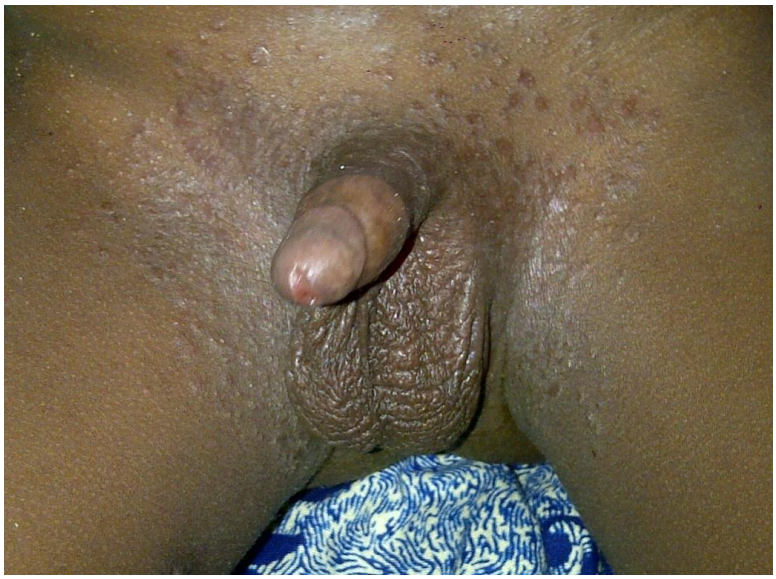


Figure 71: Diaper dermatitis in a dark-skinned child. (Courtesy: Dr Adewale Owa – University College Hospital, Ibadan)

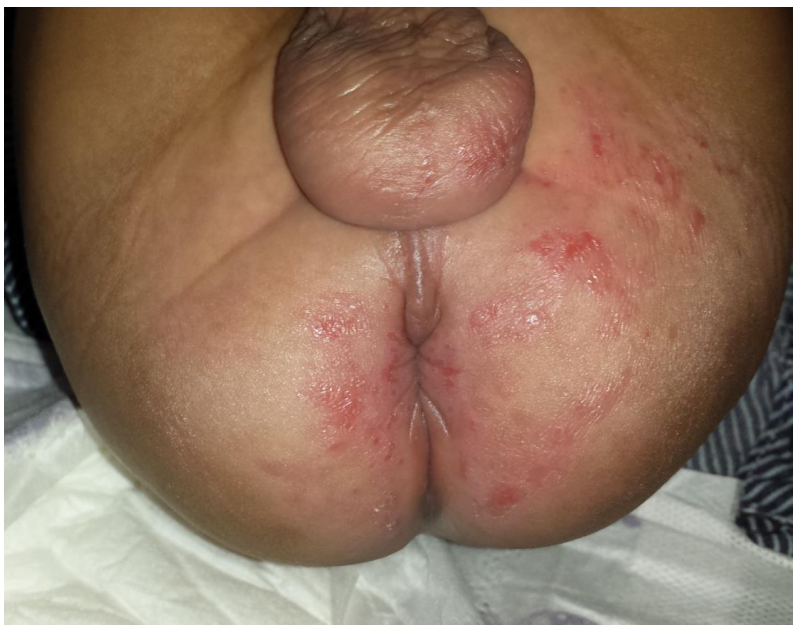


Figure 72: Diaper dermatitis

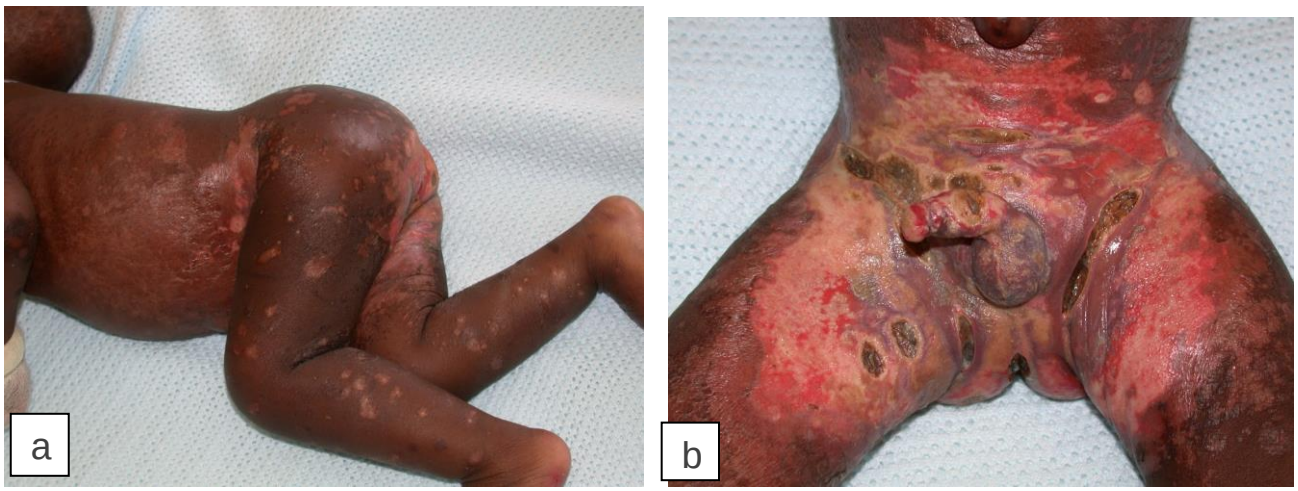


Figure 73: Necrotic ulcers of ecthyma complicating diaper dermatitis.

Psoriasis

Definition: Psoriasis is a chronic inflammatory skin disease characterized by excessively rapid keratinocyte proliferation.

Epidemiology: The prevalence of psoriasis in HIV-infected persons is the same as in the general population, however the disease is more severe in HIV-infected persons with falling CD4 counts.

Aetiology: Psoriasis has a strong genetic predisposition. In HIV, it is postulated that the immune dysregulation in advanced disease favors development of psoriasis.

Clinical features: **P**soriasis in HIV-infected persons has unusual presentations. It is severe and is associated with frequent exacerbations. Several morphological types often coexist in the same patient. The common presentations include plaque, erythrodermic, inverse psoriasis and reactive arthritis-like psoriasis syndrome.

Treatment: Treatment is generally challenging. Initiation of antiretroviral therapy and avoidance of triggers like smoking, beta-blockers and lithium improves response. Topical steroids, vitamin-D derivatives, coal tar and dithranol can be used in mild disease. Acitretin and phototherapy, if available, are recommended in moderate to severe disease. If these fail, under careful supervision, immunosuppressants like methotrexate and cyclosporine may be used.

Further reading

1. Morar N, Willis-Owen SA, Maurer T, Bunker CB. Lancet Infect Dis. 2010;10(7):470-8 HIV-associated psoriasis: pathogenesis, clinical features, and management.
2. Utikal J, Beck E, Dippel E, Klemke CD, Goerdt S. Reiter's syndrome-like pattern in AIDS-associated psoriasiform dermatitis. J Eur Acad Dermatol Venereol. 2003; 17(1):114-6.

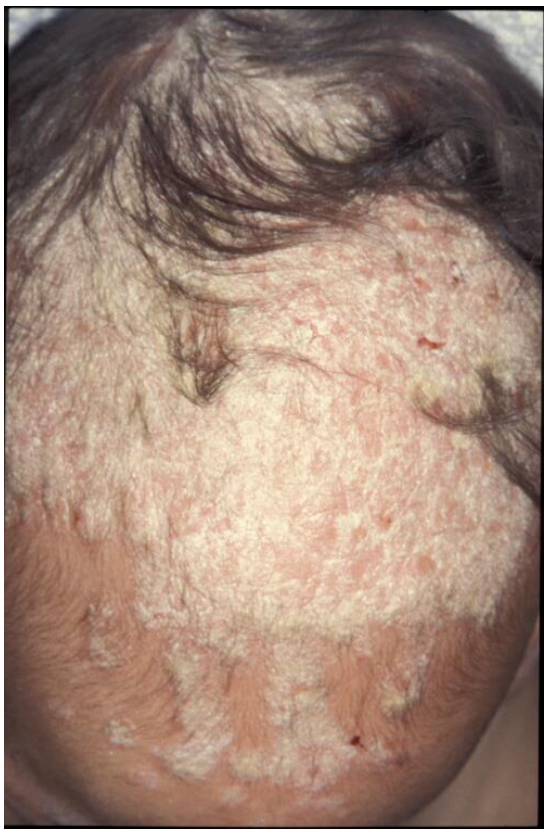


Figure 74: Scaly plaques of psoriasis on the scalp extending to the forehead.

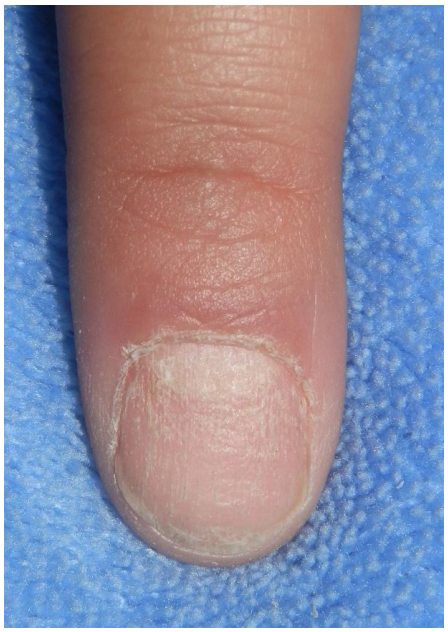


Figure 75: Pitting and longitudinal ridges on the finger nail of a child with psoriasis.

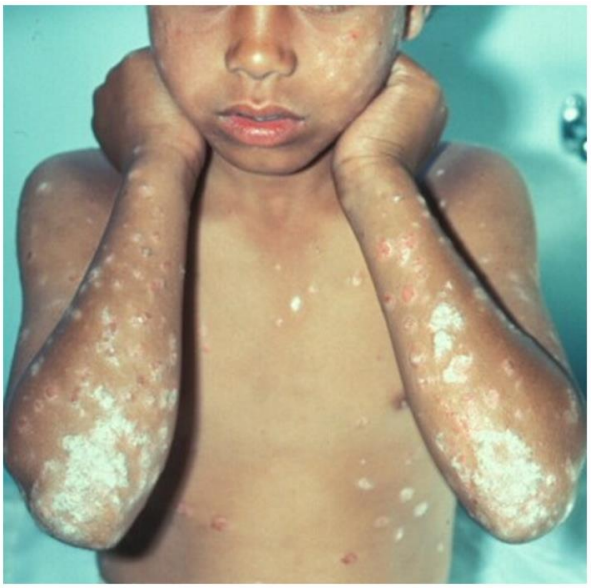


Figure 76: Silvery scales accentuated in the flexor surfaces of a child with psoriasis.

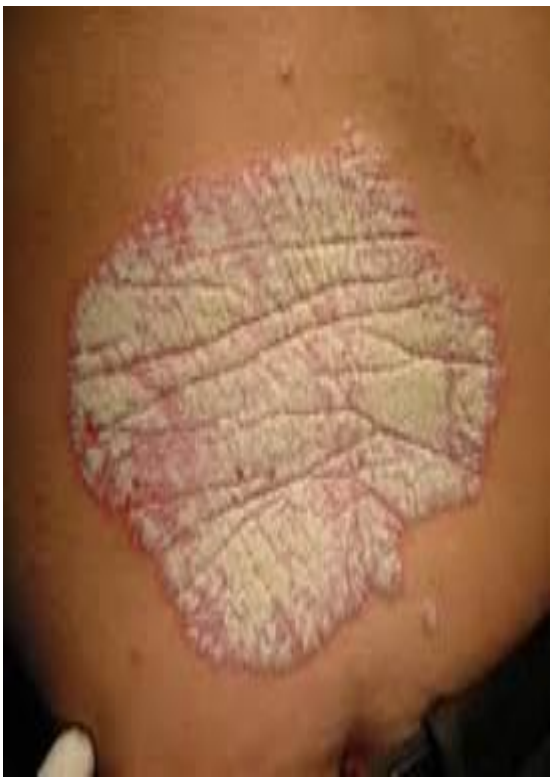


Figure 77: Thick scaly plaque of psoriasis on an erythematous background.

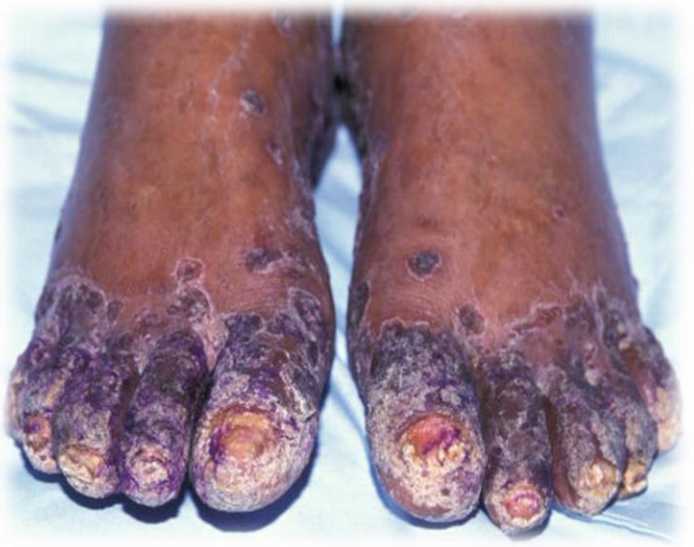


Figure 78: Hyperkeratotic psoriasis with severe nail dystrophy in HIV.

Pityriasis Rosea

Introduction: Pityriasis rosea is an acute, self-limiting disease, probably infective in origin, affecting mainly children and young adults, and characterized by a distinctive skin eruption and minimal constitutional symptoms.

Clinical features: Prodromal symptoms are usually absent. The first manifestation of the disease is usually the appearance of the herald patch, which is larger and more conspicuous than the lesions of the later eruption and is usually situated on the thigh or upper arm, the trunk or the neck; rarely it may be on the face, scalp or the penis. It is a sharply defined, erythematous, round or oval plaque, soon covered by fine scale.

The eruption consists of discrete oval lesions, dull pink in colour and covered by fine, dry, silvery-grey scales. The centre tends to clear and assumes a wrinkled, atrophic appearance and a tawny colour, with a marginal collarette of scale attached peripherally, with the free edge of the scale internally. The long axes of the lesions characteristically follow the lines of cleavage parallel to the ribs in a Christmas-tree pattern on the upper chest and back. The skin lesions commonly fade after 3–6 weeks, but some clear in 1 or 2 weeks and a few persist for as long as 3 months.

Treatment: Most cases require no treatment. Symptomatic treatment with antihistamines and topical steroids is often required and in severe cases UVB has sometimes been used. Oral erythromycin and high-dose acyclovir (20mg/kg) five times daily for 1 week), used early after the onset of the eruption, may lead to a more rapid clearance of skin lesions.

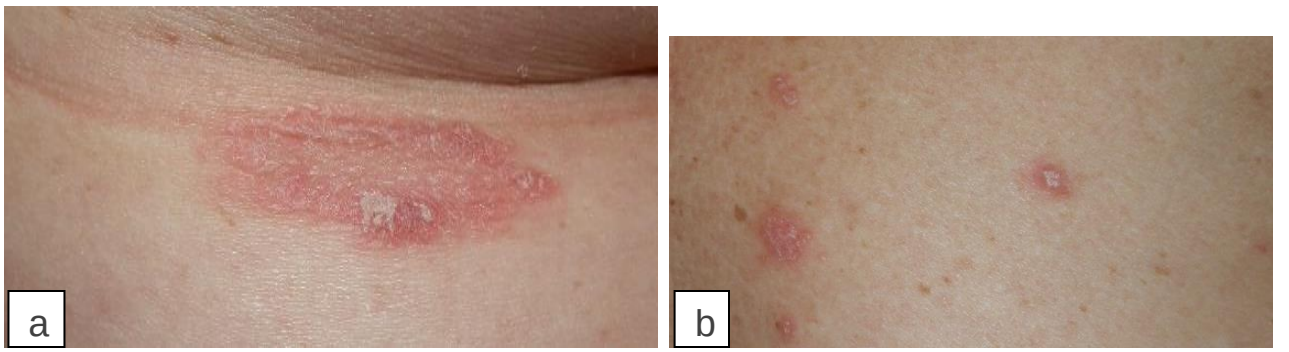


Figure 79a and b: (a) herald patch in a patient with pityriasis rosea. Note the later lesions in (b).

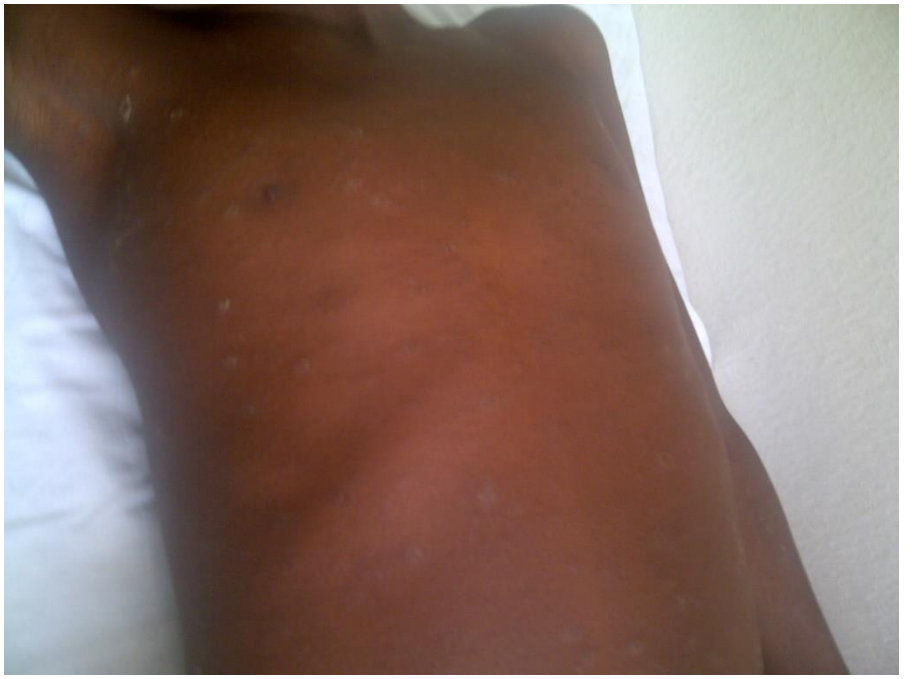


Figure 80: Pityriasis rosea- pigmented scaly plaques on the trunk.

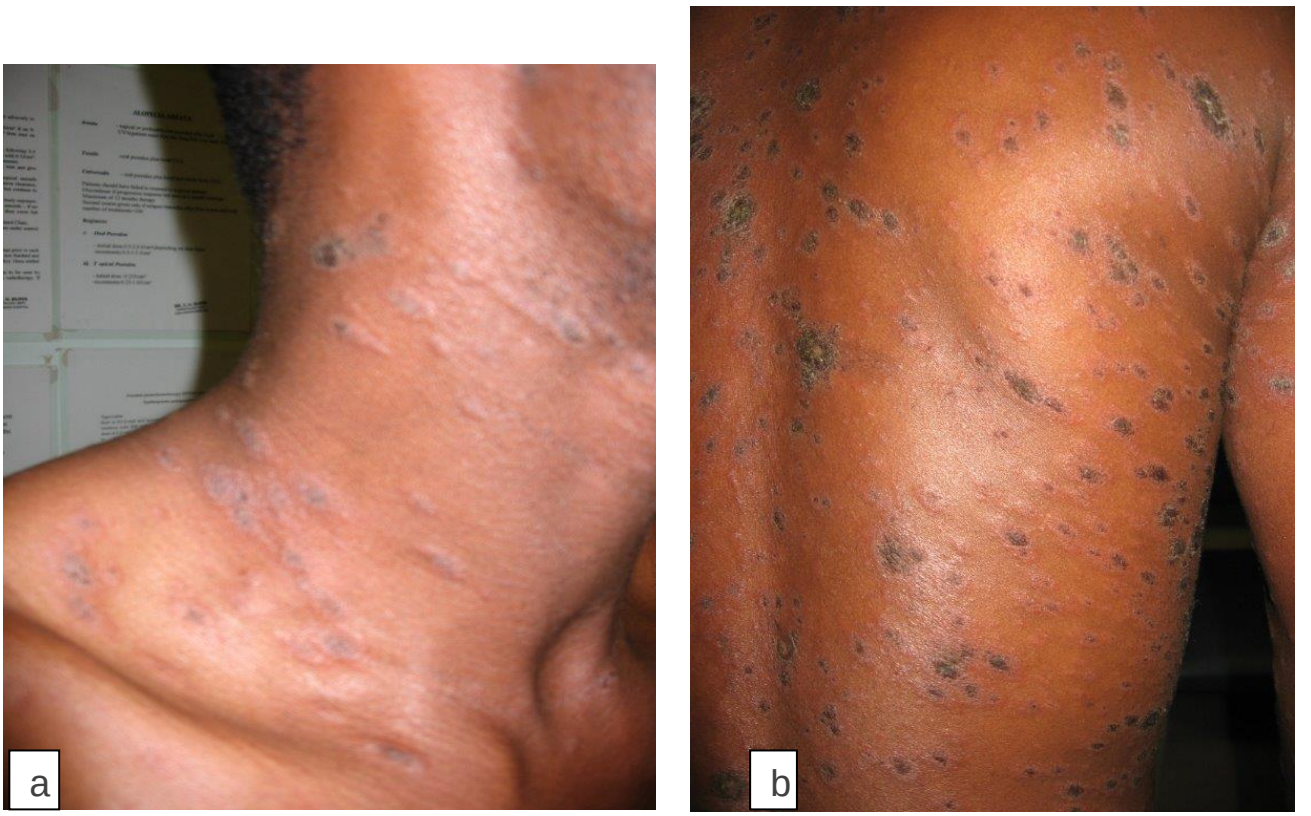


Figure 81a and b: Pityriasis rosea in an adult.

Xerosis

Description: This is the dryness of skin and a common cause of pruritus in HIV-infected persons.

Aetiology: Changes in cutaneous micro-circulation and nutrient supply to the skin.

Clinical presentation: dryness of skin, pruritus, excoriations.

Epidemiology: One of the most common non-infectious skin diagnoses in HIV-infected individuals. It is mainly seen in the extremities.

Prevention: Affected individuals should avoid soap and excessive washing.

Treatment: Skin hydration such as soaking in tub (using tepid or lukewarm water) followed by application of emollient. Mid-potency steroids (ointment is better than cream, since it contains lubricant).

Complications: Secondary bacterial infections.

Further reading

1. Blanes M, Belinchón I, Merino E et al. Current Prevalence and Characteristics of Dermatoses Associated with Human Immunodeficiency Virus Infection. Actas Dermosifiliogr. 2010; 101(8):702–709.
2. Cedeno-Laurent F, Gómez-Flores M et al. New insights into HIV-1-primary skin disorders. J Int AIDS Soc 2011, 14:5. doi:10.1186/1758-2652-14-5.
3. Maurer TA. Dermatologic Manifestations of HIV Infection. International AIDS Society 2006; 13 (5): 149-154.
4. Singh F, Rudikoff D. HIV-associated pruritus: etiology and management. Am J Clin Dermatol 2003; 4 (3): 177-188.

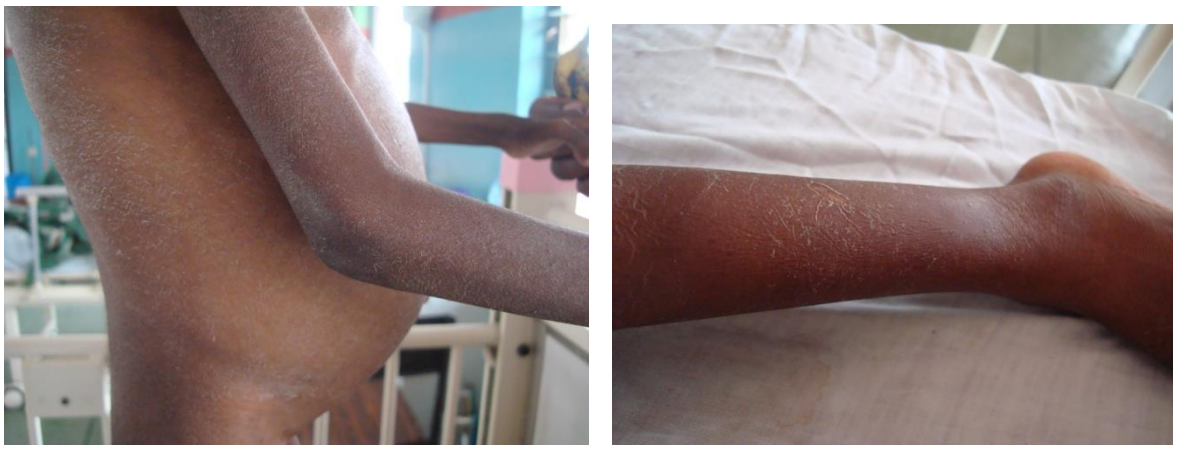


Figure 82 Xerosis in an HIV-infected child. Note the fine scale:

Acquired Ichthyosis

Description: The term ichthyosis is derived from Greek word ‘ichthys’, meaning fish and is basically a heterogeneous group of cutaneous keratinization disorders.

Aetiology: Can be congenital or acquired. Acquired Ichthyosis can be secondary to HIV, sarcoidosis, hypothyroidism and as a paraneoplastic phenomenon. In HIV, it is thought to result from wasting syndrome.

Clinical presentation: There are symmetrical large scales of the skin.

Epidemiology: Acquired Ichthyosis is among the most frequently encountered dermatologic disorders found in HIV-infected persons with advanced disease.

Diagnosis: Xerosis is a clinical diagnosis.

Prevention: Affected individuals should avoid soap

Treatment: ART, skin hydration and lubrication.

Further reading

1. Okulicz JF, Schwartz RA. Hereditary and acquired ichthyosis vulgaris. Int J Dermatol 2003; 42: 95–98.
2. Tlacuilo-Parra JA, Guevara-Gutie´rrez E, Salazar-Pa´ramo M. Acquired ichthyosis associated with systemic lupus erythematosus. Lu pus (2004) 13, 270 -273.

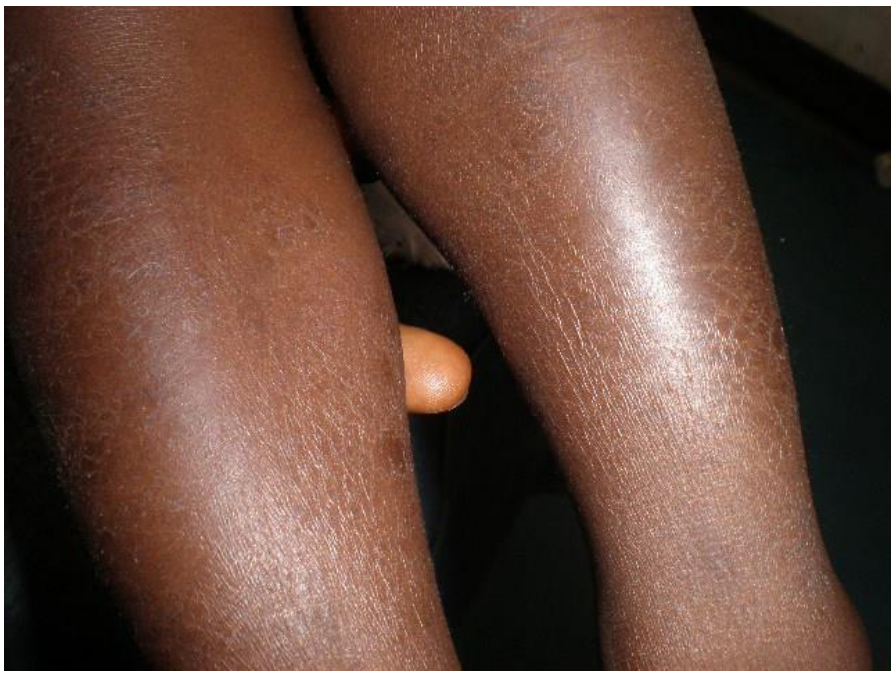


Figure 83: Ichthyosis on the shins - Note the crazy paving (fish scale) pattern.

CHAPTER 6: DRUG ERUPTIONS

Introduction: Drug eruptions are more common in HIV-infected individuals, up to 100-fold by some estimates - Mild and transient to life threatening, skin deep or multisystem. The reason for the increased incidence of drug eruptions in HIV-infected individuals may be as a result of the use of multiple medications including treatment for opportunistic infections and antiretroviral therapy; genetic predisposition; and HIV-associated immune dysregulation, which lowers the threshold of T cell activation coupled with persistent stimulation of CD8 T cells.

Classification

Two types of reactions to medications and they are either predictable (type A) and unpredictable (type B).

Type A includes lipodystrophy and pigmentation. Type B reactions include morbilliform eruptions, Steven Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, erythroderma, vasculitis and fixed drug eruptions, lichenoid reactions.

Further reading

1. Luther J, Glesby MJ. Dermatologic adverse effects of antiretroviral therapy: recognition and management. Am J Clin Dermatol. 2007; 8(4):221-33.
2. Introcaso CE, Hines JM, Kovarik CL. Cutaneous toxicities of antiretroviral therapy for HIV: part I. Lipodystrophy syndrome, nucleoside reverse transcriptase inhibitors, and protease inhibitors. J Am Acad Dermatol. 2010 ;63(4):549-61; doi: 10.1016/j.jaad.2010.01.061.
3. Introcaso CE, Hines JM, Kovarik CL. Cutaneous toxicities of antiretroviral therapy for HIV: part II. No nucleoside reverse transcriptase inhibitors, entry and fusion inhibitors, integrase inhibitors, and immune reconstitution syndrome. J Am Acad Dermatol. 2010; 63(4):563-9.
4. Sharma A, Vora R, Modi M et al. Adverse effects of antiretroviral treatment. Indian J Dermatol Venereol Leprol 2008; 74:234-7.

Table 5: Cutaneous reactions due to antiretroviral agents including both types A and B reactions

Antiretroviral drug	**Cutaneous reaction**
Nucleoside reverse transcriptase inhibitor (NRTI)	
Zidovudine	Mucocutaneous and nail hyperpigmentation, rarely: Hypertrichosis, vasculitis, paronychia
Stavudine	Lipodystrophy
Didanosine	Vasculitis, SJS, alopecia
Abacavir	Hypersensitivity reaction -Maculopapular eruption, urticaria, erythema multiforme
Lamivudine	Paronychia, allergic contact dermatitis
Non-nucleoside reverse transcriptase inhibitor (NNRTI)	
Nevirapine	DRESS, SJS
Efavirenz	Skin eruption (usually mild)
Etravirine	Maculopapular eruption (mild to moderate)
Protease inhibitors (PI)	
General	Lipodystrophy, hypersensitivity reaction
Indinavir	Paronychia, porphyria, SJS, alopecia, gynaecomastia
Nelfinavir	Maculopapular eruption, urticaria
Atazanavir	Maculopapular eruption, asymptomatic jaundice and sclera icterus
Darunavir	Maculopapular eruption
Integrase inhibitor	
Raltigravir	Diaphoresis

Type A reactions

Antiretroviral Lipodystrophy

Lipodystrophy syndrome (includes lipoatrophy and lipohypertrophy) is one of the long-term toxicities of stavudine (d4T) which was one of the back bones of first line antiretroviral therapy. Protease inhibitors (PIs) are also implicated in causing this syndrome.

Lipoatrophy is characterized by loss of subcutaneous tissue from facial pads, extremities, and buttocks. Apart from abnormal fat redistribution in stavudine toxicity, metabolic abnormalities including hyperlipidaemia may also be associated. Studies have reported a prevalence of between 18% and 33%. Stavudine is thought to cause lipoatrophy by inducing adipocyte apoptosis.

As a result of lipodystrophy and other toxicity effects of stavudine, national treatment programmes have dropped d4T and moved to zidovudine or abacavir based regimens. Replacing stavudine with abacavir or zidovudine resulted in improvement in established stavudine-induced lipoatrophy in HIV-infected subjects.

Further reading

1. Amaya RA, Kozinetz CA, McMeans A et al. Lipodystrophy syndrome Antiretroviral in human immunodeficiency virus-infected children. Pediatr Infect Dis J. 2002; 21:405-10.
2. Vigano` A, Thorne C, Brambilla P et al. Antiretroviral therapy, fat redistribution and hyperlipidaemia in HIV-infected children in Europe. AIDS. 2004; 18:1443 - 51.
3. Sanchez Torres AM, Munoz Muniz R, Madero R et al. Prevalence of fat redistribution and metabolic disorders in human immunodeficiency virus-infected children. Eur J Pediatr. 2005; 164:271 - 6.
4. McComsey GA, Ward DJ, Hessenthaler SM et al. Improvement in Lipoatrophy Associated with Highly Active Antiretroviral Therapy in HIV-infected Patients Switched from Stavudine to Abacavir or Zidovudine: The Results of the TARHEEL Study. Clin Infect Dis 2004; 38:263-270.
5. Ene L, Goetghebuer T, Hainaut M et al. Prevalence of lipodystrophy in HIV-infected children: a cross-sectional study. Eur J Pediatr. 2007; 166:13-21.
6. Piloya T, Bakeera-Kitaka S, Kekitiinwa A et al. Lipodystrophy among HIV-infected children and adolescents on highly active antiretroviral therapy in Uganda: a cross sectional study. J Int AIDS Soc. 2012; 15(2):17427. doi: 10.7448/IAS.15.2.17427.

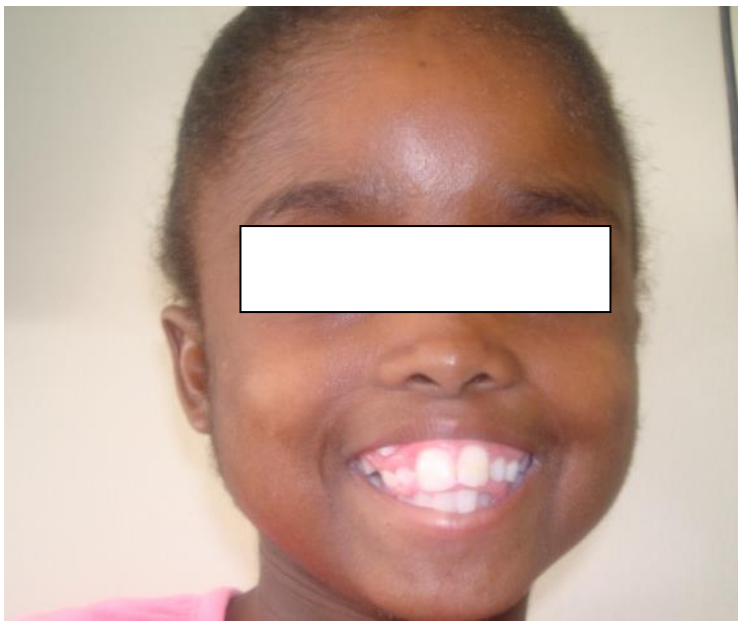


Figure 84 Nine year old girl who had been on stavudine based regimen from the first year of life. Stavudine was substituted with abacavir 6 months prior on account of lipoatrophy.

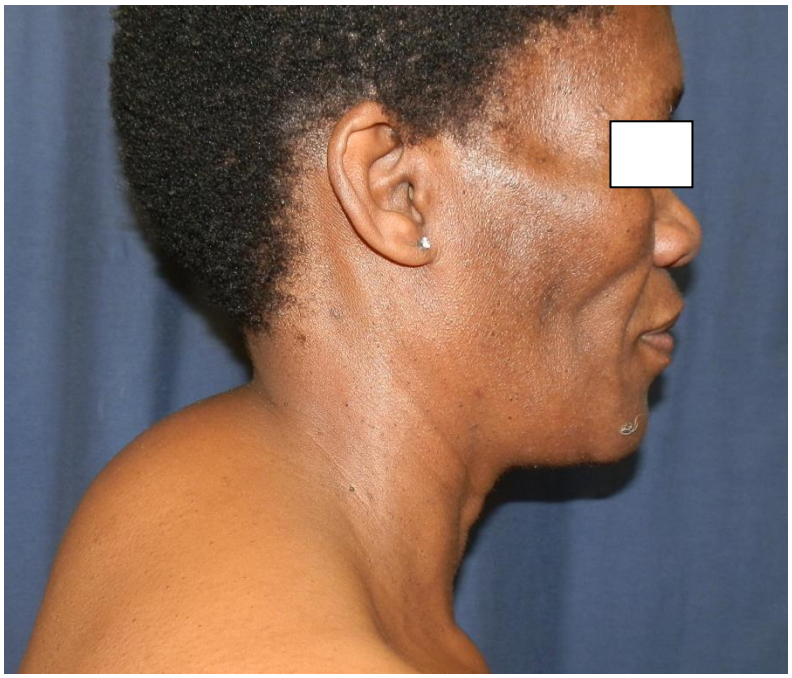


Figure 85: An adult with stavudine-associated lipodystrophy. Note the temporal wasting loss of buccal fat pad and the enlarged dorsocervical fat pad.

Type B reactions

Morbilliform drug eruptions

Definition and clinical presentation: Morbilliform (measles-like) drug eruption or maculopapular exanthems usually manifest 7–14 days after drug exposure. The lesions can progress and become confluent resulting in erythroderma. There are no associated systemic features. The rash is transient and treatment should not be interrupted. However, morbilliform rash can be the initial presentation of more serious reactions such as DRESS.

Aetiology: There is a very wide spectrum of drugs that cause morbilliform eruptions.

Epidemiology: This accounts for 95% of all cutaneous drug reactions.

Treatment: Usually not necessary, but topical steroids may speed up resolution.

Further reading

1. Bigby M. Rates of cutaneous reactions to drugs. Arch. Dermatol. 2001;137 (6): 765–770.

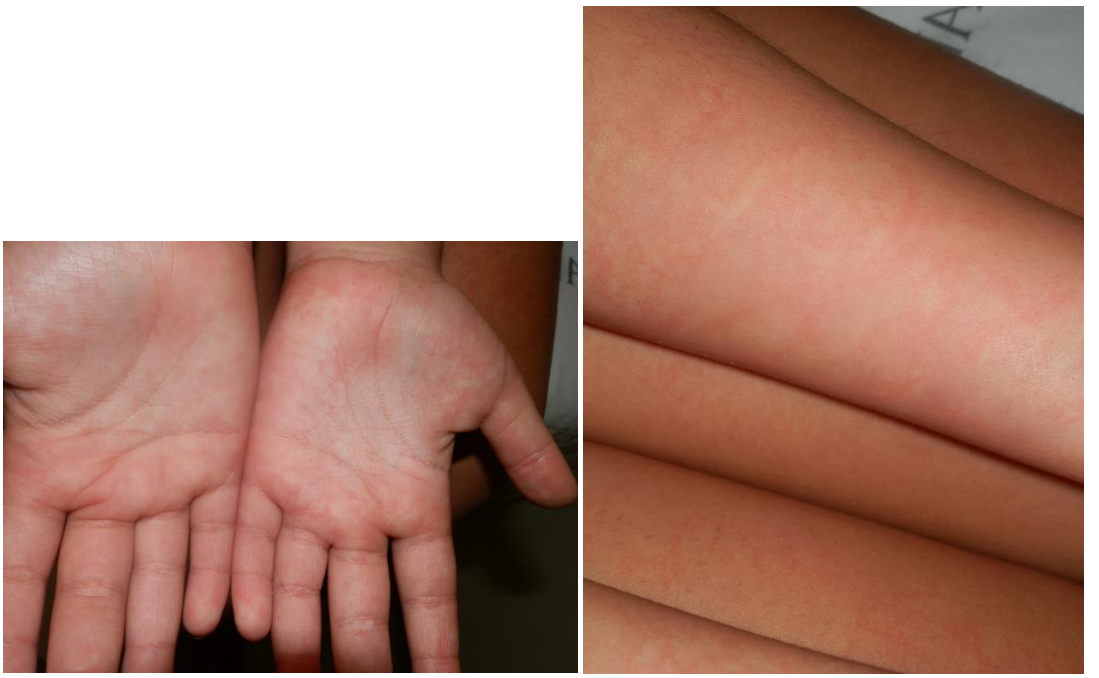


Figure 86: Transient morbilliform drug eruption on a young girl.

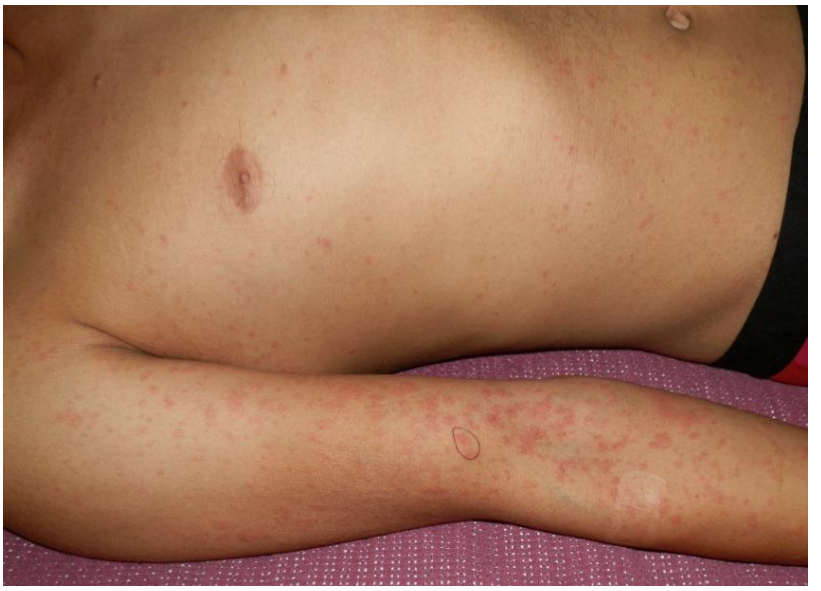


Figure 87: Morbilliform rash (measles-like) in an adolescent with a drug reaction.

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

Definition and presentation: Also known as drug hypersensitivity syndrome is a drug reaction characterized by a long latency period (> 3 weeks), a rash, fever, oedema, lymphadenopathy, leukocyte abnormalities (leucocytosis, eosinophilia and/or atypical lymphocytosis) and hepatitis. The eruption is usually urticaria-like or maculopapular, but may present as vesicles, pustules or purpura.

Aetiology: A large number of drugs are associated with DRESS; however, in HIV-infected persons anti-tuberculosis drugs, co-trimoxazole and nevirapine are often implicated.

Epidemiology: **The incidence in HIV-infected people is much higher**

Treatment: Immediate withdrawal of the offending drug improves outcomes but treatment is mainly supportive. Topical steroids are helpful but in severe cases systemic steroids are used.

Complications: DRESS has mortality of up to 10%. Complications include liver failure, renal failure, myocarditis, pneumonitis and pancreatitis.

Further reading

1. Cacoub P, Musette P, Descamps V et al. The DRESS syndrome: a literature review. Am J Med. 2011; 124(7):588-97.
2. Noguera-Morel L, Hernández-Martín Á, Torrelo A. Cutaneous drug reactions in the paediatric population. Pediatr Clin North Am. 2014; 61(2):403-26.
3. Cacoub P, Musette P, Descamps V et al. The DRESS syndrome: a literature review. Am J Med. 2011;124(7):588-97.
4. Walsh SA, Creamer D. Drug reaction with eosinophilia and systemic symptoms (DRESS): a clinical update and review of current thinking. Clin. Exp. Dermatol. 36(1), 6–11 (2011).

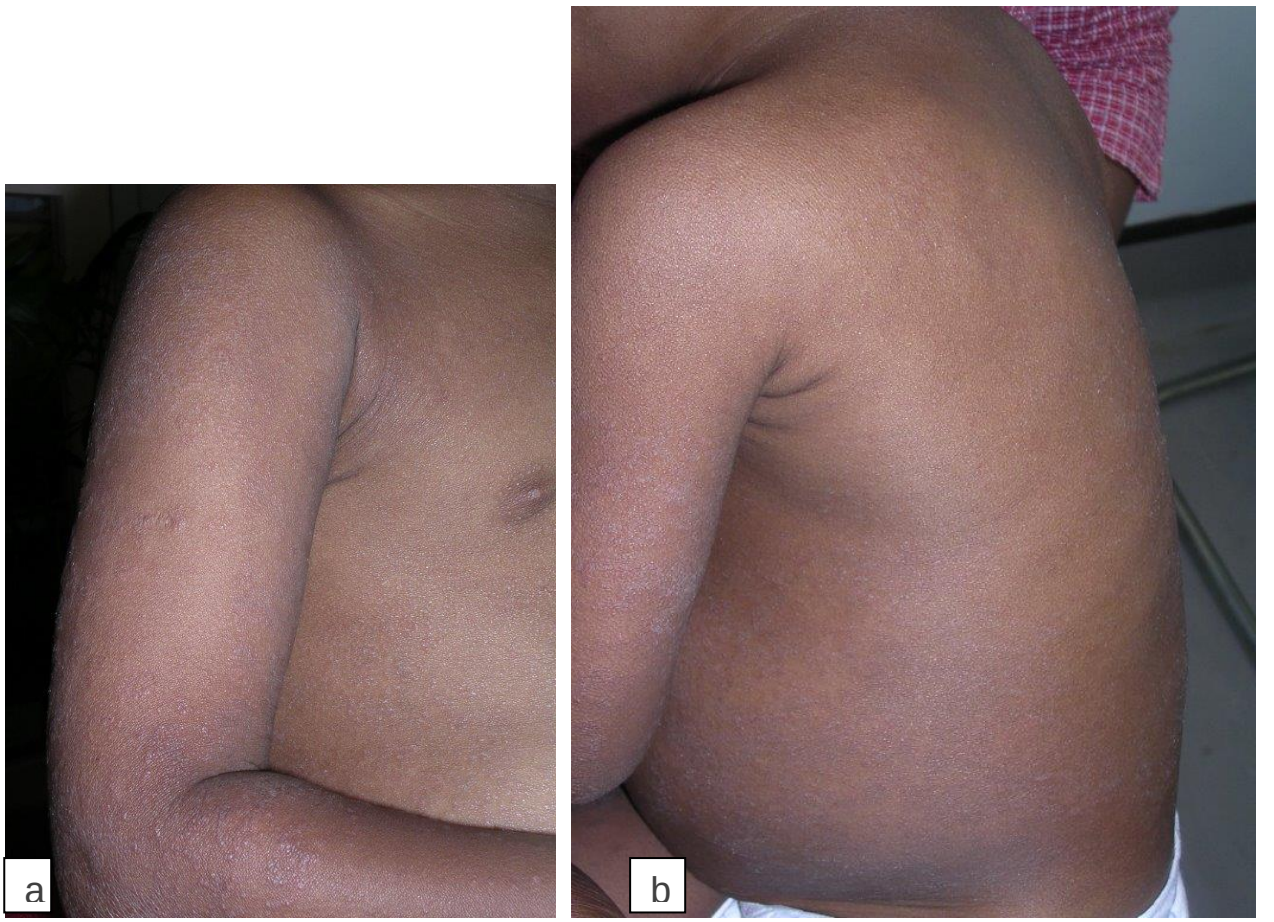


Figure 88a and b: DRESS

Abacavir Hypersensitivity

Abacavir (ABC) is a nucleoside analogue reverse transcriptase inhibitor. Approximately 3-5% of individuals who receive abacavir develop an immune-mediated hypersensitivity reaction (HSR) which occurs within the first six weeks of therapy. The HSR is rare but life threatening and is associated with individuals who carry the *57:01 variant in the human leukocyte antigen B (HLA-B) gene.

Diagnosis: The most common symptoms are fever, skin rash, gastrointestinal disorders and respiratory symptoms. A reduction in the incidence of abacavir hypersensitivity and unwarranted interruptions of therapy have been demonstrated with prospective screening for HLA-B*57:01 allele.

Considering the lower risk for abacavir hypersensitivity reaction and cost implications, implementation of genetic testing in this regard, in African settings in routine clinical practice may not be feasible. The importance of clinical monitoring of patients on abacavir cannot be overemphasized.

Treatment: Clinical management of suspected hypersensitivity reaction is discontinuation of abacavir and supportive care with analgesics, antihistamines, adequate fluids and appropriate laboratory monitoring for systemic organ involvement. Rechallenge with abacavir is contraindicated due to the risk of precipitating a life-threatening reaction.

Further reading

1. Borrás-Blasco J, Navarro-Ruiz A, Borrás C et al. Adverse cutaneous reactions associated with the newest antiretroviral drugs in patients with human immunodeficiency virus infection. J. Antimicrob. Chemother. 2008; 62 (5): 879-888.
2. Calmy A, Hirschel B, Cooper DA et al. Clinical update: adverse effects of antiretroviral therapy. Lancet; 370 (2007): 12–14.
3. Rauch A, Nolan D, Martin A et al. Prospective genetic screening decreases the incidence of abacavir hypersensitivity reactions in the Western Australian HIV cohort study. Clin Infect Dis 2006; 43: 99–102.
4. Martin MA, Kroetz DL. Abacavir Pharmacogenetics - From Initial Reports to Standard of Care. Pharmacotherapy 2013; 33(7): 765-75
5. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med 2008; 358:568-79.
6. Introcaso CE, Hines JM, Kovarik CL. Cutaneous toxicities of antiretroviral therapy for HIV: part I. Lipodystrophy syndrome, nucleoside reverse transcriptase inhibitors, and protease inhibitors. J Am Acad Dermatol. 2010; 63(4):549-61; doi: 10.1016/j.jaad.2010.01.061.

Nevirapine Hypersensitivity

Nevirapine (NVP) induced rash or toxicity occur in estimated 7-15% of patients receiving the drug. NVP rash can vary from a mild morbilliform rash to Stevens-Johnson syndrome. The rash typically develops within six weeks of initiating therapy. The introduction of NVP at a low dose with escalation over a 2-week period is recommended.

Patients with higher CD4 cell counts, including patients using NVP as post-exposure prophylaxis, are reported to have a higher risk of systemic hypersensitivity reaction, and therefore NVP is not recommended as part of post-exposure prophylaxis regimens.

A patient on NVP who develops a rash should be assessed for hepatotoxicity. If a morbilliform exanthem occurs in the setting of a fever, hepatitis, or other systemic symptoms, NVP must be discontinued immediately.

Further reading

1. Introcaso CE, Hines JM, Kovarik CL. Cutaneous toxicities of antiretroviral therapy for HIV: part II. Non-nucleoside reverse transcriptase inhibitors, entry and fusion inhibitors, integrase inhibitors, and immune reconstitution syndrome. J Am Acad Dermatol. 2010; 63(4):563-9.
2. Namayanja GK, Nankya JM, Byamugisha JK. Stevens - Johnson syndrome due to nevirapine. Afr Health Sci. 2005;5 (4):338-40.
3. Kiertiburanakul S, Sungkanuparph S, Charoenyingwattana A et al. Risk factors for nevirapine-associated rash among HIV-infected patients with low CD4 cell counts in resource-limited settings. Curr HIV Res 2008;65–9.

Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

SJS and TEN represent a spectrum of rare but potentially fatal mucocutaneous diseases characterized by widespread epidermal necrosis and mucosal involvement. SJS and TEN are considered to be part of a spectrum of severe cutaneous adverse reactions with increasing severity and extent of skin detachment, ranging from SJS (less than 10% body surface area skin detachment, 1-5% mortality) to TEN (greater than 30% skin detachment, 25-35% mortality).

In HIV-infected patients, the most common antiretroviral drug implicated to cause SJS/TEN is nevirapine and less commonly protease inhibitors. Co-trimoxazole and antituberculosis drugs are also implicated. Re-exposure to the drug results in recurrence.

Diagnosis: The reaction develops around 7-14 days after initiation of the drug. The rash is preceded by a prodrome with constitutional symptoms of high fever, malaise, myalgia and arthralgia. This is often misdiagnosed as an upper respiratory infection and treated with drugs that are later incorrectly blamed as offenders. Mucocutaneous lesions develop abruptly as macules that progress to papules, vesicles, bullae or confluent erythema.

Although minor presentations may occur, significant involvement of oral, nasal, eye (acute conjunctivitis, eyelid oedema, and crusting to conjunctival membrane or pseudomembrane, corneal erosions, conjunctival fornix foreshortening, and corneal ulcers), vaginal, urethral, gastrointestinal, and lower respiratory tract mucous membranes may develop in the course of the illness.

Treatment: Treatment should involve a multi-disciplinary team in a high-level health facility. Identification and withdrawal of the suspected offending agent is important. Supportive care involves analgesia and maintenance of adequate fluid and electrolyte balance. Frequent ophthalmological assessment and antiseptic/antibiotic eye drops 2-hourly are advocated. Barrier nursing and infection control prevention measures are important.

The use of prophylactic broad-spectrum systemic antibiotics, intravenous immunoglobulin (IVIG) and steroids is controversial. Topical cleansing/antibacterial agents could include 0.5% silver nitrate solution on gauze or 10% chlorhexidine gluconate washes or saline washes or polymixin/bacitracin or 2% mupirocin.

For wound care, silver sulfadiazine needs to be avoided. Removal of necrotic epidermis is discouraged, as intact epidermis prevents bacterial inoculation onto the underlying viable dermis. Paraffin gauze or hydrogel dressings may be beneficial. Biological dressings may be required (xenografts, allografts, skin substitutes).

Complications: Acute complications are similar to those of extensive burns. The high morbidity and mortality associated with the condition occurs mainly from infection. Long-term sequelae of SJS/TEN include; recurrence, dyspigmentation, oesophogeal and genital tract stenosis, eye problems, genital fibrosis. Multidisciplinary care during the acute stage is necessary to prevent these complications.

Further reading

1. Introcaso CE, Hines JM, Kovarik CL. Cutaneous toxicities of antiretroviral therapy for HIV: part II. Non-nucleoside reverse transcriptase inhibitors, entry and fusion inhibitors, integrase inhibitors, and immune reconstitution syndrome. J Am Acad Dermatol. 2010; 63(4):563-9.
2. Tartarone A, Lerose R. Stevens-Johnson syndrome and toxic epidermal necrolysis: what do we know? Ther Drug Monit. 2010; 32(6):669-72. doi: 10.1097/FTD.0b013e3181f2f24f.
3. Mason AR, Cortes GY, Pollack RB. Nevirapine-Induced Stevens–Johnson Syndrome in a Pediatric Patient. Pediatr Dermatol. 2008; 25(1):128-9. doi: 10.1111/j.1525-1470.2007.00605.x.
4. Chung WH, Hung SI, Hong HS et al, Medical genetics: a marker for Stevens-Johnson syndrome. Nature. 2004; 428(6982):486.
5. Wei CY, Ko TM, Shen CY et al. A recent update of pharmacogenomics in drug-induced severe skin reactions. Drug Metab Pharmacokinet. 2012;27 (1):132-41.
6. Peters PJ, Polle N, Zeh C et al. Nevirapine-associated hepatotoxicity and rash among HIV-infected pregnant women in Kenya. J Int Assoc Physicians AIDS Care (Chic). 2012;11(2):142-9.

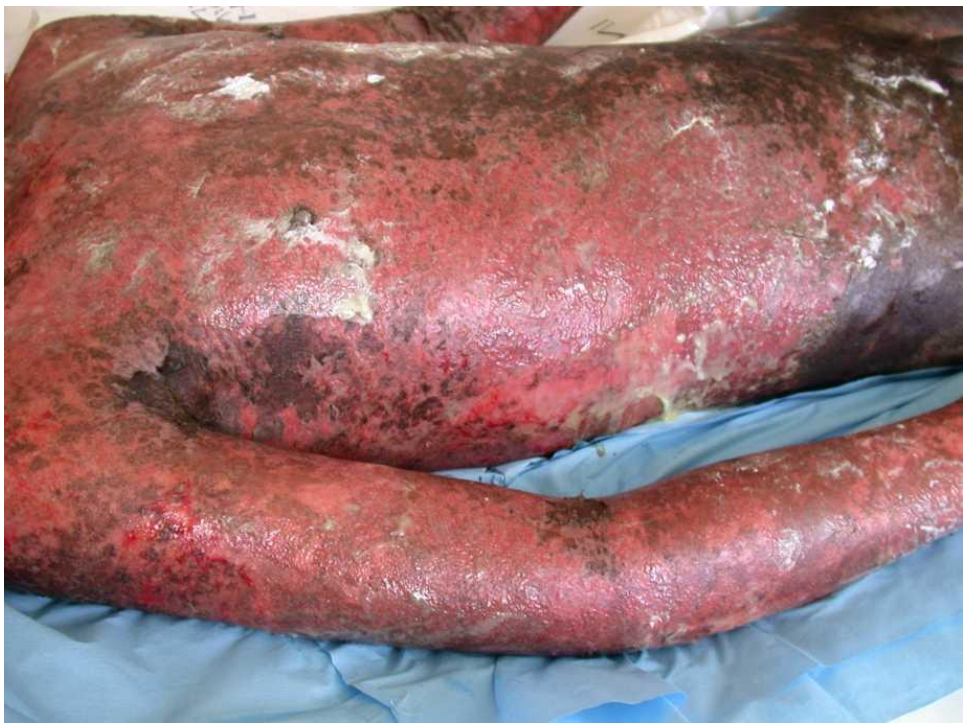


Figure 89: Extensive epidermal necrosis with areas of stripping in a case of TEN

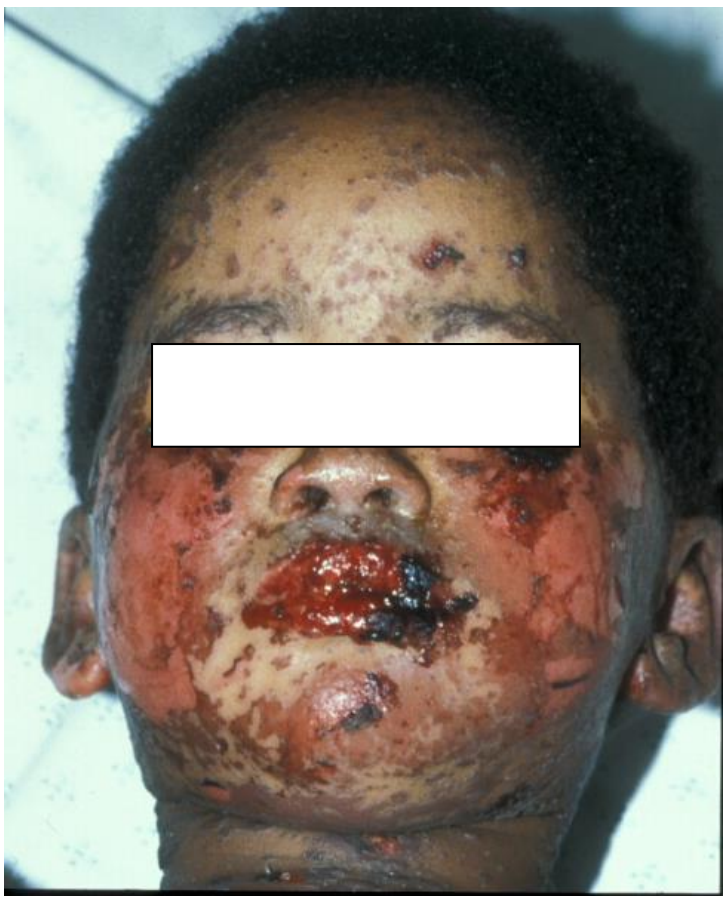


Figure 90: Epidermal necrosis with stripping and haemorrhagic cheilitis in a child with toxic epidermal necrosis.

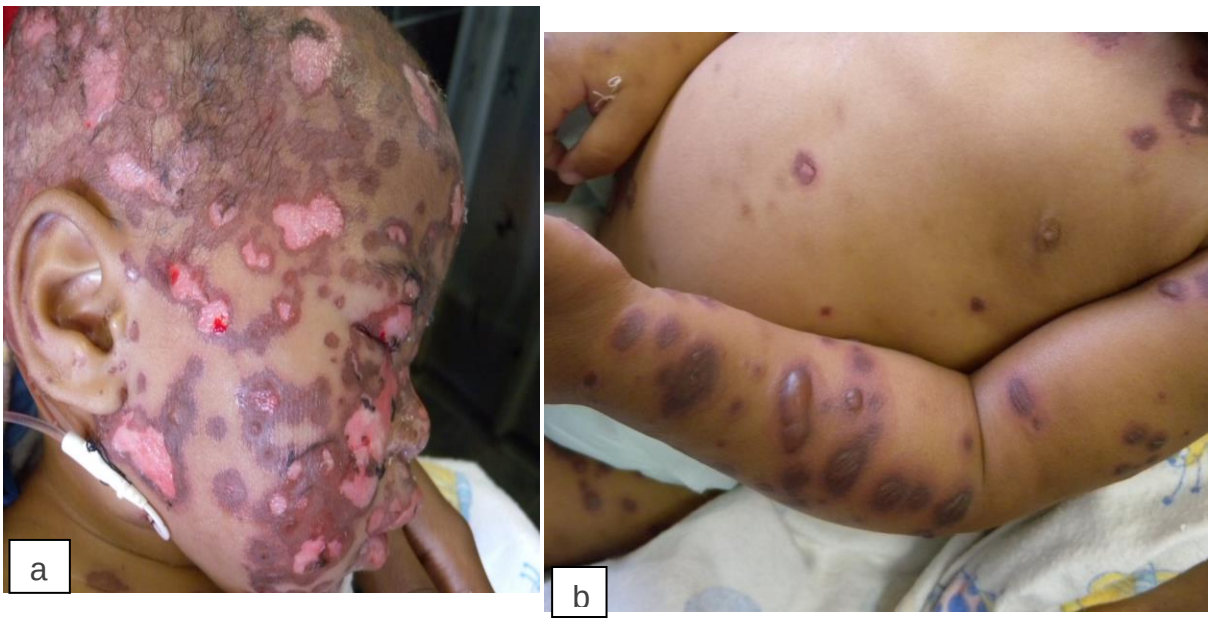


Figure 91a and b: Focal areas of epidermal necrosis with stripping in a case of SJS.

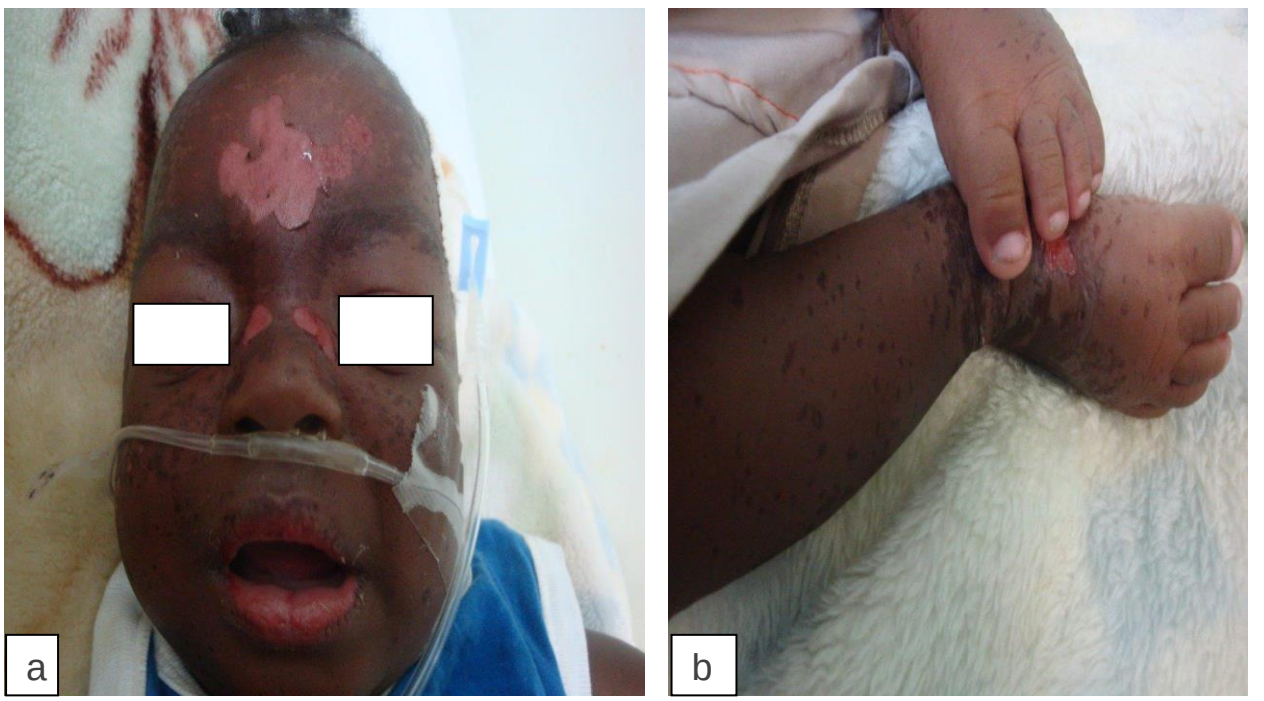


Figure 92a and b: SJS- Focal areas of epidermal necrosis with stripping.

Fixed Drug Eruptions

A fixed drug eruption characteristically recurs in the same site or sites each time the drug is administered. With each exposure, the number of involved sites may increase. Usually, just one drug is involved, although independent lesions from more than one drug have been described.

Cross-sensitivity to related drugs may occur, such as between tetracycline-type drugs, and between anticonvulsants. Fixed drug eruptions may occur with protease inhibitors. There may be a refractory period after the occurrence of a fixed eruption. Acute lesions usually develop 30 min to 8 hours after drug administration as sharply marginated, round or oval itchy plaques of erythema and oedema becoming dusky violaceous or brown, and sometimes vesicular or bullous.

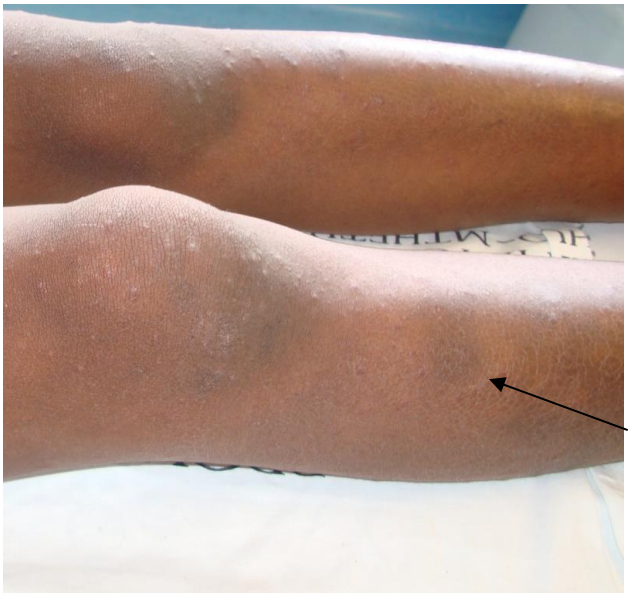


Figure 93: Mild fixed drug eruption/hyperpigmentation following cotrimoxazole prophylaxis therapy.

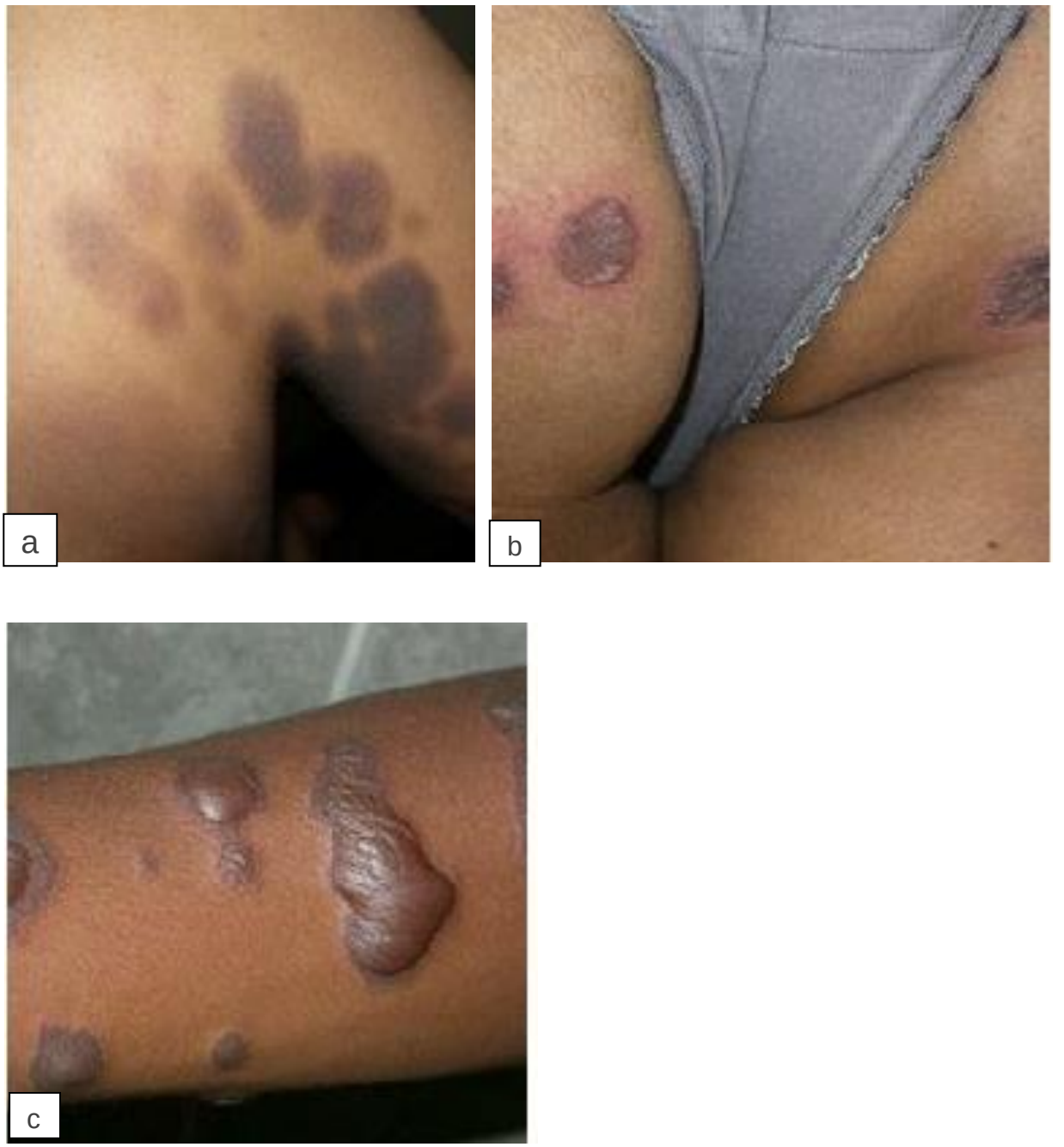


Figure 94a and b: Fixed drug eruption. a. Early lesions with rim of erythema and small blister. b. Bullous fixed drug eruption. c. Classic round pigmented macules of resolved fixed drug eruption.

CHAPTER 7: SKIN MANIFESTATIONS OF IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

Immune reconstitution syndrome (IRIS) is an inflammatory condition that may occur when HIV patients are started on antiretroviral medications. The cutaneous side effects of ART need to be differentiated from skin manifestations of IRIS. The restoration of immunity by effective ART in HIV-infected patients can cause temporary worsening of several infections and inflammatory skin disorders.

IRIS typically occurs in patients with low CD4 counts within the first 8 weeks of therapy (range – less than 1 week to several months). The most common types of infections seen as part of IRIS are ones that frequently affect the skin, including human papillomavirus in the form of genital, flat, or common warts, reactivation of the varicella-zoster virus or cytomegalovirus, cutaneous mycobacterial infection, or molluscum contagiosum. Inflammatory skin disorders associated with IRIS include atopic dermatitis and eosinophilic folliculitis.

In the management of cutaneous IRIS, ART needs to be continued while antibiotics, antivirals and steroids are added as appropriate.

Further reading

1. S. Handa, J.S. Bingham. Dermatological immune restoration syndrome: does it exist? J Eur Acad Dermatol Venereol, 15 (2001), 430–432. doi: 10.1046/j.1468-3083.2001.00337.x
2. Introcaso CE, Hines JM, Kovarik CL. Cutaneous toxicities of antiretroviral therapy for HIV: part II. Non-nucleoside reverse transcriptase inhibitors, entry and fusion inhibitors, integrase inhibitors, and immune reconstitution syndrome. J Am Acad Dermatol. 2010; 63(4):563-9.
3. Kong HH, Myers SA. Cutaneous effects of highly active antiretroviral therapy in HIV-infected patients. Dermatol Ther, 18 (2005), 58–66.
4. Lehloenya R, Meintjes G. Dermatologic manifestations of the immune reconstitution inflammatory syndrome. Dermatologic Clinics. 2006 Oct;24(4):549-70.

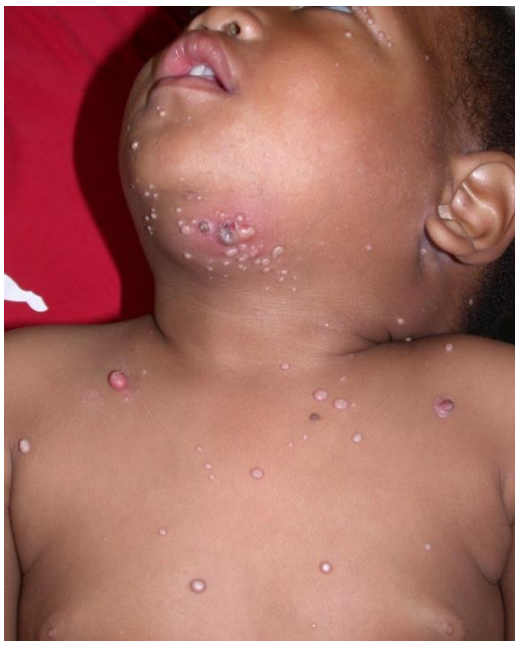


Figure 95: A flare-up of molluscum contagiosum following initiation of antiretroviral therapy.

CHAPTER 8: DISEASES OF SKIN APPENDAGES

Hair and HIV

Clinical presentations and epidemiology: Roughly 7% of HIV-infected persons present with telogen effluvium presenting as diffuse alopecia. The other findings include lengthening of the eyelashes, fine texture and straightening in late-stage disease. The hair also breaks more easily.

Aetiology and Treatment: The mechanism is thought to be multifactorial including nutritional deficiency, as a result of scalp inflammatory disorders like seborrheic dermatitis and autoimmune apoptosis of stem cells in the hair follicle. Alopecia, involving the scalp, has been reported in patients with HIV infection treated with indinavir and lopinavir/ritonavir. The alopecia will generally reverse after substituting the offending drug(s).

1. Smith KJ, Skelton HG, DeRusso D, Sperling L, Yeager J, Wagner KF, Angritt P. Clinical and histopathologic features of hair loss in patients with HIV-1 infection. J Am Acad Dermatol. 1996;34(1):63-8.
2. Kaplan MH, Sadick NS, Talmor M J Am Acad Dermatol. Acquired trichomegaly of the eyelashes: a cutaneous marker of acquired immunodeficiency syndrome. 1991; 25(5 Pt 1):801-4.
3. Chrysos G, Mikros S, Kokkoris S, Pastelli A, Kontochristopoulos G. Alopecia induced by lopinavir plus ritonavir therapy in an HIV patient. J Drugs Dermatol. 2007;6(7):742-3.

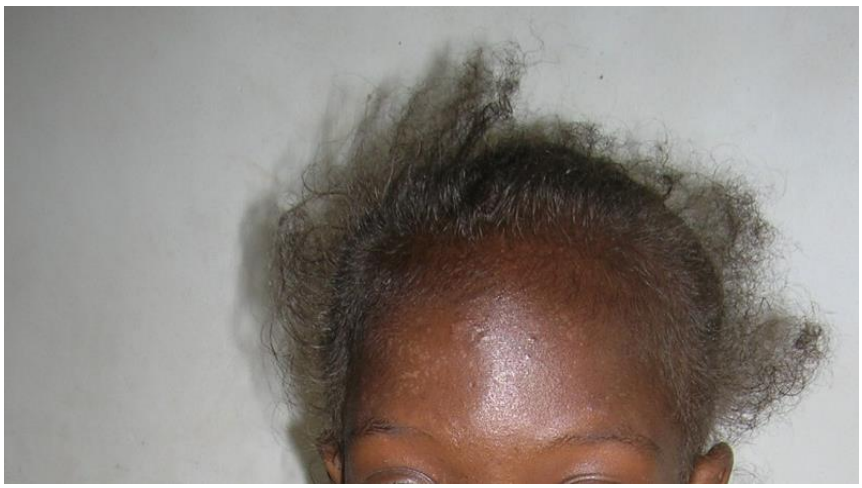


Figure 96: Hair changes in HIV infection.

Nail Changes in HIV

Nail abnormalities are reported twice as often in HIV-infected persons compared to the normal population.

The most common nail abnormality in HIV is onychomycosis occurring in a third of patients. It often presents with uncommon forms, namely proximal or superficial onychomycosis. There is often co-infection with mold fungi or candida.

Melanonychia is the darkening of the finger and toe nails. In HIV-infected individuals, it is characterized by longitudinal hyper pigmented lines in the nails. The increase in nail pigmentation is caused by amplified pigment production by melanocytes due to activation of nail matrix melanocytes. Longitudinal melanonychia associated may be associated with treatment by zidovudine.

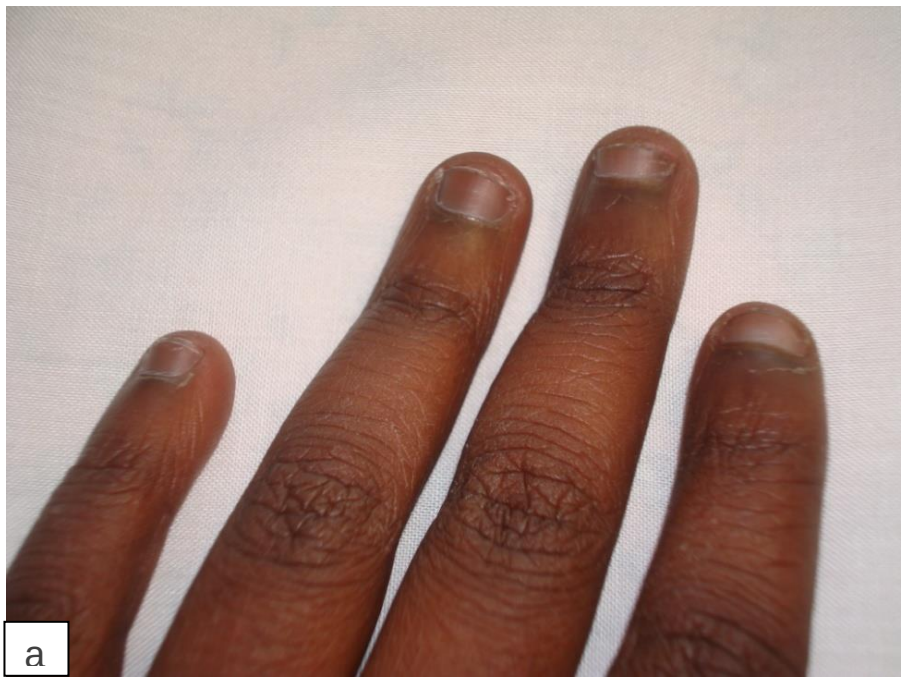
Other features that are significantly more common in HIV include transverse ridging, clubbing, splinter hemorrhages, absence of lunula, periungual erythema and proximal or total leukonychia.

Treatment

Susceptibility to antifungal therapy is normal but onychomycosis in HIV-infected patients is more difficult to treat, probably as a result of co-infections. Thus, it is important to select a broad-spectrum antifungal therapy possibly for extended periods. There is no specific therapy for the other conditions except antiretroviral therapy.

Further reading

1. Cribier B, Mena ML, Rey D et al. Nail changes in patients infected with human immunodeficiency virus. A prospective controlled study. Arch Dermatol. 1998;134(10):1216-20.
2. Graham SM, Dley HM, Ngwira B. Finger clubbing and HIV infection in Malawian children. Lancet. 1997; 349:31.
3. Moreno-Coutiño G, Arenas R, Reyes-Terán G. Improvement in onychomycosis after initiation of combined antiretroviral therapy. Int J Dermatol. 2013;52(3):311-3.
4. Gahalaut P, Mishra N, Chauhan S et al. Anolunula in fingernails among patients infected with HIV. ISRN Dermatol. 2014:271230. doi: 10.1155/2014/271230.
5. Ehsanzadeh-Cheemeh P, Grimes RM et al. Melanonychia in patients infected with Human Immunodeficiency Virus. Advances in Infectious Diseases, 2011, 1, 15-19. doi:10.4236/aid.2011.12002.



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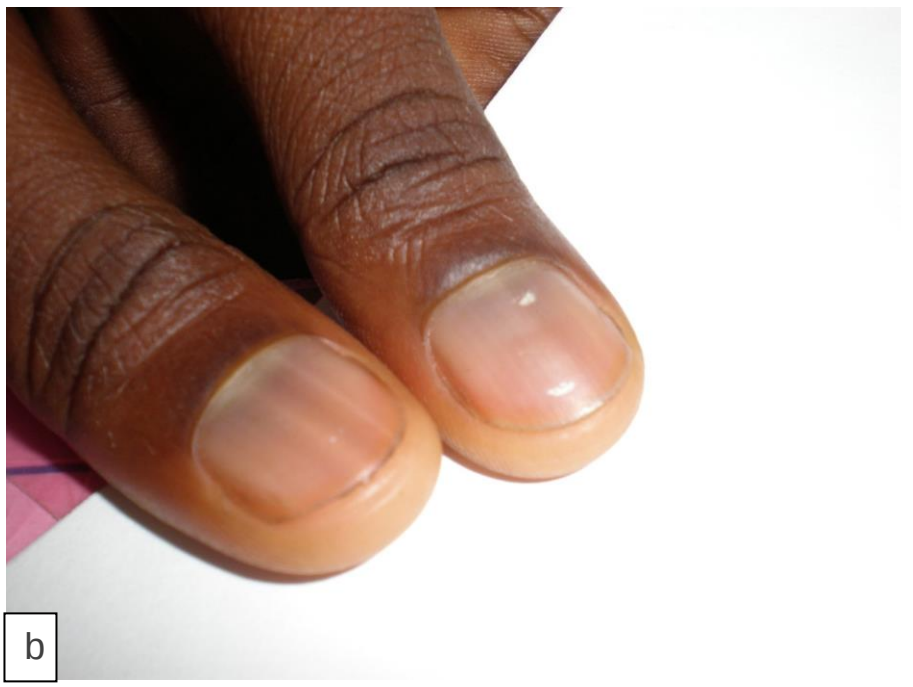

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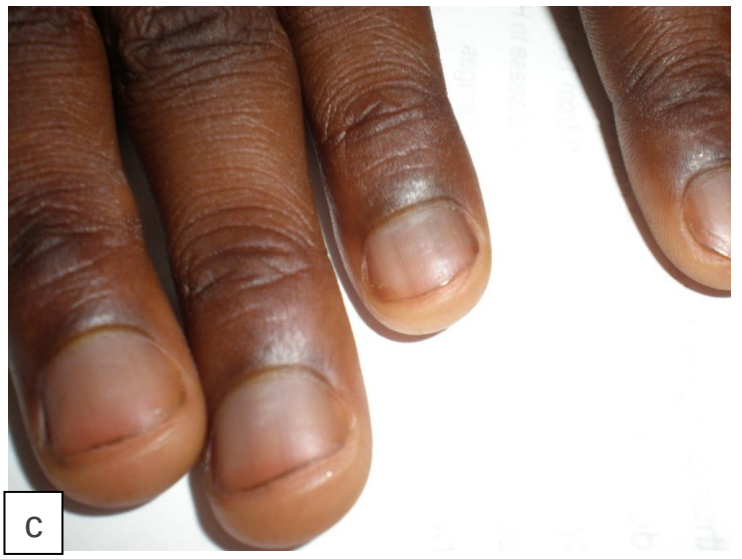

Figure 97a, b and c: Melanonychia

Digital Clubbing

Digital clubbing has been described in various pulmonary, cardiovascular, infectious, hepatobiliary and gastrointestinal diseases. It is characterized by bulbous enlargement of the distal phalanges due to an increase in soft tissue. Common causes of digital clubbing include cyanotic heart disease, neoplasms of the lungs, pulmonary tuberculosis, bronchiectasis, liver cirrhosis, and inflammatory bowel disease.

Its presence in concomitant HIV disease may be caused by lymphoid interstitial pneumonitis (LIP) or chronic lung disease.

Further reading

1. Dever LL, Matta JS. Digital clubbing in HIV-infected patients: an observational study. AIDS Patient Care STDS. 2009;23 (1):19-22. doi: 10.1089/apc.2008.0102.

PART II: SYSTEMIC MANIFESTATIONS AND OPPORTUNISTIC INFECTIONS IN PAEDIATRIC HIV

Regina Oladokun, Ombeva Malande, Brian Eley

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

1. Adedigba M, Ogunbodede E, Jeboda S, et al. Patterns of oral manifestations of HIV/AIDS among 225 Nigerian patients. Oral Dis 2008; 14(4):341–6.
2. Dave S, Pernas F, Roy S. The benign lymphoepithelial cyst and a classification system for lymphocytic parotid gland enlargement in the pediatric HIV population. Laryngoscope 2007; 117(1):106–13.
3. Schrot R, Adelman H, Linden C, et al. Cystic parotid gland enlargement in HIV disease: the diffuse infiltrative lymphocytosis syndrome. JAMA 1997;278:166–7.
4. Favia G, Capodiferro S, Scivetti M, et al. Multiple parotid lymphoepithelial cysts in patients with HIV infection: report of two cases. Oral Dis 2004; 10:151–4.
5. Huang R, Pearlman S, Friedman W, et al. Benign cystic vs. solid lesions of the parotid gland in HIV patients. Head Neck 1991; 3: 522–7.
6. Mandel L, Surattanont F. Regression of HIV parotid swellings after antiviral therapy: case reports with computed tomographic scan evidence. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2002; 94: 454-9.

7. Morales-Aguirre JJ, Patino-Nino AP, Mendoza-Azpiri M, et al. Parotid cysts in children infected with human immunodeficiency virus. Arch Otolaryngol Head Neck Surg 2005; 131: 353–355.
8. Young JA, Warfield AT. The salivary glands in: Gray W, McKee GT editors, Diagnostic Cytopathology 2nd Ed. London: Churchill Livingstone 2003; 305 – 23.

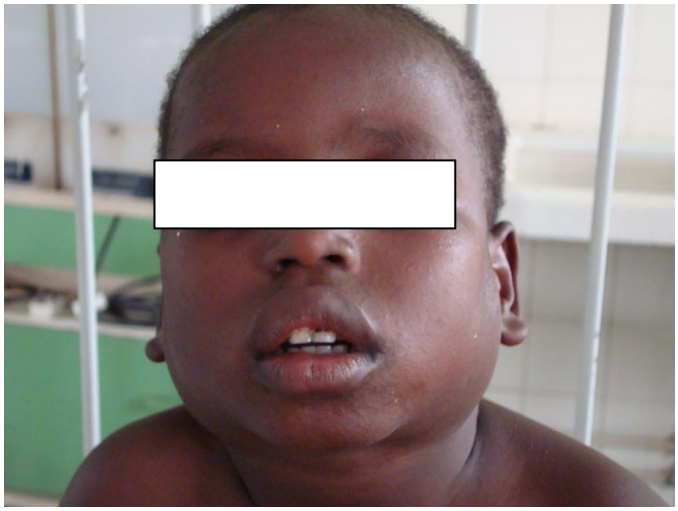

Figure 98: Bilateral parotid enlargement in a 4-year-old child erroneously diagnosed as a case of mumps. More detailed history, examination and antibody testing confirmed HIV infection.

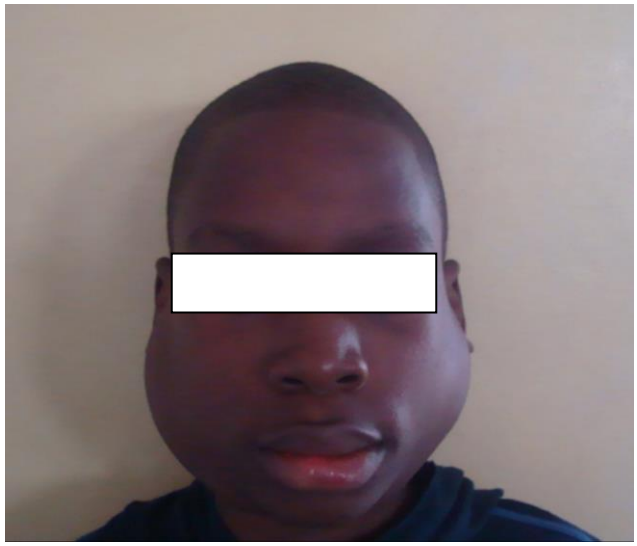

Figure 99: Bilateral parotid swelling in a 12-year-old child.

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

1. Lubega S, Zirembuzi GW, Lwabi P. Heart disease among children with HIV/AIDS attending the Paediatric infectious disease clinic at Mulago Hospital. Afr Health Sci 2005; 5:219-226.
2. Okoromah CAN, Ojo OO, Ogunkunle OO. Cardiovascular dysfunction in HIV-infected children in a sub-Saharan African country: comparative cross-sectional observational study. J Trop Pediatr 2012; 58:3-11.
3. Barbaro G. Cardiovascular Manifestations of HIV Infection. Circulation. 2002; 106 (11):1420-1425.
4. Alqaqa A, Suleiman A, Birnhak S et al. Cardiac sequelae of human immunodeficiency virus disease. Am J Med Sci. 2014; 348(1):82-6.

5. Lipshultz SE, Easley KA, Orav EJ, et al. Left ventricular structure and function in children infected with human immunodeficiency virus: the prospective P2C2 HIV multicenter study. Circulation. 1998; 97:1246–1256.

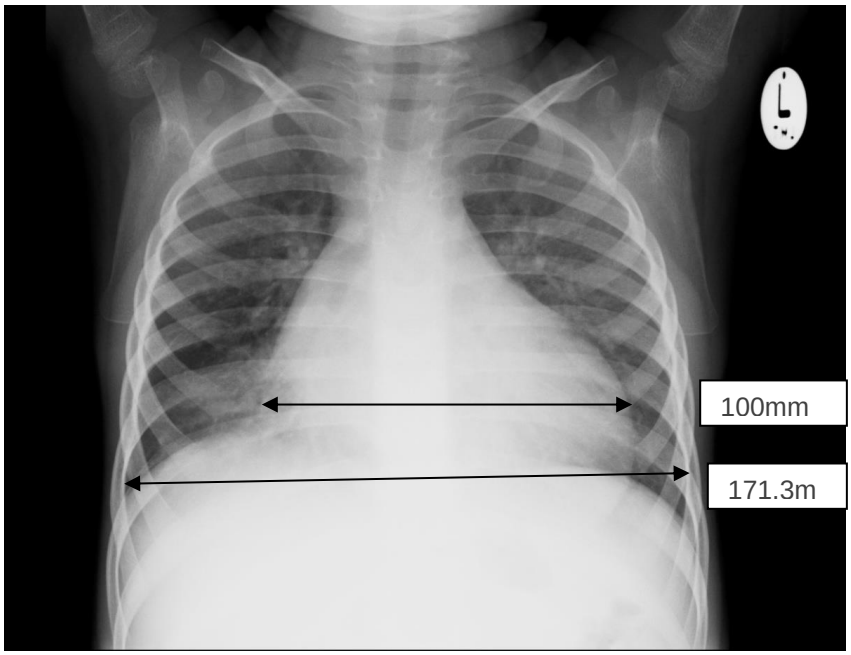

Figure 100: Chest X-ray showing enlarged heart in a child with HIV associated dilated cardiomyopathy

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

1. Ray PE, Xu L, Rakusan T et al. A 20-year history of childhood HIV-associated nephropathy. Pediatr Nephrol, 2004. 19(10):1075-92.
2. McCulloch MI, Ray PE. Kidney disease in HIV-positive children. Semin Nephrol. 2008; 28(6):585-94.
3. Ray PE. Taking a hard look at the pathogenesis of childhood HIV-associated nephropathy. Pediatr Nephro. 2009; 24 (11): 2109-19.

4. Bhimma R, Purswani MU, Kala U. Kidney disease in children and adolescents with perinatal HIV-1 infection. J Int AIDS Soc. 2013 16:18596. doi: 10.7448/IAS.16.1.18596.

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.

Further reading

1. Gelbard HA, Epstein LG. HIV-1 encephalopathy in children. Curr Opin Pediatr 1995;7: 655-62.
2. Kovacs A. Early immune activation predicts central nervous system disease in HIV-infected infants: implications for early treatment. Clin Infect Dis. 2009; 48(3):347-9.
3. Donald KA, Hoare J, Eley B et al. Neurologic complications of pediatric human immunodeficiency virus: implications for clinical practice and management challenges in the African setting. Semin Pediatr Neurol. 2014; 21(1):3-11.

4. Shanbhag MC, Rutstein RM, Zaoutis T et al. Neurocognitive functioning in pediatric human immunodeficiency virus infection: Effects of combined therapy. Arch Pediatr Adolesc Med. 2005; 159:651-656.
5. DeCarli C, Civetello LA, Brouwers P et al. The prevalence of computed axial tomographic abnormalities of the cerebrum in 100 consecutive children symptomatic with the human immunodeficiency virus. Ann Neur 1993; 34: 198–205.
6. Lindsey JC, Malee KM, Brouwers P et al. Neurodevelopmental functioning in HIV-infected infants and young children before and after the introduction of protease inhibitor-based highly active antiretroviral therapy. Pediatrics. 2007 ;119(3): e681-93.
7. Tamula MA, Wolters PL, Walsek C et al. Cognitive decline with immunologic and virologic stability in four children with human immunodeficiency virus disease. Pediatrics. 2003; 112 (3 Pt 1):679-84.

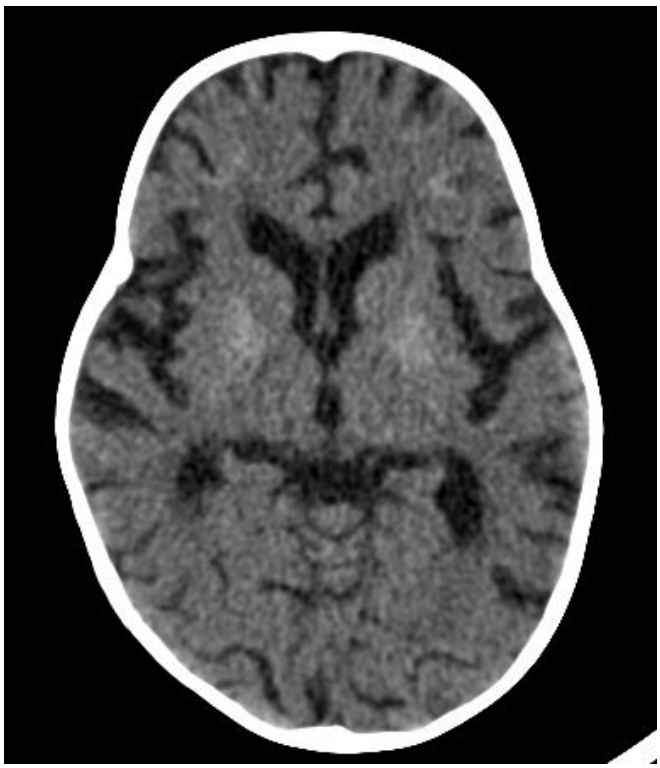

Figure 101: CT brain of an 18/12 old girl with HIV encephalopathy: The image shows global brain shrinkage, bibasal ganglia and subcortical calcification.

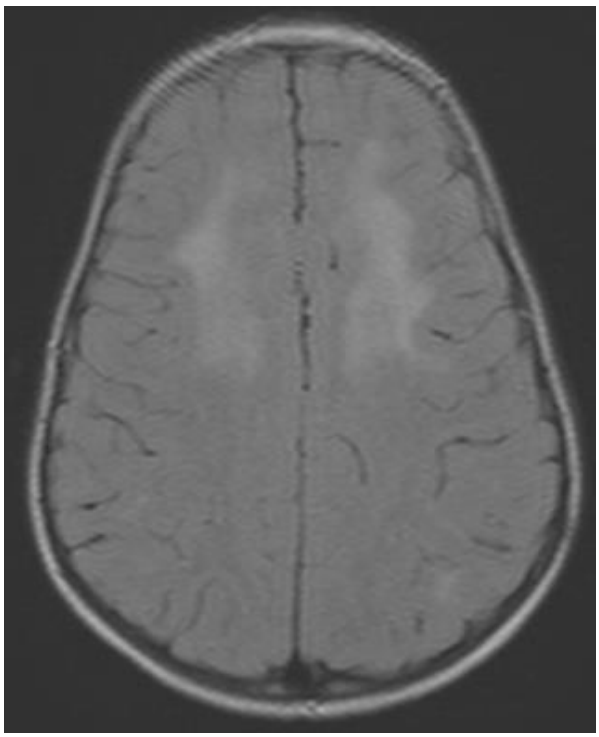

Figure 102: MRI brain of a 20-month old child with HIV encephalopathy showing white matter enhancement.

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CHAPTER 11: MALNUTRITION AND HIV

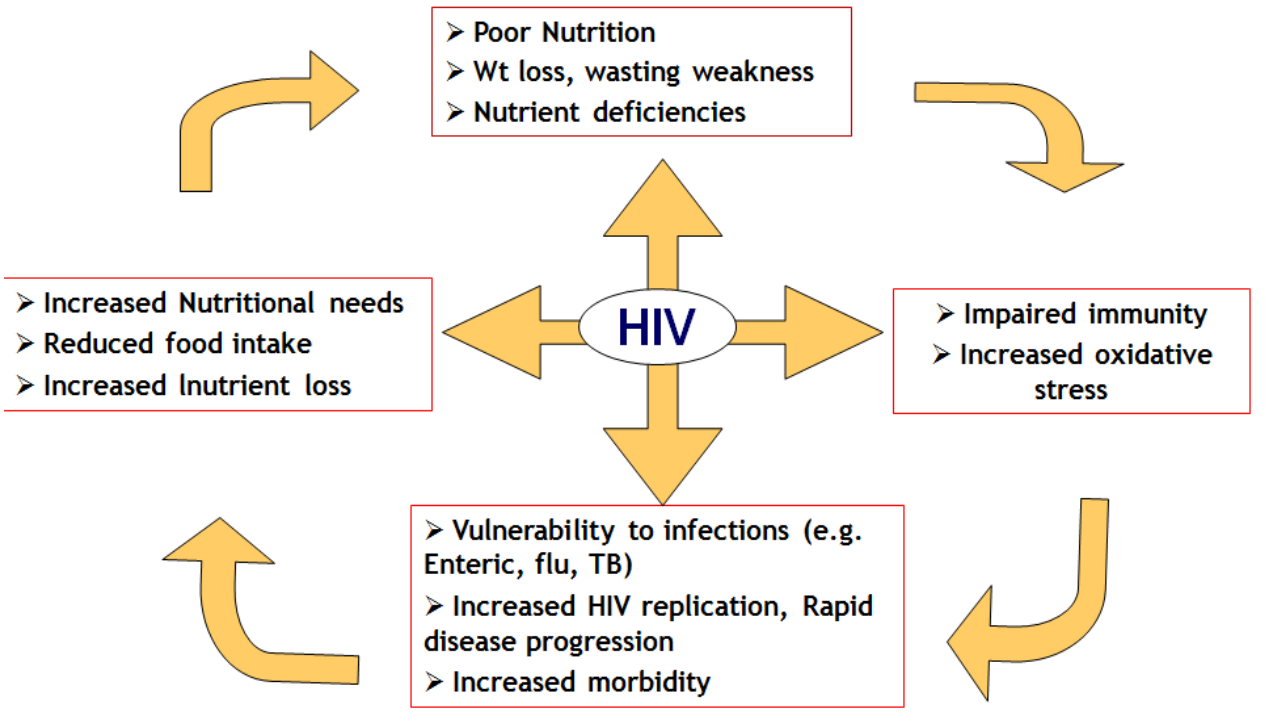


Figure 103: Interaction between HIV infection and nutritional status in children

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

1. WHO. Antiretroviral Therapy for HIV infection in children and infants: Toward Universal Access. Recommendations for a public health approach. 2010 revision. Available from: http://whqlibdoc.who.int/publications/2010/9789241599801_eng.pdf.
2. Duggal S, Chugh TS, Duggal AS. HIV and Malnutrition: Effects on Immune System. Clinical and Developmental Immunology 2012; 1-8.

Figure 104: Plump nuts.

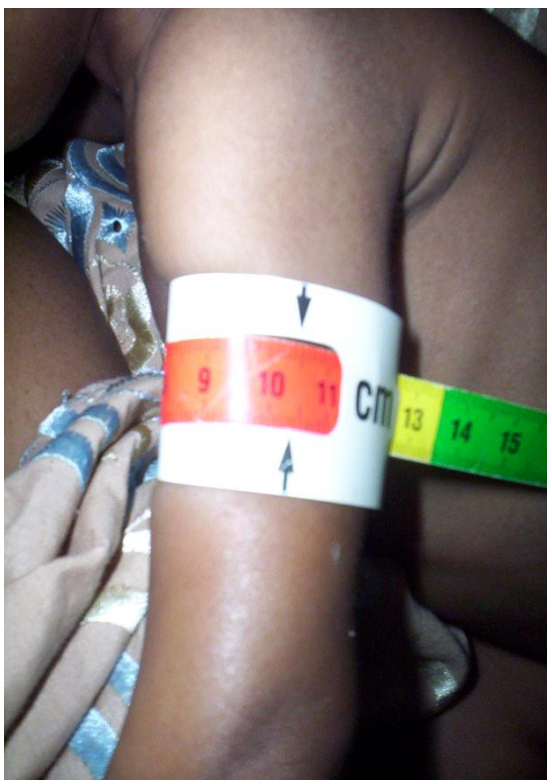


Figure 105: Severe malnutrition: MUAC 10.5 cm.

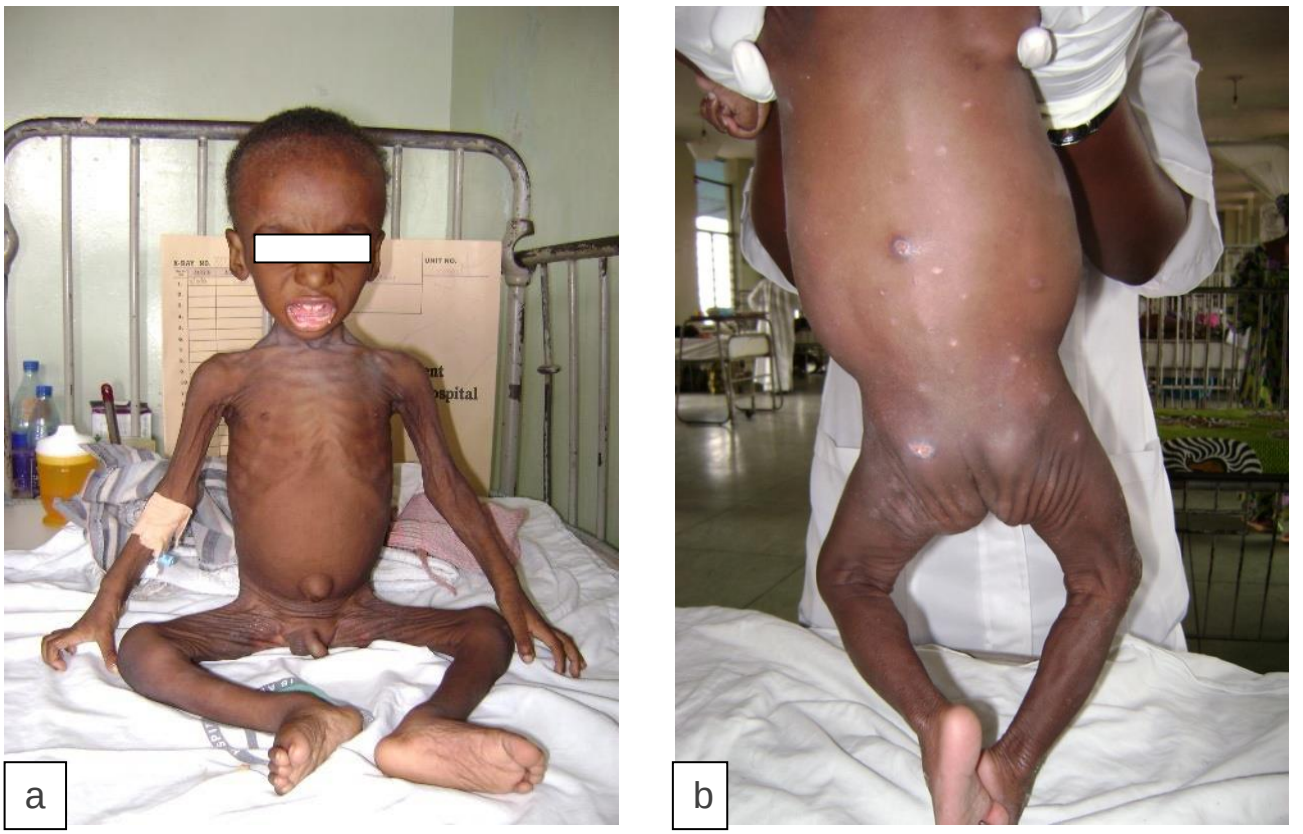


Figure 106 a and b: (a) Severe wasting, (b) Marasmus with gluteal skin folds ("baggy pants" sign).

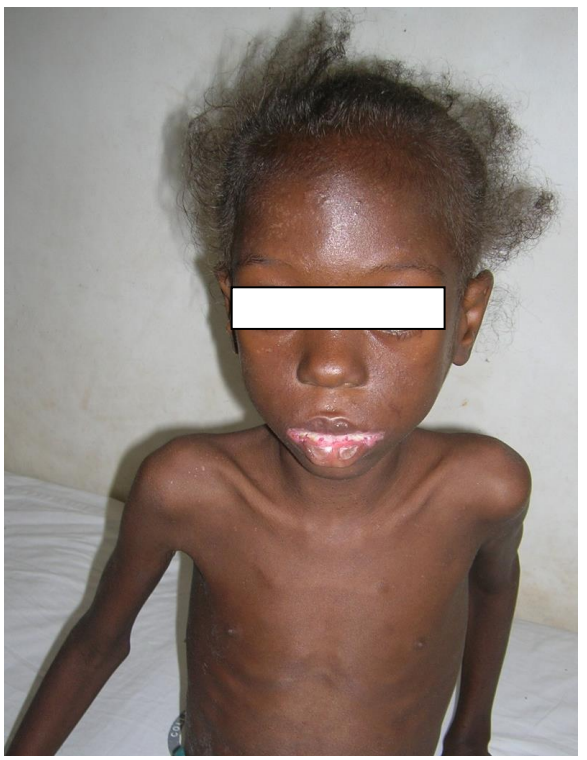


Figure 107: Severe wasting with hair changes in HIV infection.

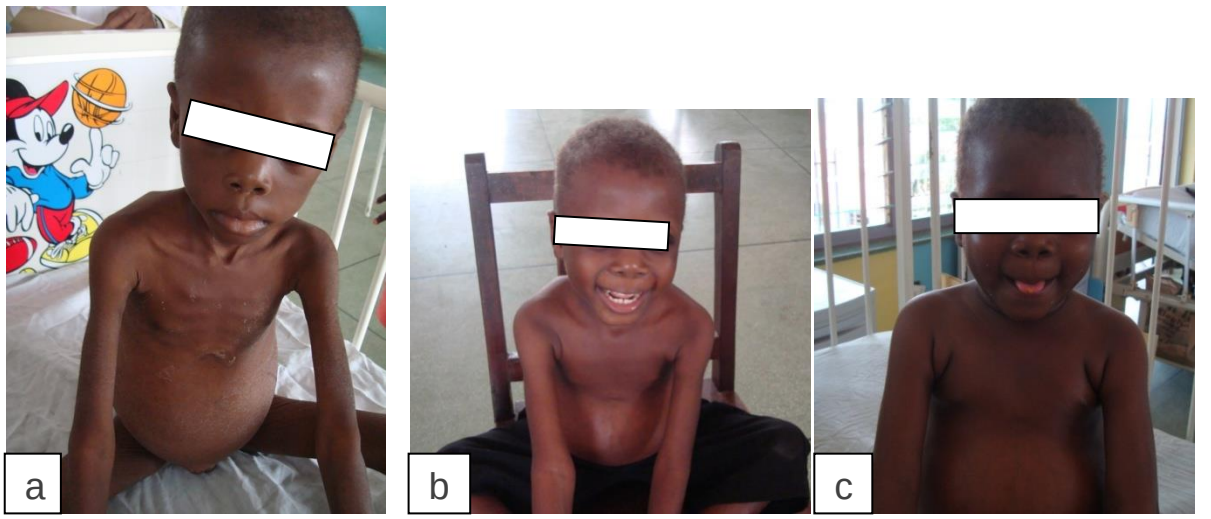


Figure 108a, b and c: (a) At first diagnosis (b) After 2 weeks on care (c) After 4 weeks on care.

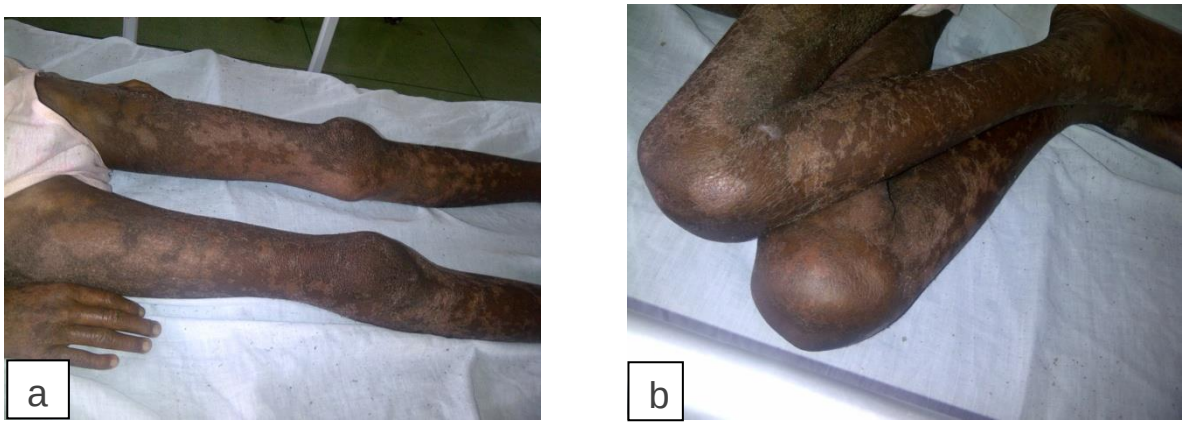
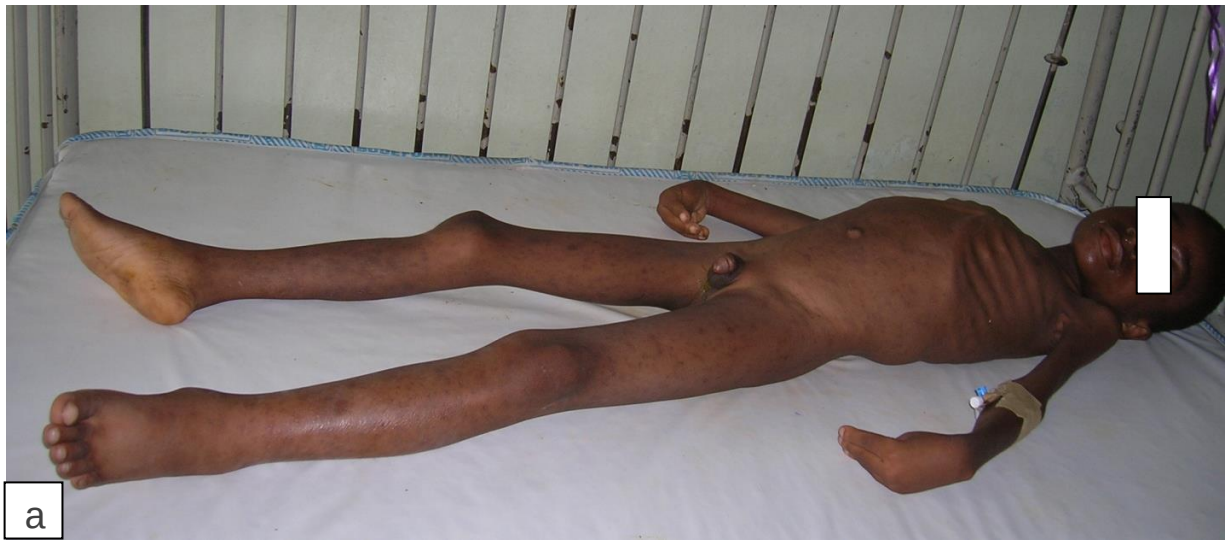


Figure 109a and b: (a, b) Severe wasting and flaky paint desquamation on the lower limbs of an HIV-infected child.



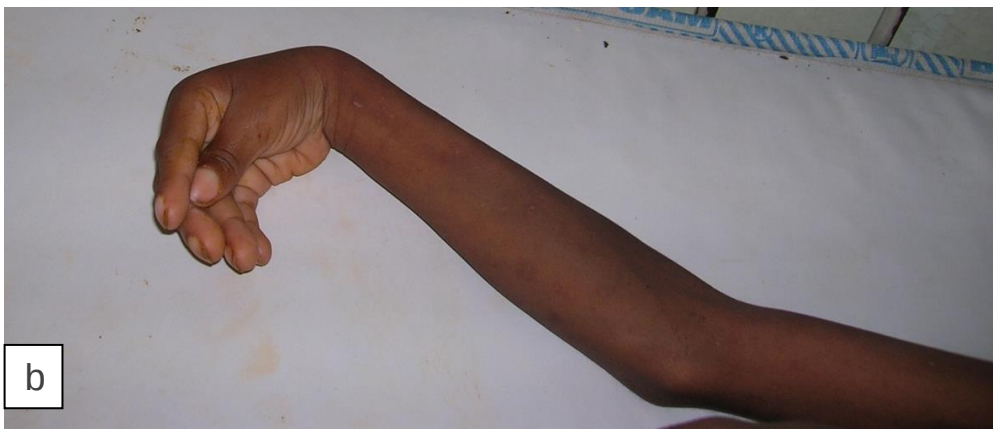


Figure 110a and b: 8-year-old boy with severe acute malnutrition plus oedema. He had symptomatic hypocalcaemia with carpal spasm demonstrated. The spasm resolved with intravenous calcium gluconate.

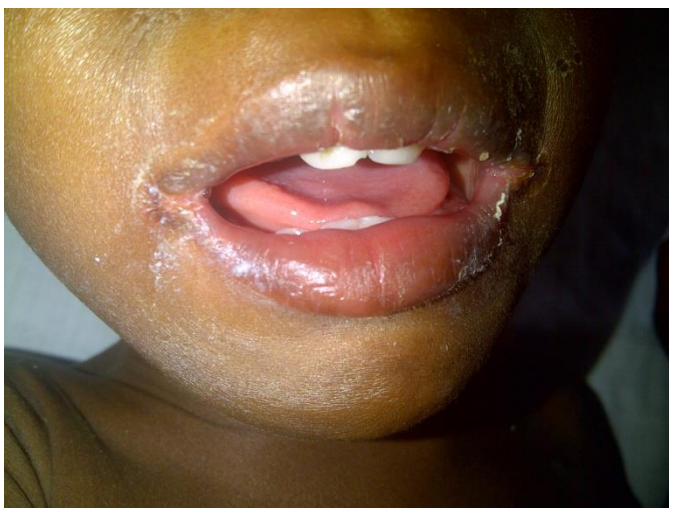


Figure 111: Angular stomatitis due to riboflavin (vitamin B2) deficiency.

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

1. Chintu C, Mudenda V, Lucas S, et al. Lung diseases at necropsy in African children dying from respiratory illnesses: a descriptive necropsy study. Lancet 2002; 360:985–990.
2. Graham SM, Mankhambo L, Phiri A et al. Impact of human immunodeficiency virus infection on the aetiology and outcome of severe pneumonia in Malawian children. Pediatr Infect Dis J. 2011;30 (1):33-8.
3. Bakeera-Kitaka S, Musoke P, Downing R, et al. Pneumocystis carinii in children with severe pneumonia at Mulago Hospital, Uganda. Ann Trop Paediatr. 2004; 24:227–235.
4. Zar HJ, Dechaboon A, Hanslo D, et al. Pneumocystis carinii pneumonia in South African children infected with human immunodeficiency virus. Pediatr Infect Dis J. 2000; 19: 603–607.
5. Morrow BM, Samuel CM, Zampoli M et al. Pneumocystis pneumonia in South African children diagnosed by molecular methods. BMC Res Notes. 2014; 7:26. doi: 10.1186/1756-0500-7-26.
6. World Health Organization. Pocket Book of Hospital Care for Children: Guidelines for the Management of Common Illnesses with Limited Resources. Geneva: World Health Organization; 2005.

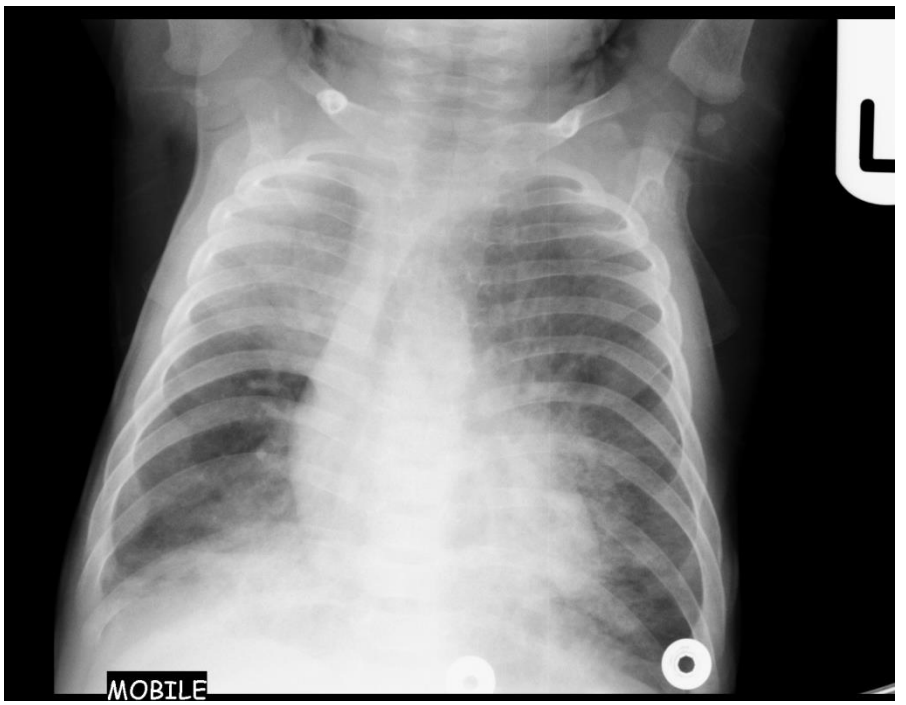


Figure 112: Chest X-ray of a 3-month-old child newly diagnosed with HIV infection. The X-ray shows confluent air space opacification in the right upper lobe and lower lobe on a background of bilateral ground-glass air space opacification. BAL specimen was positive for PCP.

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.

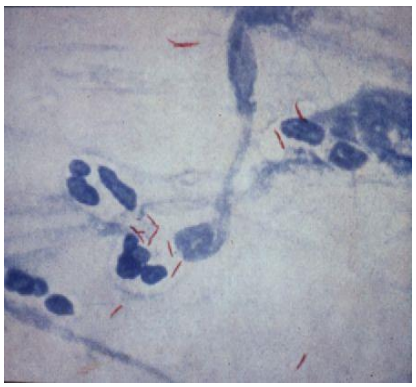


Figure 113: Acid fast bacilli (AFB) on smear microscopy

Figure 114: GeneXpert machines

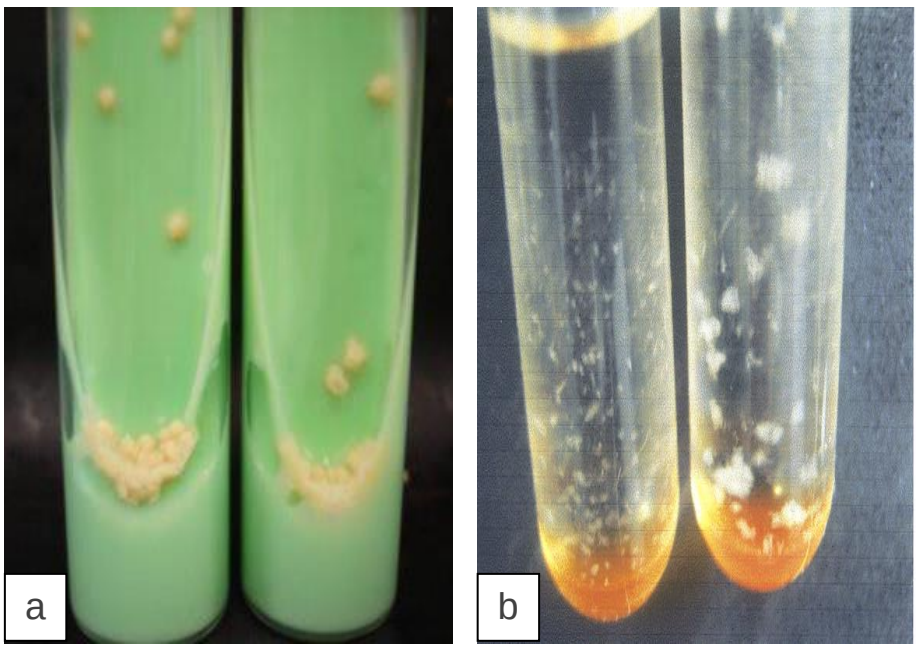


Figure 115a and b: a) Lowenstein Jensen (solid) medium -Culture positive TB. b) MGIT (liquid) medium – Culture positive TB.

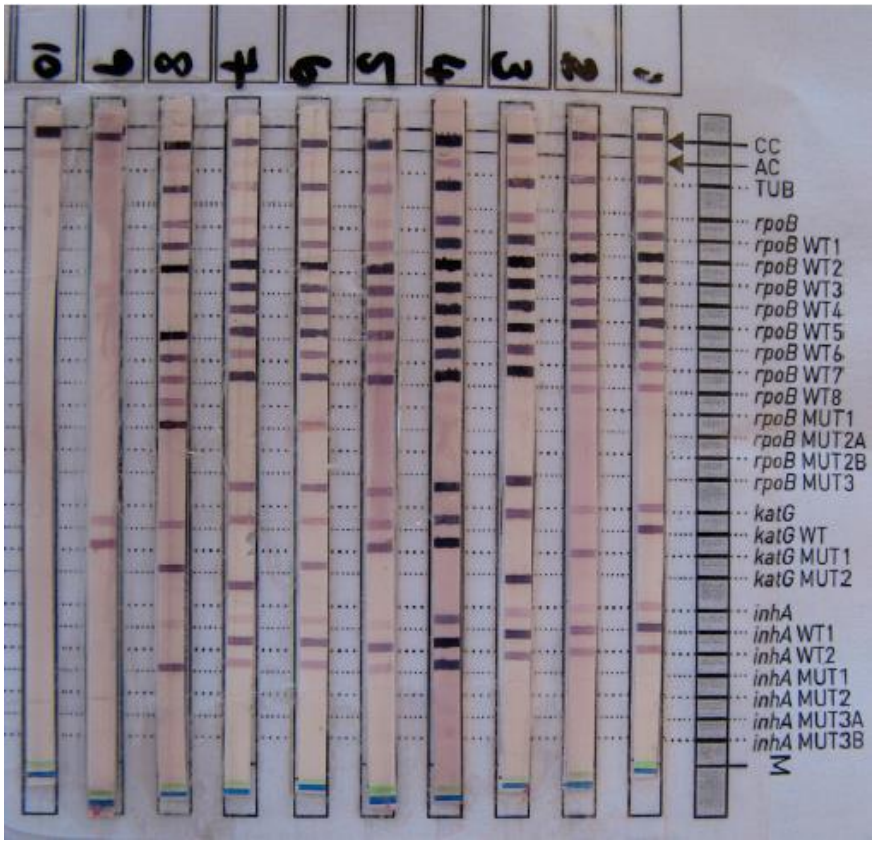


Figure 116: PCR Line Probe Assay. There are 27 bands per strip consisting of 6 controls plus wild and resistant probes (rpoB probes: 8 wild type susceptible + 4 resistant mutants), (katG probes: 1 wild type (susceptible) + 2 resistant mutants), (inhA probes: 2 wild type (susceptible) + 4 resistant mutants).

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

1. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Available at: http://www.who.int/hiv/pub/guidelines/arv2013/en/.
2. Elenga N, Kouakoussui KA, Bonard D et al. Diagnosed tuberculosis during the follow-up of a cohort of human immunodeficiency virus-infected children in Abidjan, Côte d'Ivoire: ANRS 1278 study. Pediatr Infect Dis J. 2005; 24(12):1077-82.
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.
4. Swaminathan S. Tuberculosis in HIV-infected children. Paediatr Respir Rev. 2004; 5(3):225-30.
5. Zar HJ, Hanslo D, Apolles P et al. Induced sputum versus gastric lavage for microbiological confirmation of pulmonary tuberculosis in infants and young children: a prospective study. Lancet 2005; 365 (9454):130-4.
6. Sekadde MP, Wobudeya E, Joloba ML et al. Evaluation of the Xpert MTB/RIF test for the diagnosis of childhood pulmonary tuberculosis in Uganda: a cross-sectional diagnostic study. BMC Infect Dis. 2013; 13:133. doi: 10.1186/1471-2334-13-133.

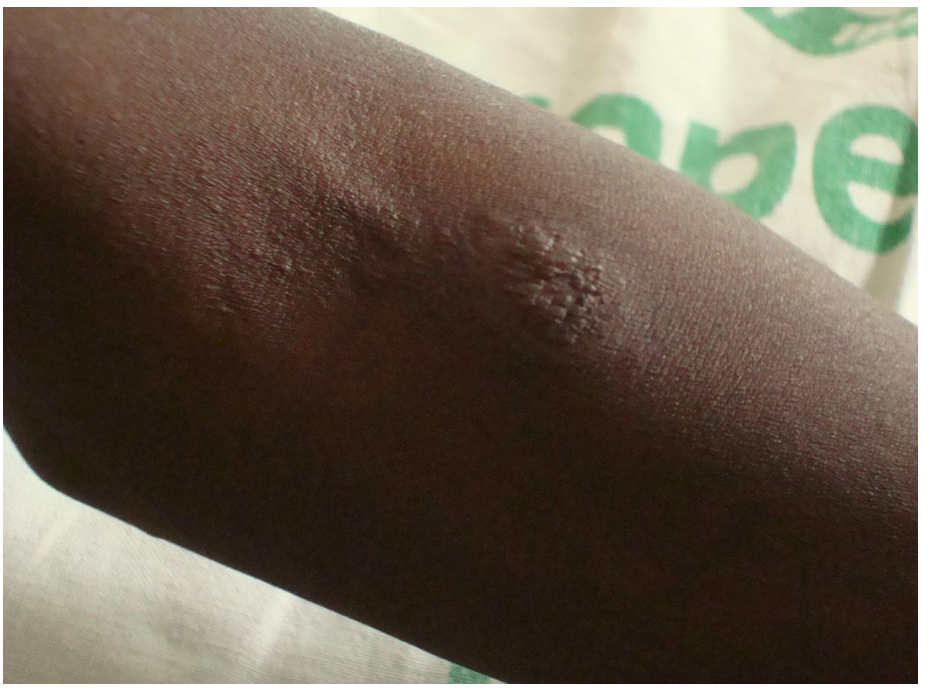


Figure 117: Positive Mantoux test. Mantoux test may be negative in HIV-infected children as a result of immunosuppression.

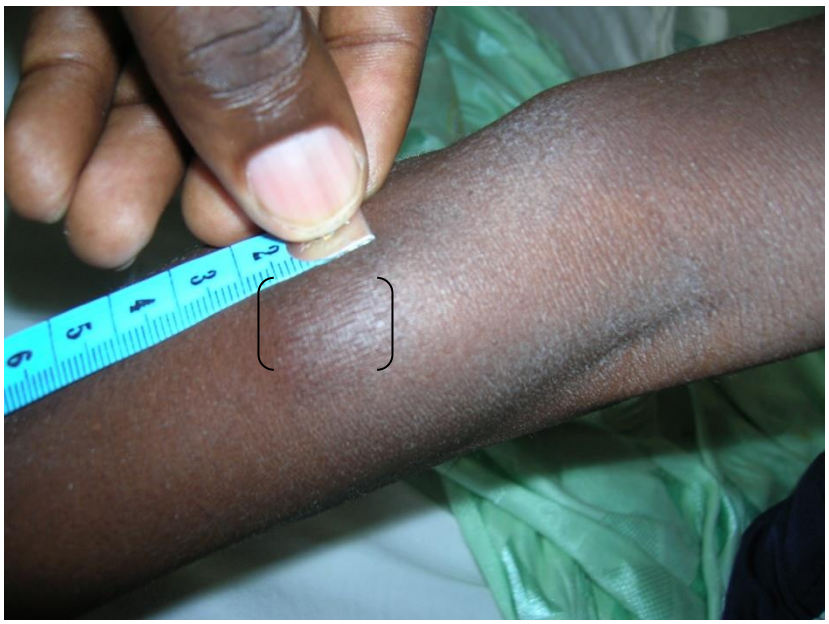


Figure 118: Positive Mantoux test in a very dark-skinned child.

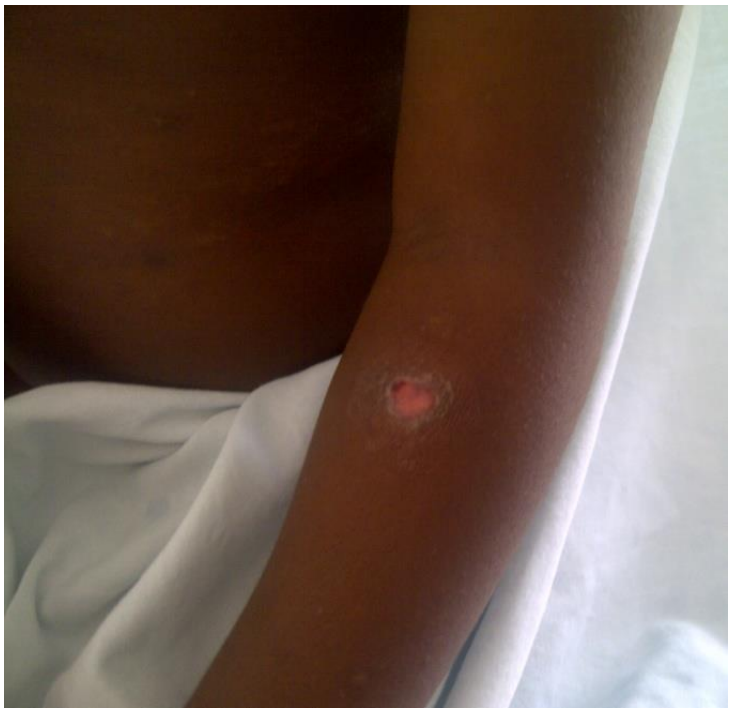


Figure 119: Ulcerated Mantoux test.

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.

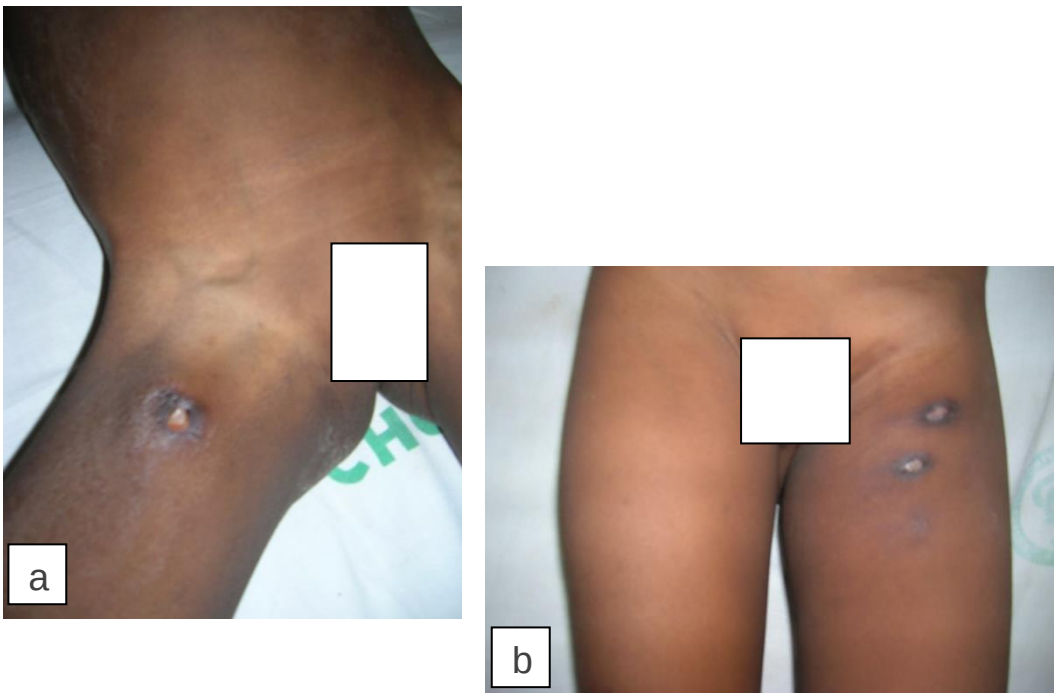
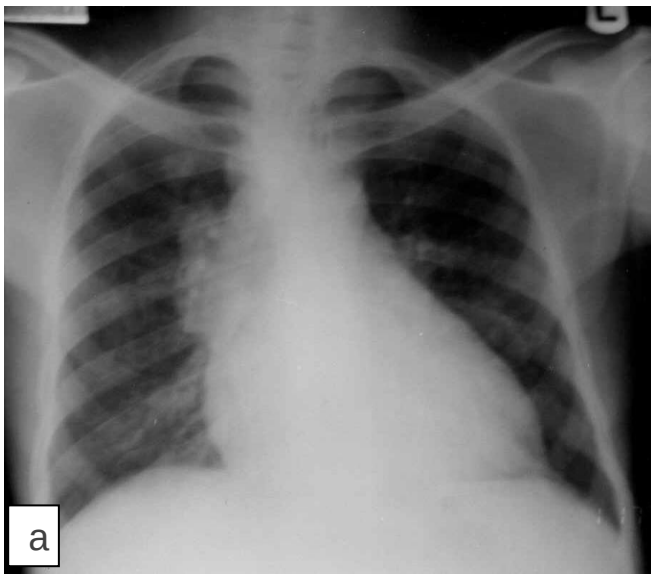


Figure 121: TB-HIV co-infection. Tuberculous lymphadenitis with formation of sinuses (scrofula).



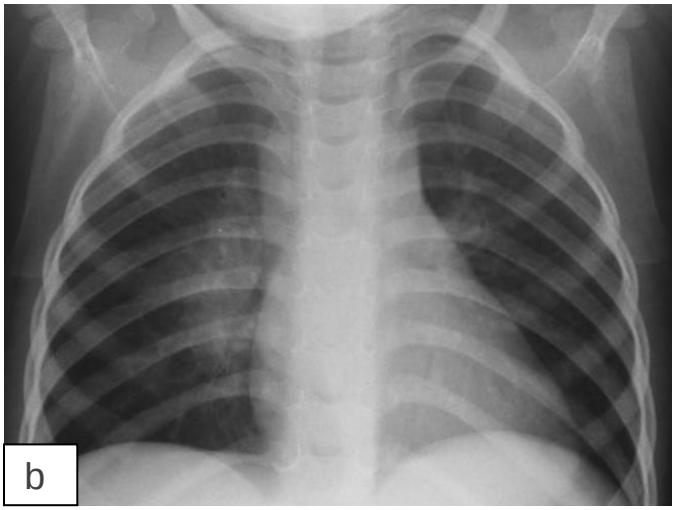
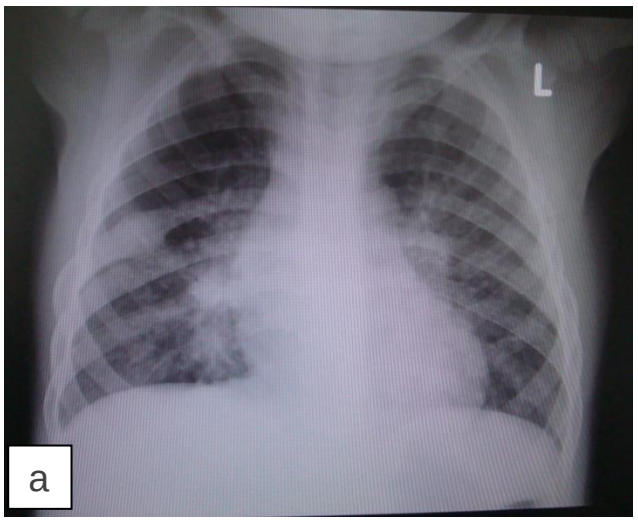


Figure 122a and b: CXR - Primary pulmonary tuberculosis.



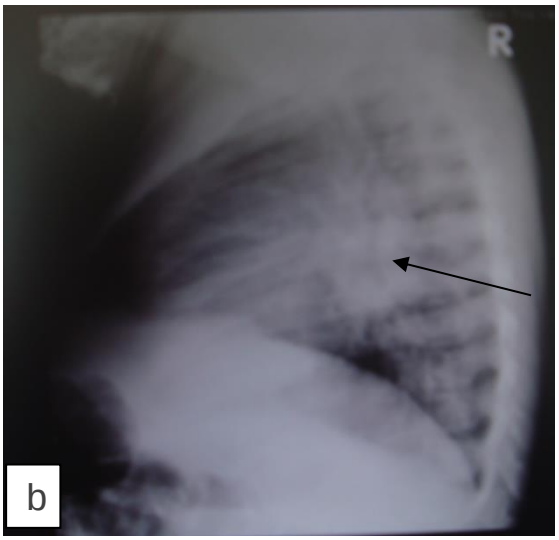


Figure 123a and b: Black arrow demonstrates perihilar and sub-carinal enlarged lymph nodes encircling the carina with some airway obstruction ("doughnut" or "hamburger" sign) as seen on the lateral view.

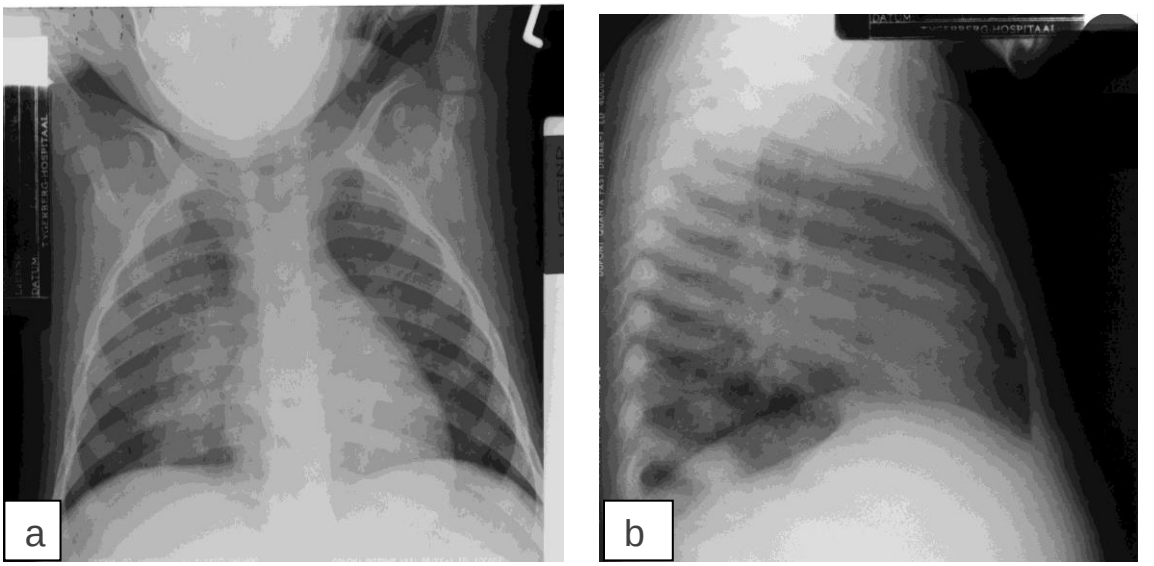


Figure 124: CXR: Perihilar opacities in PA and lateral views.

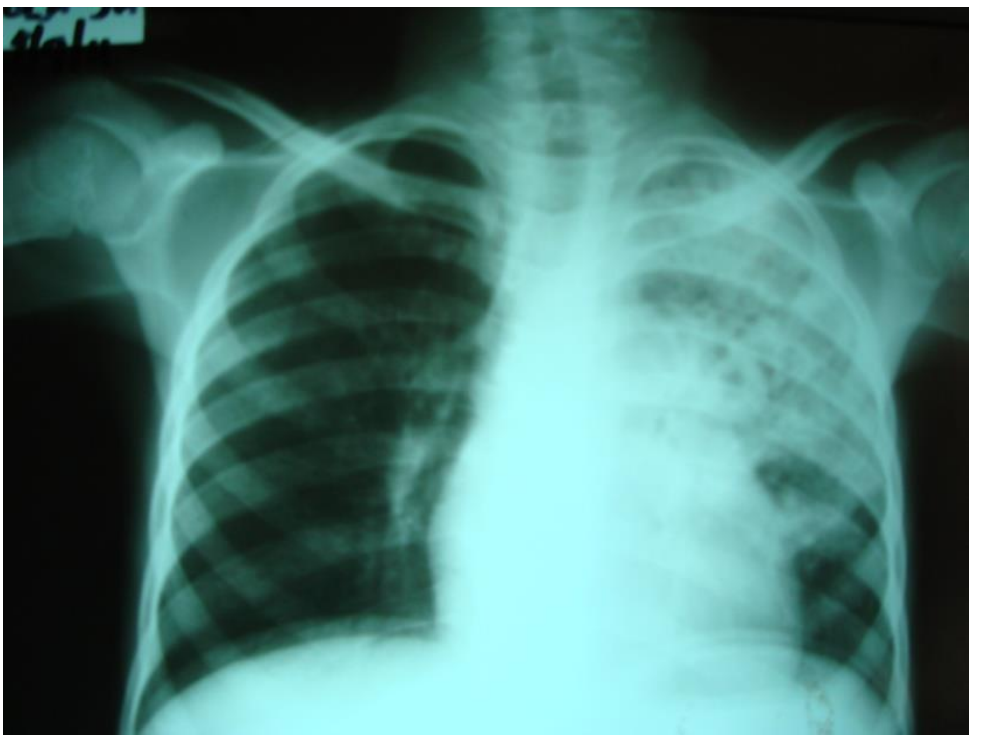


Figure 125: Chest radiograph showing cavities in the left hilar region in a 10-year-old girl that presented with chronic cough and wasting.

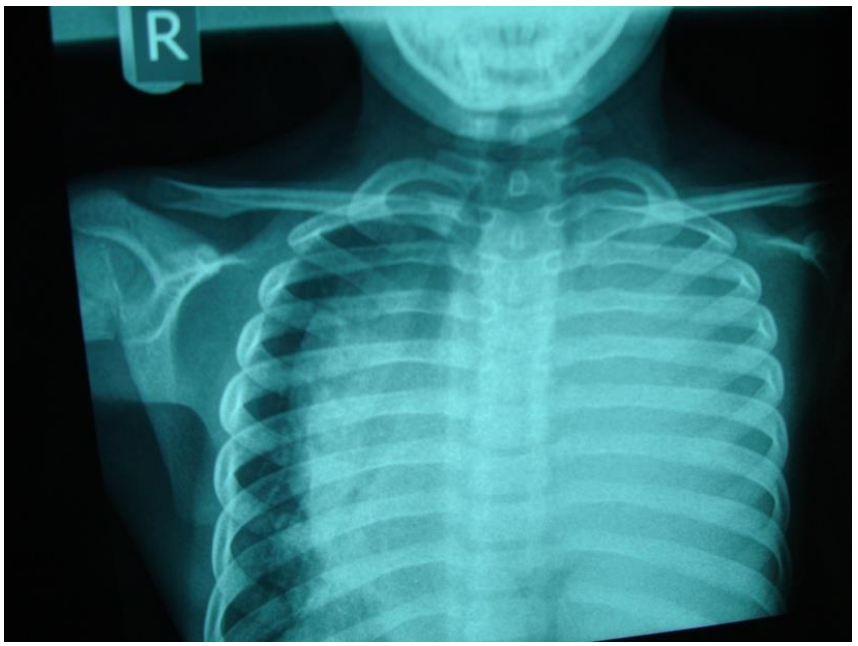


Figure 126: Massive left pleural effusion. The trachea is deviated to the left.

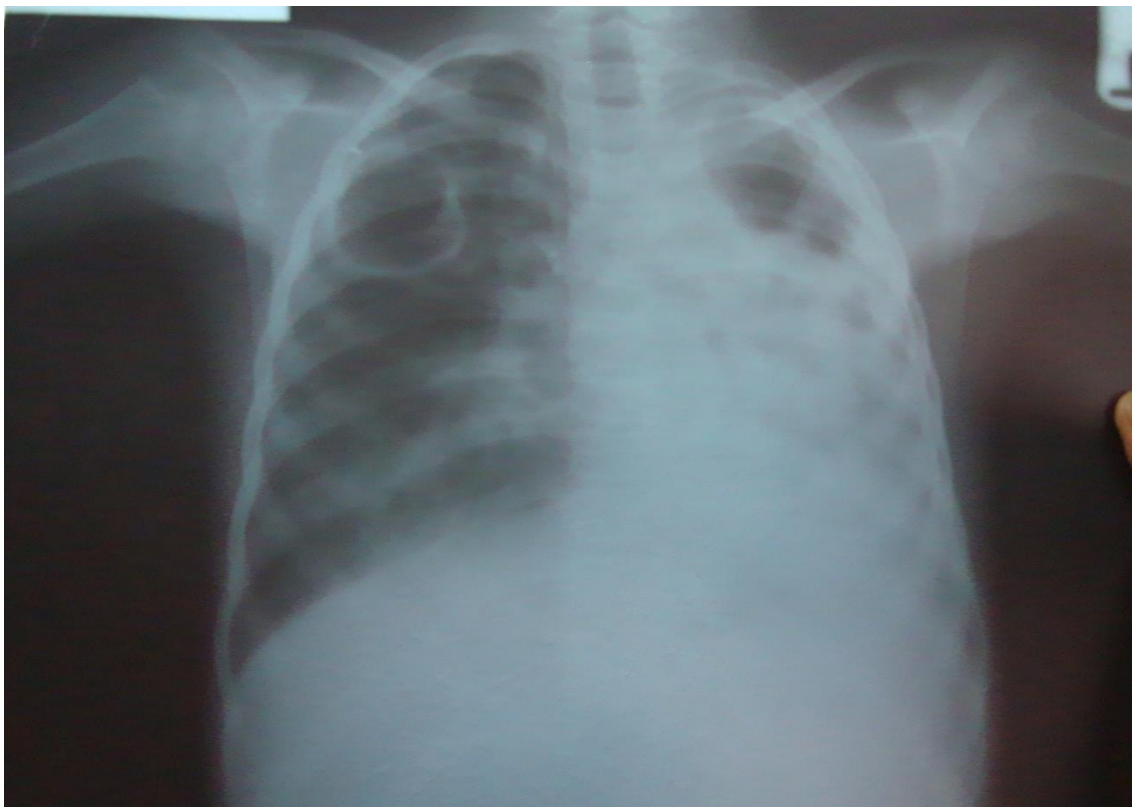


Figure 127: Chest radiograph of a 12-year-old HIV-infected child with MDR TB. Note the cavity on the right upper zone.

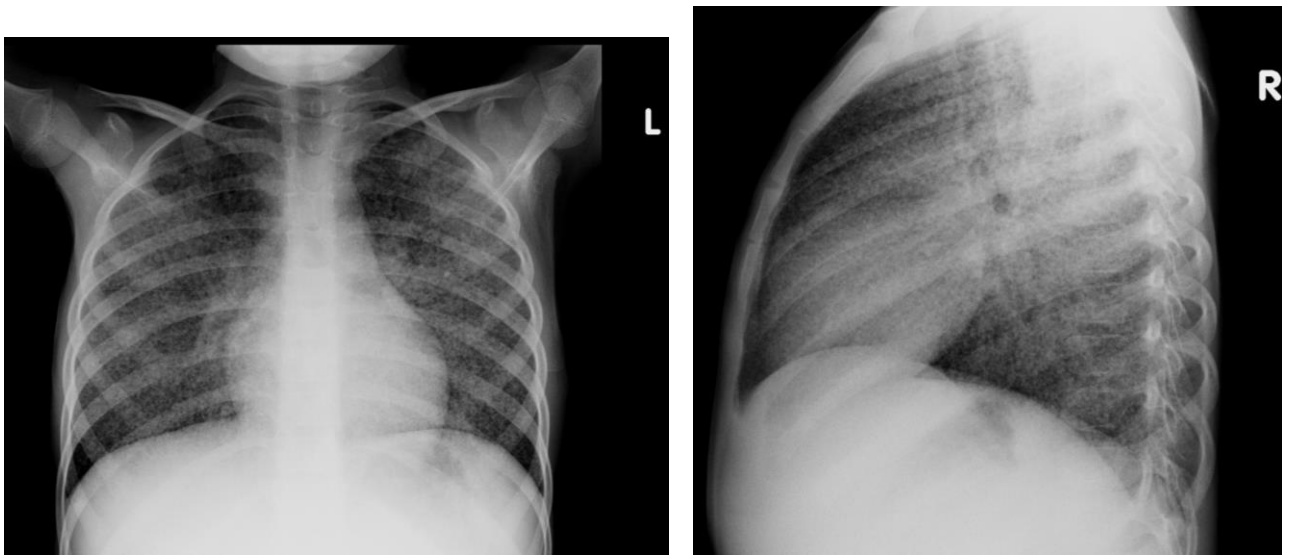


Figure 128: CXR - PA and lateral views showing multiple micro nodules in keeping with miliary TB. Differential diagnosis - LIP in the HIV-infected child.

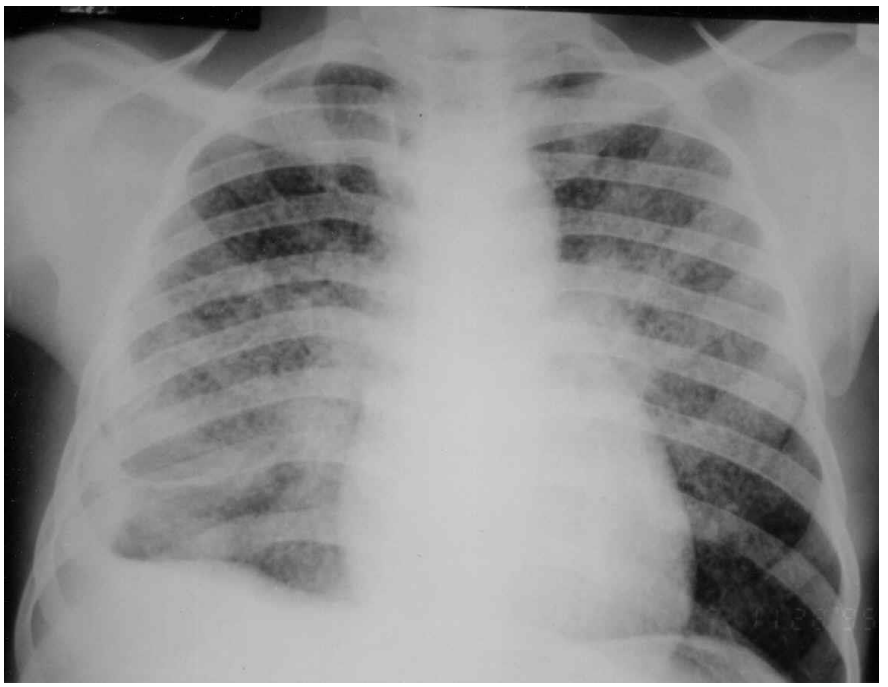


Figure 129: CXR - Miliary shadow.

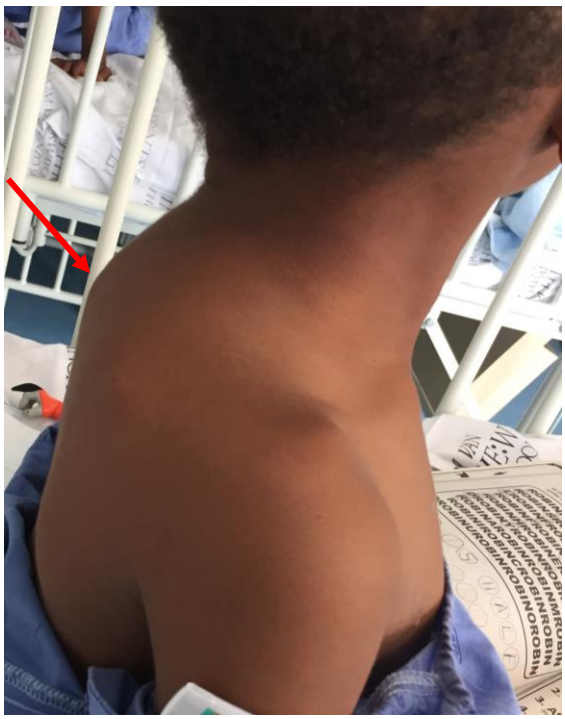


Figure 130: TB spine - Gibbus formation involving the upper thoracic spine (red arrow).

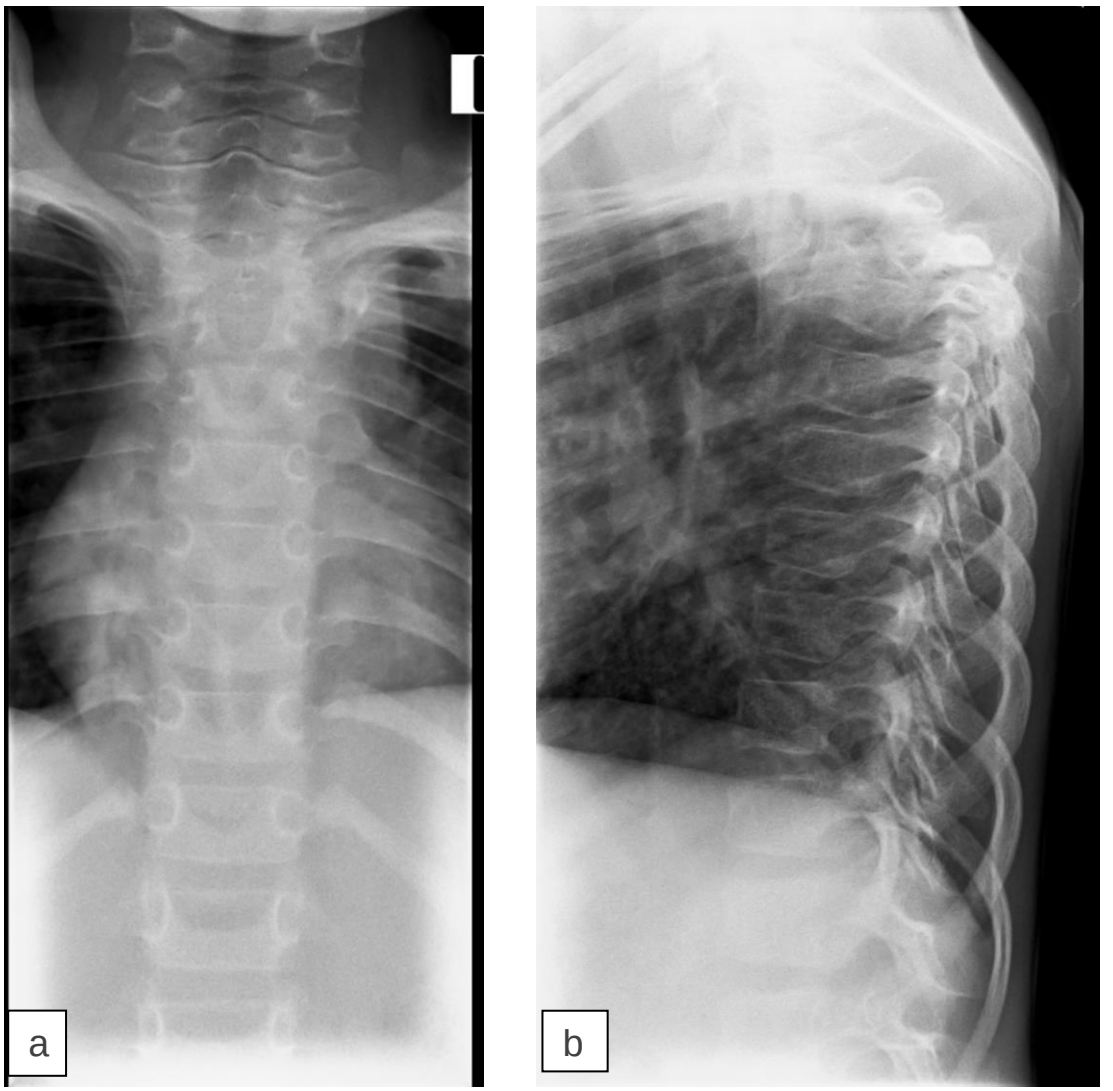


Figure 131a and b: Thoracolumbar spine X-rays (AP and lateral views) of the child above: TB spine involving T3, T4, T5 and T6 with vertebral body destruction and gibbus formation. Paraspinal mass demonstrated on the lateral.

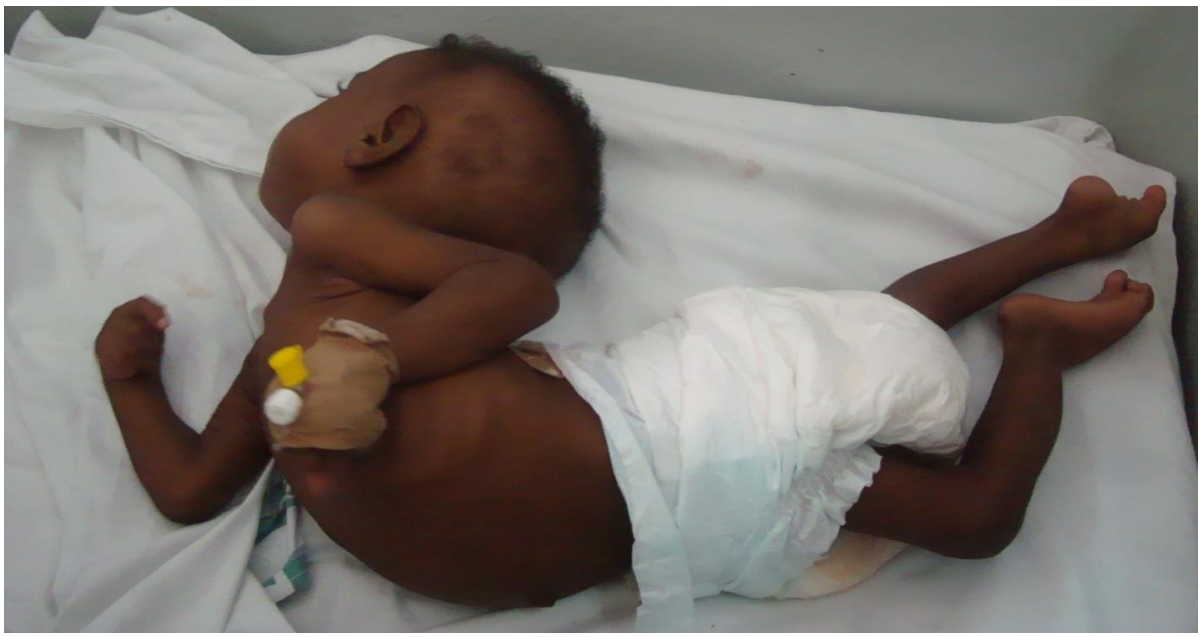


Figure 132: 12-month-old child with late diagnosis of HIV infection, presented with TB meningitis.

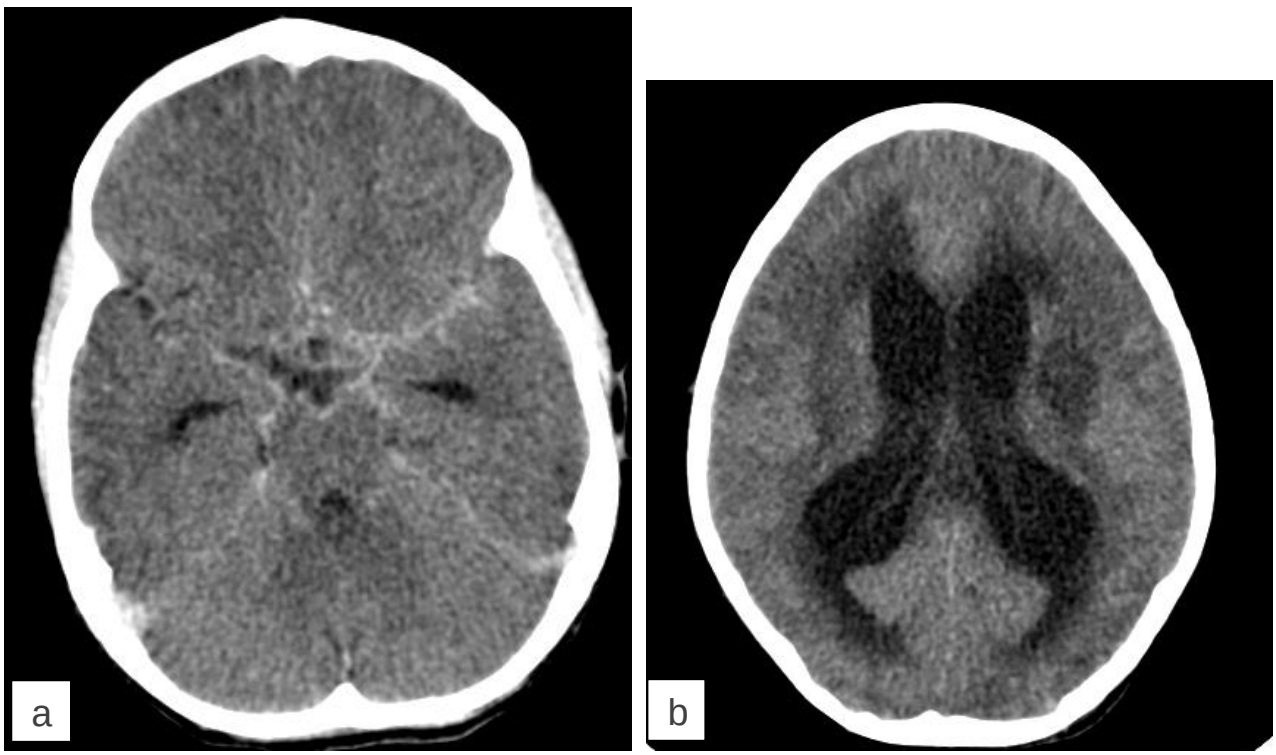


Figure 133a and b: (a) CT brain of a child with TBM showing basal meningeal enhancement. However, TBM imaging may be atypical with the usually typical signs absent or more subtle. (b) CT brain of the same child as above with TBM, showing hydrocephalous and basal ganglia infarct.

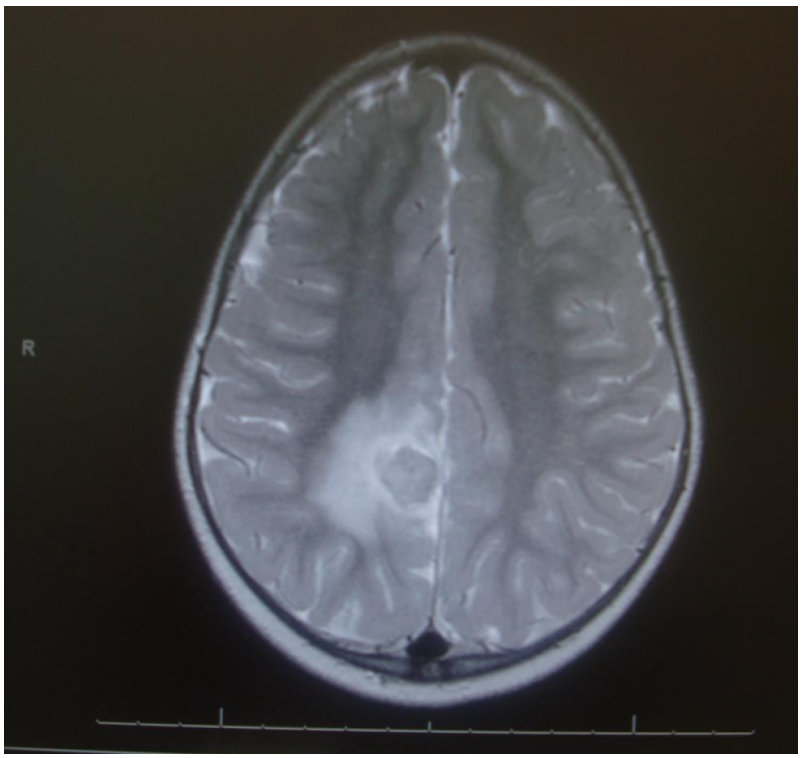


Figure 134: Tuberculoma. Magnetic Resonance Imaging showing rim-enhanced granulomas in the right para-falcine region posteriorly. The centre of the lesion is hypodense. Note the surrounding vasogenic oedema.

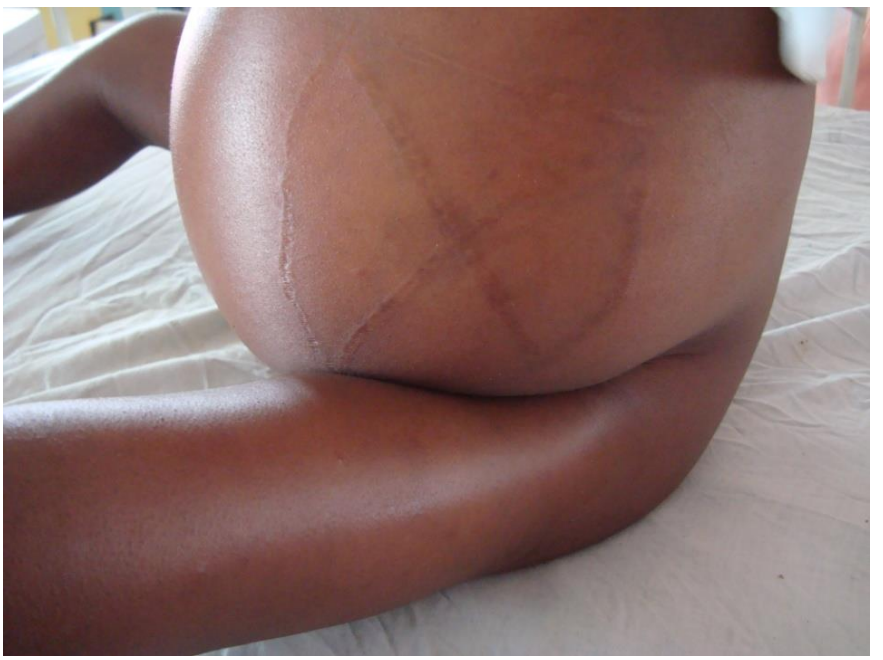


Figure 135: Local scarification marks on the abdomen of a 4-year-old boy newly diagnosed with HIV infection. He had hepatosplenomegaly and ascites from TB abdomen.

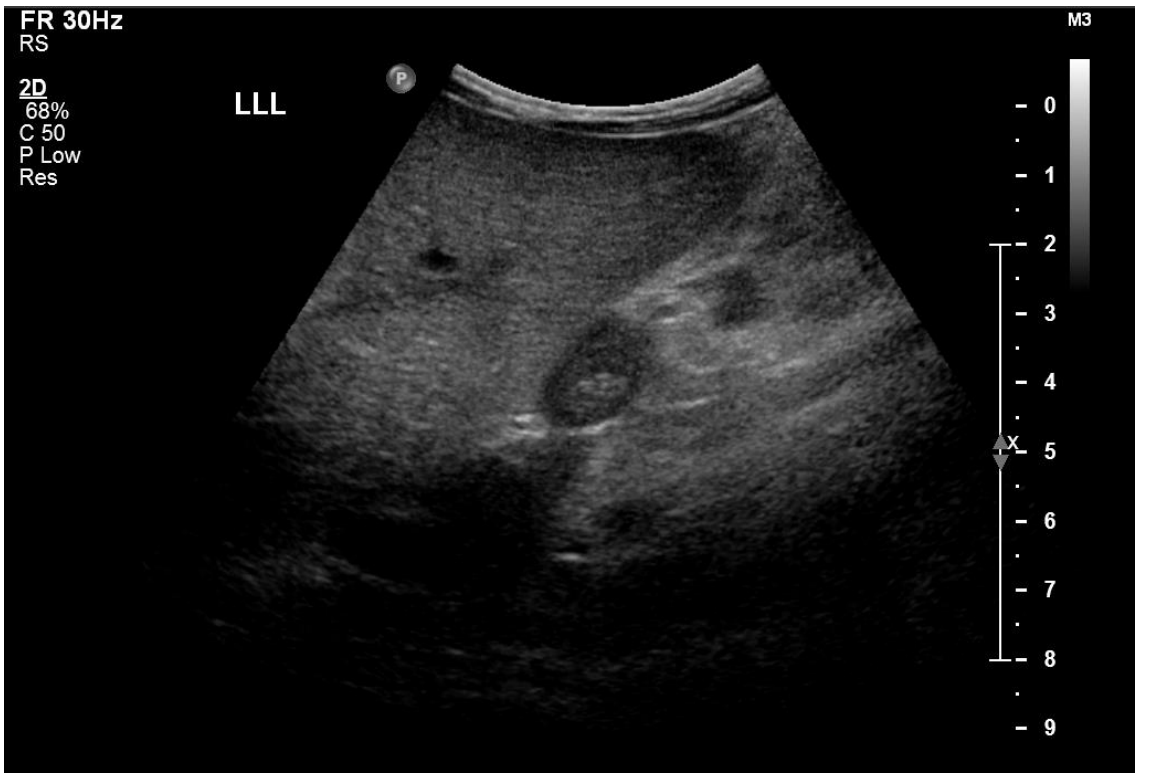


Figure 136: TB abdomen - Significant perioral, para-aortic and splenic hilar lymph nodes. Numerous splenic microabscesses are also shown.

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

1. WHO. Revised BCG vaccination guidelines for infants at risk for HIV infection. Wkly Epidemiol Rec 200; 82 (21): 193-6.
2. Nuttall JJ, Davies MA, Hussey GD, Eley BS. Bacillus Calmette–Gue´rin (BCG) vaccine-induced complications in children treated with highly active antiretroviral therapy. Int J Infect Dis 2008; 12:e99–105.
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.
4. Hesseling AC, Johnson LF, Jaspan H, et al. Disseminated Bacille Calmette-Guérin disease in HIV-infected South African infants. Bull World Health Organ 2009; 87:505-11.
5. Chan PK, Ng BK, Wong CY. Bacille Calmette-Guérin osteomyelitis of the proximal femur. Hong Kong Med J. 2010; 16(3):223-6.

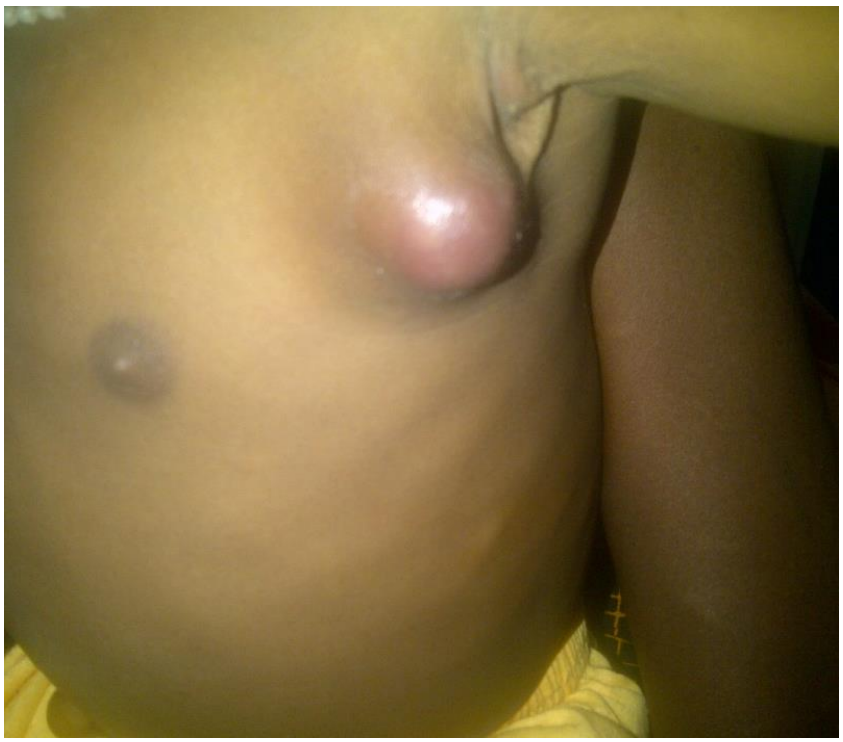


Figure 137: BCG disease of the axillary lymph node with abscess formation.

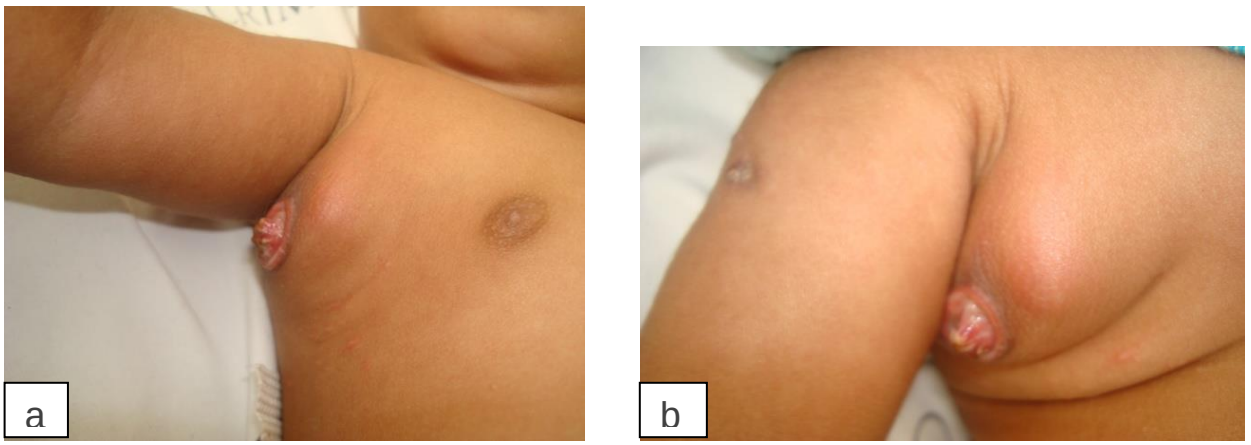


Figure 138: BCG adenitis in a 3 month old HIV exposed infant. Incision and drainage of the lesion was carried out 2 weeks previously resulting in a fungating ulcer. HIV DNA PCR was negative.

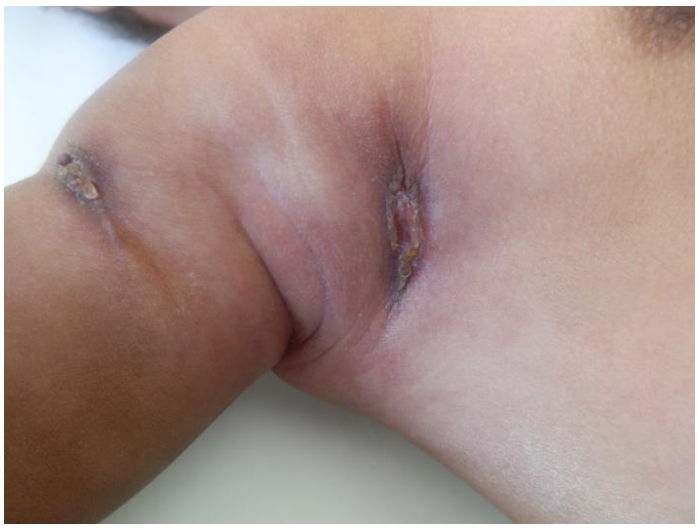


Figure 139: Scrofuloderma – ulceration in the axilla and arm of an HIV-infected child with BCG vaccination.

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

1. Gona P, Van Dyke RB, Williams PL, et al. Incidence of opportunistic and other infections in HIV-infected children in the HAART era. JAMA. 2006; 296 (3):292-300.
2. Dankner WM, Lindsey JC, Levin MJ, Pediatric ACTGPT. 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):40-48.
3. Chiou CC, Groll AH, Mavrogiorgos N et al. Esophageal candidiasis in human immunodeficiency virus infected pediatric patients after the introduction of highly active antiretroviral therapy. Pediatr Infect Dis J. 2002; 21 (5):388-392.
4. Leibovitz E, Rigaud M, Chandwani S, et al. Disseminated fungal infections in children infected with human immunodeficiency virus. Pediatr Infect Dis J. 1991; 10(12):888-894.
5. Gonzalez CE, Venzon D, Lee S, Mueller BU, Pizzo PA, Walsh TJ. Risk factors for fungaemia in children infected with human immunodeficiency virus: a case-control study. Clin Infect Dis. 1996; 23(3):515-521.
6. Stevens DA. Diagnosis of fungal infections: current status. J Antimicrob Chemother. 2002;49 Suppl 1:11-19.

7. 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.

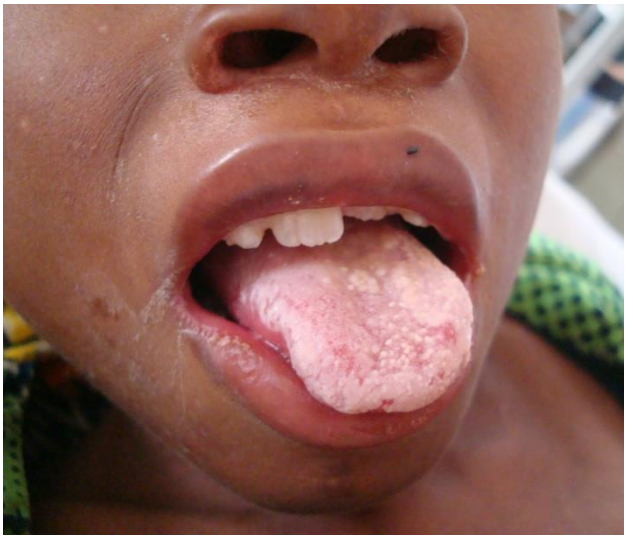


Figure 140: Oral candidiasis.

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.

Further reading

1. Mussi-Pinhata MM, Yamamoto AY, Figueiredo LT et al. Congenital and perinatal cytomegalovirus infection in infants born to mothers infected with human immunodeficiency virus. J Pediatr. 1998;132(2):285-290.

2. Zampoli M, Morrow B, Hsiao NY et al. Prevalence and outcome of cytomegalovirus-associated pneumonia in relation to human immunodeficiency virus infection. Pediatr Infect Dis J. 2011; 30 (5):413-7.
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.

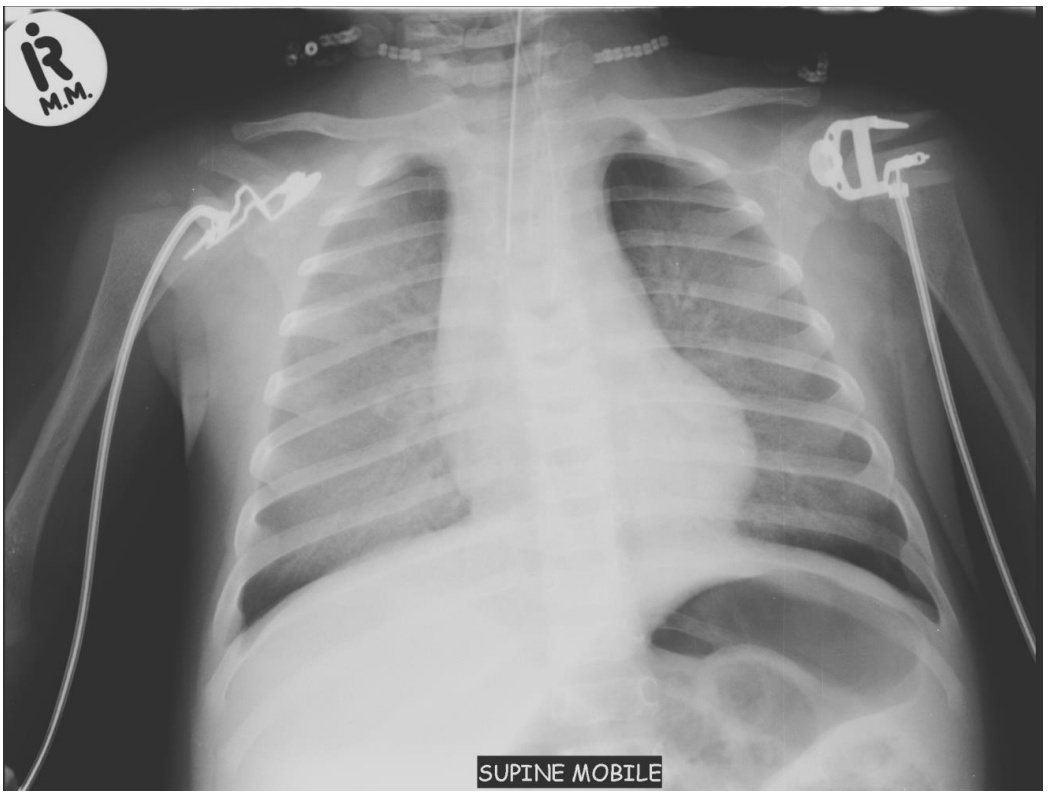


Figure 142: CMV pneumonia: Acute care setting with cardiac monitoring leads in place; widespread confluent ground-glass opacification with associated air bronchograms in a perihilar and diffuse distribution. Features are in keeping with a viral pneumonia. Differential diagnoses include PCP, other viral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

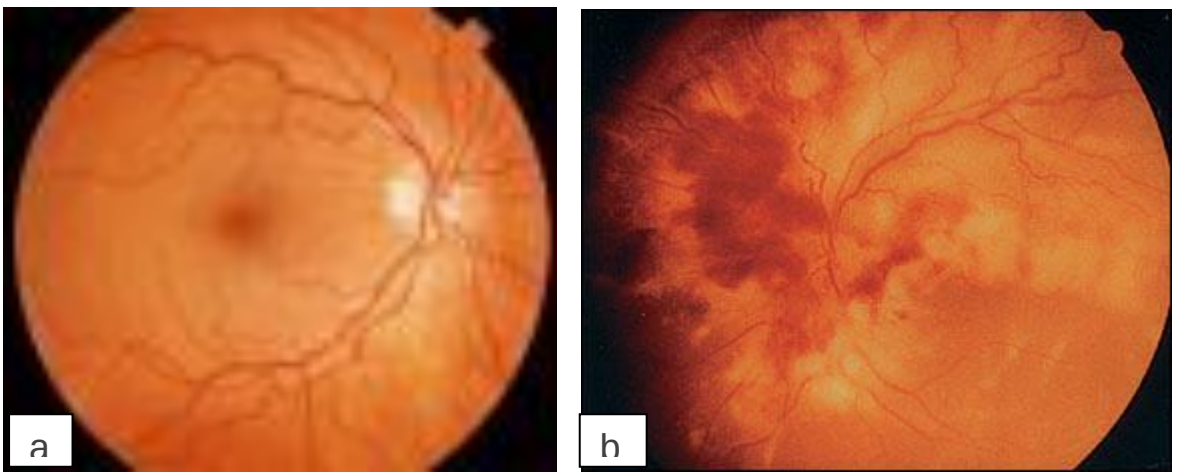


Figure 143a and b: (a). Normal retina (b) CMV retinal pathology showing necrosis and haemorrhage.

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

1. Abadi J, Nachman S, Kressel AB et al. Cryptococcosis in children with AIDS. Clin Infect Dis. 1999; 28(2):309-13.
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/.
3. Govender NP, Dlamini S. Management of HIV-associated cryptococcal disease in South Africa. S Afr Med J 2014; 104(12):896. DOI:10.7196/SAMJ.9070

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.

Further reading

1. Schwenk H, Ramirez-Avila L, Sheu SH et al. Progressive multifocal leukoencephalopathy in pediatric patients: case report and literature review. Pediatr Infect Dis J. 2014; 33 (4):e99-105.
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.

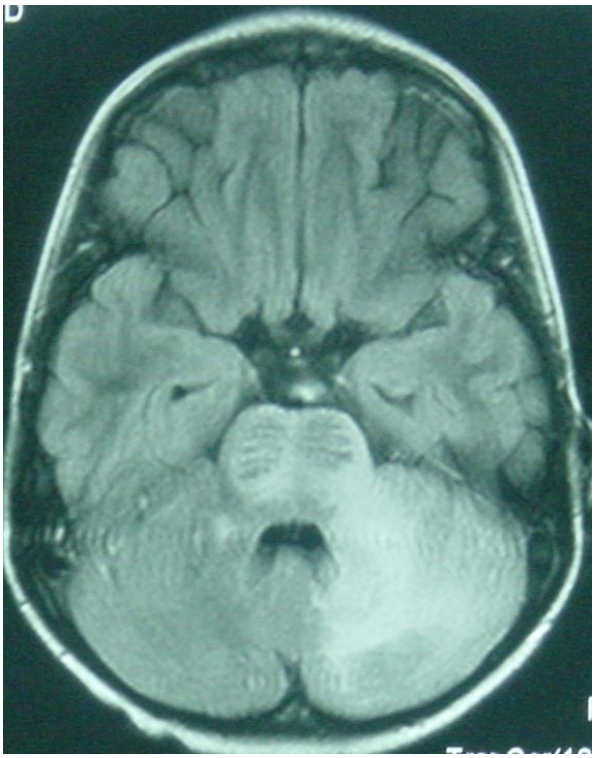


Figure 144: Brain MRI demonstrating hyperintensity of the left cerebellum extending into the middle cerebellar peduncle.

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.

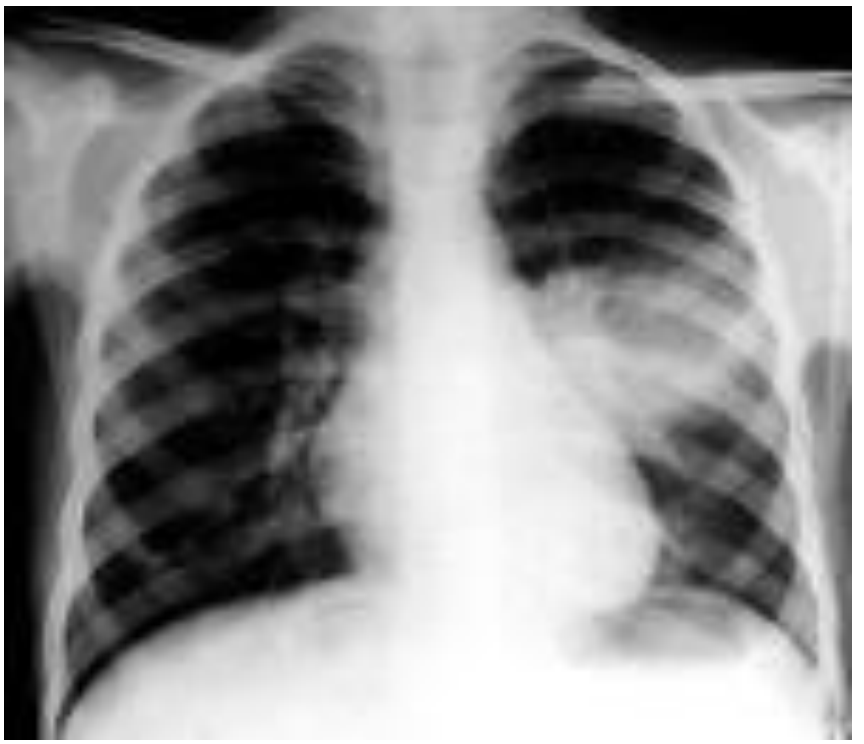


Figure 145: Pneumonia

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.

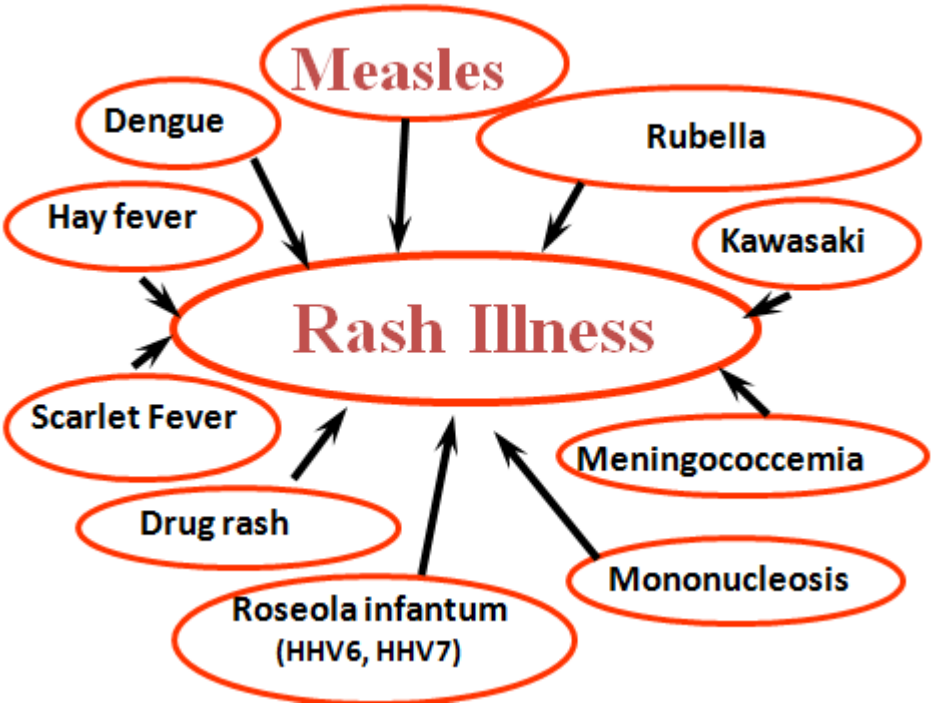


Figure 146: Differentials for rash illness

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.

Further reading

1. de Moraes-Pinto. Interaction between Pediatric HIV infection and measles. Future Virology. 2011; 6 (12):1471-1479
2. Measles vaccines. WHO position paper. Wkly Epidemiol. Rec. 2009; 84, 349–360. Available at: http://www.who.int/wer/2009/wer8435.pdf.
3. World Health Organization. Pocket Book of Hospital Care for Children: Guidelines for the Management of Common Illnesses with Limited Resources. Geneva: World Health Organization; 2005.

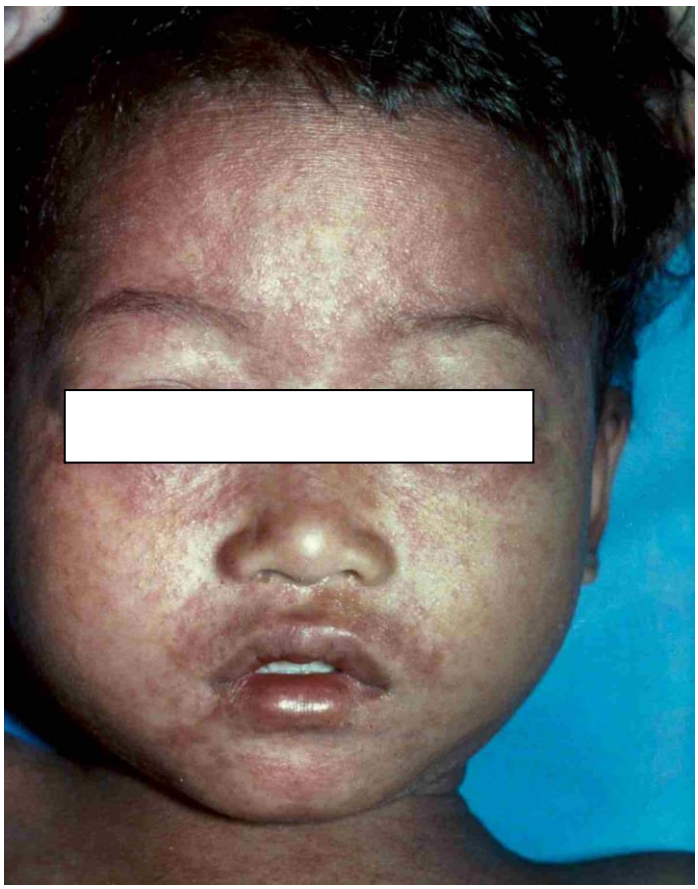


Figure 147: Confluent erythematous maculo-papular measles lesions.

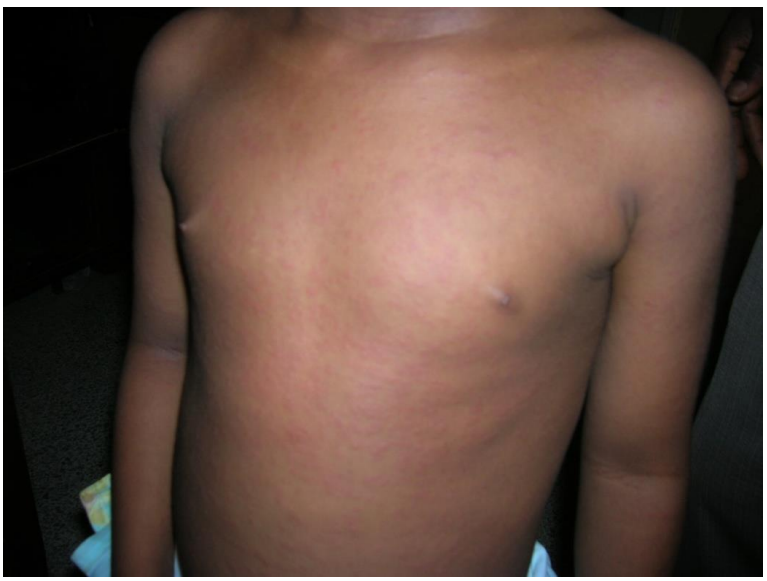


Figure 148: A case measles showing fresh maculo-papular lesions.

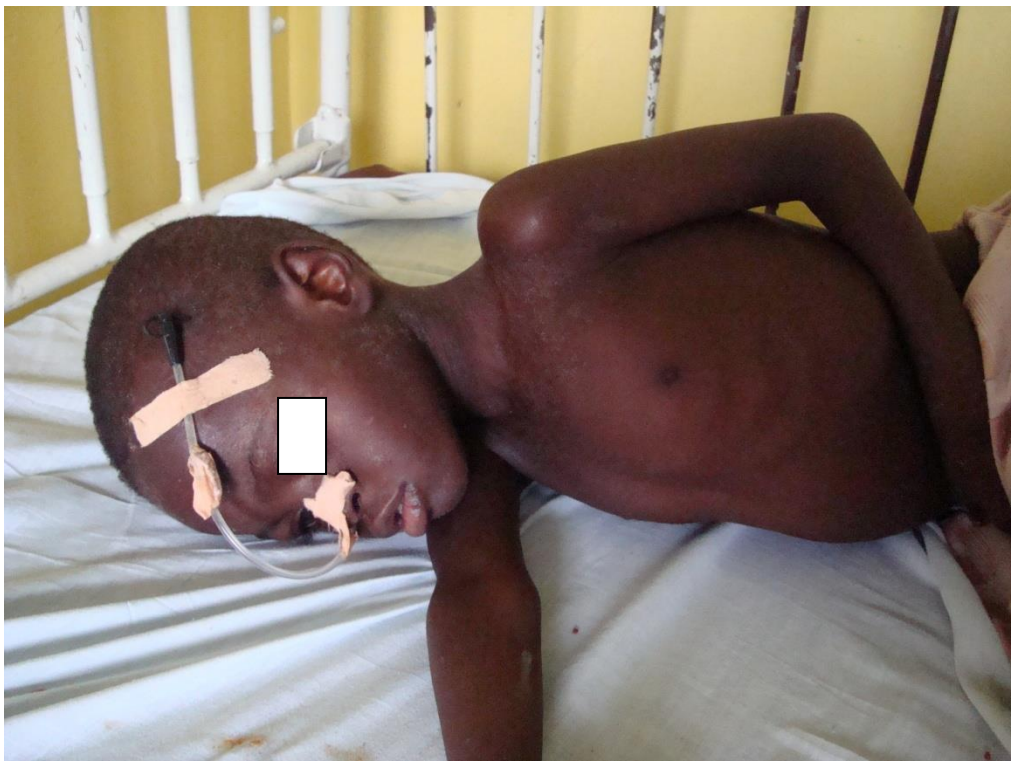


Figure 149: A case of measles shower older desquamating skin lesions.

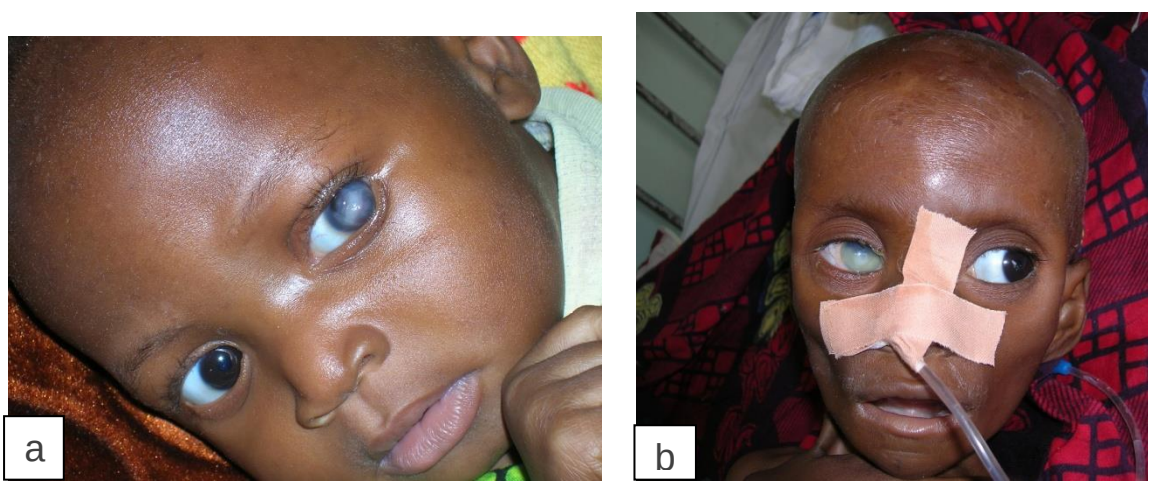


Figure 150a and b: (a) Measles keratitis (b) Post measles panophthalmitis.

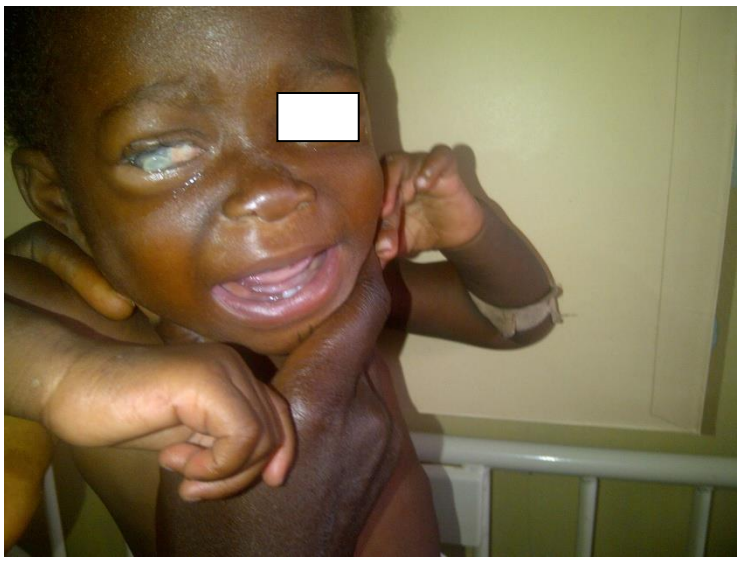


Figure 151: Uveal prolapse, post measles in a 12-month-old with newly diagnosed HIV infection.

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.

Further reading

1. Mwapasa V, Rogerson SJ, Kwiek JJ, et al. Maternal syphilis infection is associated with increased risk of mother-to-child transmission of HIV in Malawi. AIDS 2006; 20:1869.
2. Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines. MMWR. 2010;59 (12). Available at http://www.cdc.gov/std/treatment/2010/genital-ulcers.htm#syphhiv.
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.
4. Workowski KA, Berman S, Centers for Disease C, Prevention. Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep. 2010;59(RR-12):1-110. Available at http://www.ncbi.nlm.nih.gov/pubmed/21160459.

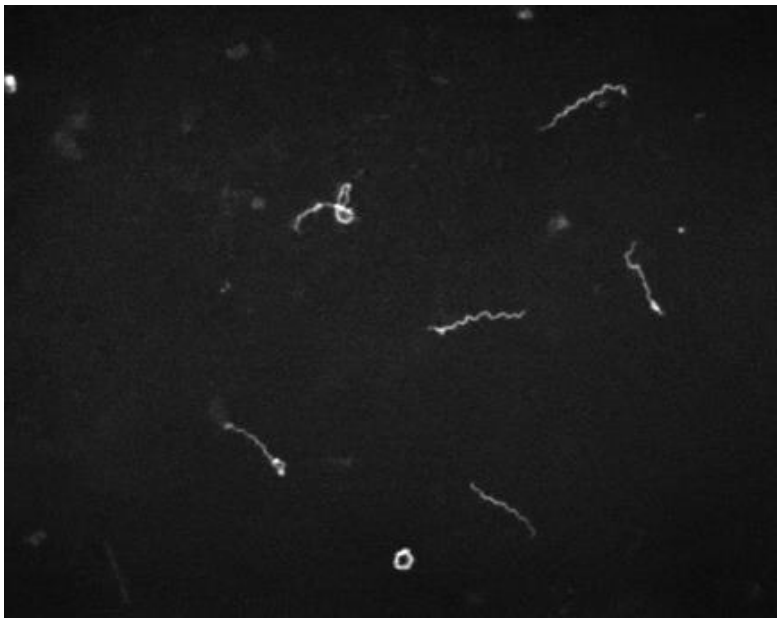


Figure 152: Treponema pallidum spirochetes on dark field microscopy.

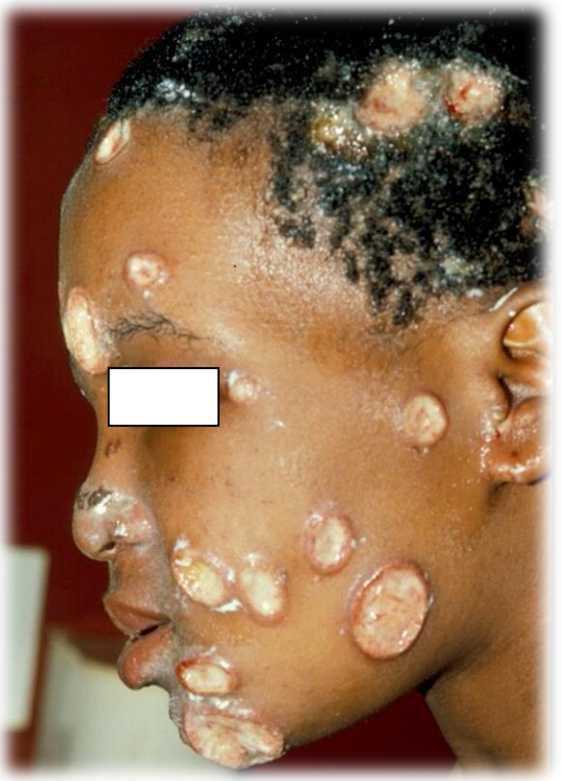


Figure 153: Extensive ulcerative nodulo-ulcerative syphilis in HIV.

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.
2. WHO 2005. Guidelines for the control of shigellosis, including epidemics due to *Shigella dysenteriae*. Available at: http://www.who.int/maternal_child_adolescent/documents/9241592330/en/.

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.

Further reading

1. Nathoo KJ, Chigonde S, Nhembe M, Ali MH, Mason PR. Community acquired bacteraemia in human immunodeficiency virus-infected children in Harare, Zimbabwe. Pediatr Infect Dis J 1996; 15:1092–1097.
2. Bronzan RN, Taylor TE, Mwenechanya J, et al. Bacteremia in Malawian children with severe malaria: prevalence, etiology, HIV coinfection, and outcome. J Infect Dis 2007; 195:895–904.
3. Hendriksen IC, Ferro J, Montoya P et al. Diagnosis, clinical presentation, and in-hospital mortality of severe malaria in HIV-co-infected children and adults in Mozambique. Clin Infect Dis. 2012;55 (8):1144-1153.
4. Guidelines for the treatment of malaria. 3rd ed. http://apps.who.int/iris/bitstream/10665/162441/1/9789241549127_eng.pdf?ua=1.
5. WHO. Management of severe malaria: a practical handbook– 3rd ed. http://apps.who.int/iris/bitstream/10665/79317/1/9789241548526_eng.pdf.

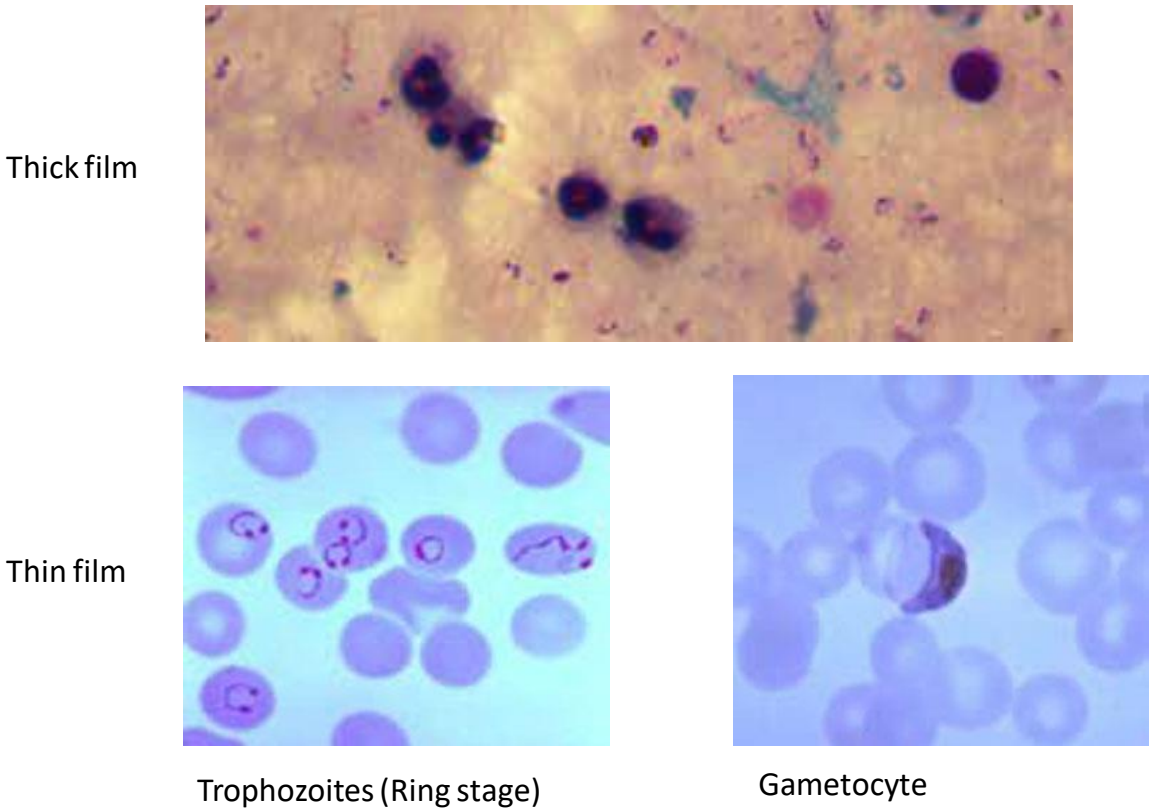


Figure 155: Appearance of P. falciparum parasite stages in Giemsa-stained thin and thick blood films.

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

1. Toro AA, Altemani AM, da Silva MT et al. Epstein-Barr virus (EBV) gene expression in interstitial pneumonitis in Brazilian human immunodeficiency virus-1-infected children: is EBV associated or not? Pediatr Dev Pathol. 2010;13 (3):184-91.
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

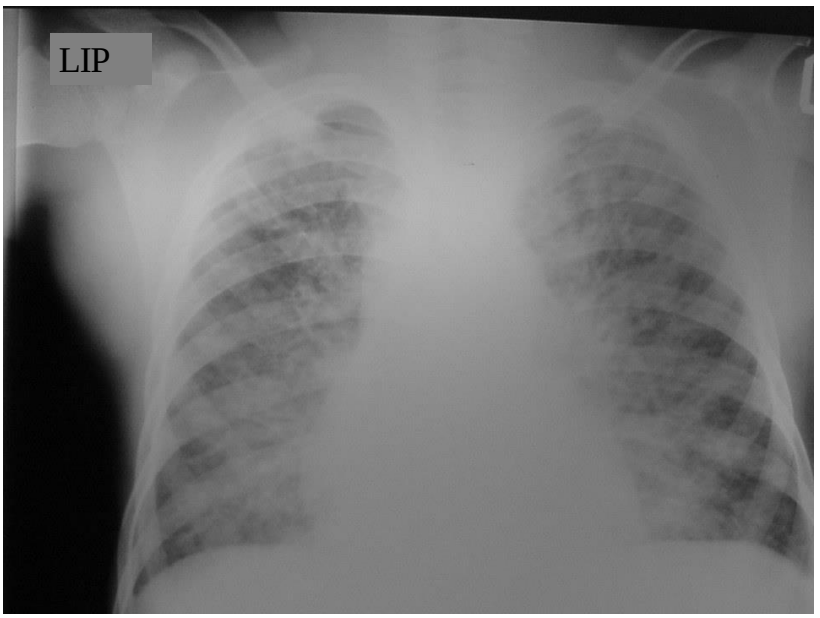


Figure 156: Bilateral reticulonodular interstitial pattern and adenopathy. LIP can be particularly difficult to differentiate from miliary TB

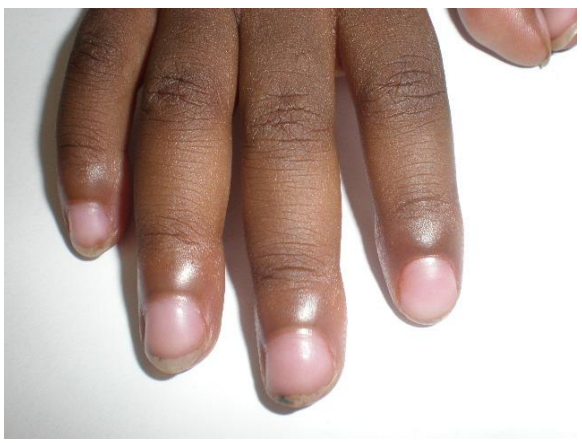


Figure 157: Digital clubbing in a child with LIP.

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.

Further reading

1. Sheikh S, Madiraju K, Steiner P et al. Bronchiectasis in pediatric AIDS. Chest 1997; 112: 1202–1207.
2. Berman DM, Mafut D, Djokic B et al. Risk factors for the development of bronchiectasis in HIV-infected children. Pediatr Pulmonol. 2007; 42 (10):871-5.
3. Masekela R, Anderson R, Moodley T et al. HIV-related bronchiectasis in children: an emerging spectre in high tuberculosis burden areas. Int J Tuberc Lung Dis. 2012; 16 (1):114-9.

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.
5. Anwar GA, Bourke SC, Afolabi G, et al. Effects of long-term low-dose azithromycin in patients with non-CF bronchiectasis. Respir Med. 2008;102 (10):1494-6.

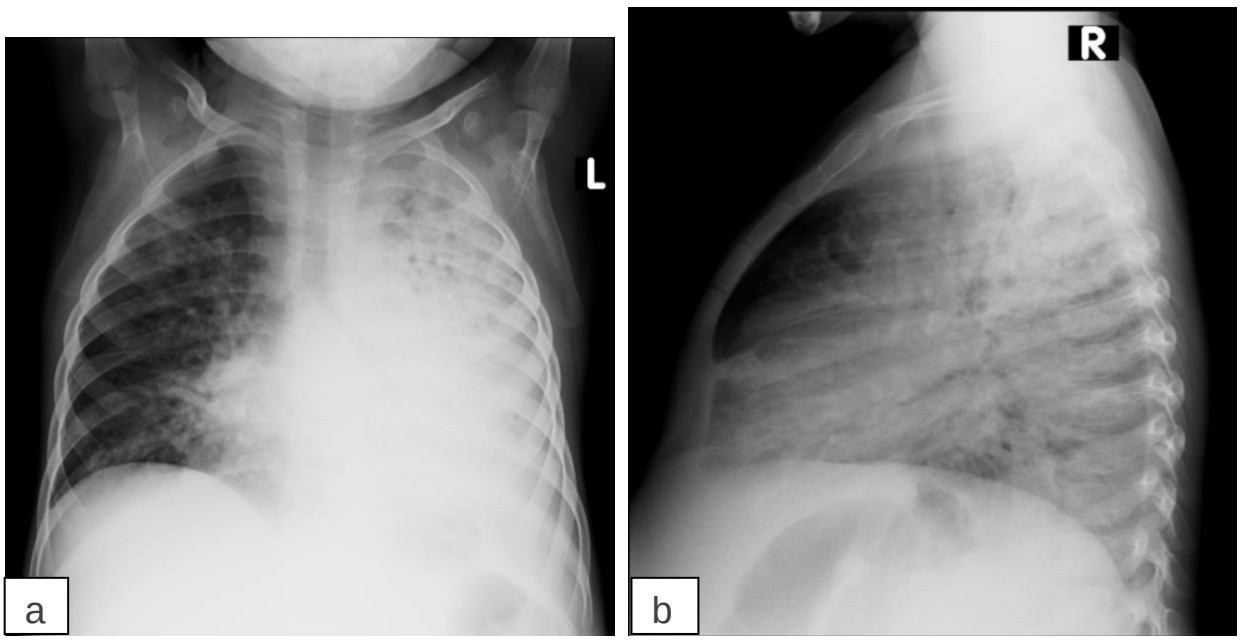


Figure 158: AP and lateral views of CXR showing widespread right-sided bronchiectasis: There is marked apical pleural thickening and underlying cystic lung disease indicative of a destroyed left lung.

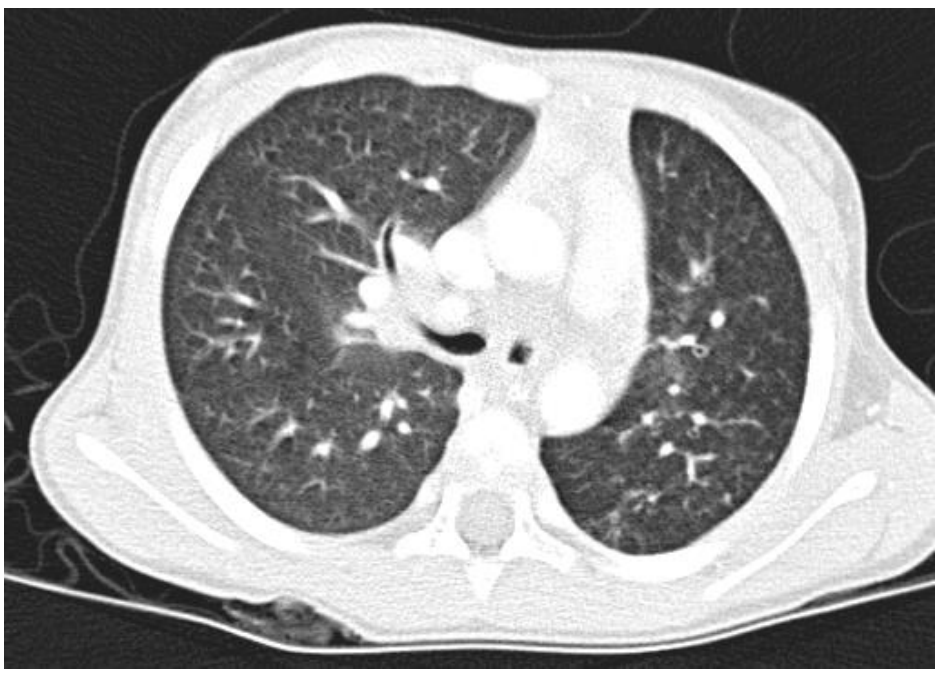


Figure 159: Bronchiectasis complication PTB. Left hemithorax is contracted from destruction and volume loss. Subcarinal lymphadenopathy is also evident.

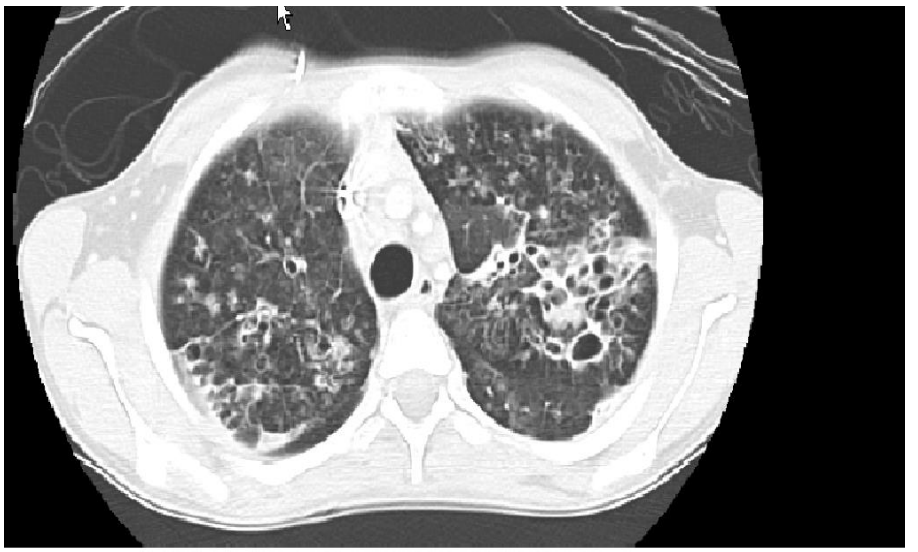


Figure 160: CT scan of a child with bronchiectasis

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

1. Cox CM, El-Mallawany NK, Kabue M et al. Clinical characteristics and outcomes of HIV-infected children diagnosed with Kaposi Sarcoma in Malawi and Botswana. Pediatr Blood Cancer 2013; 60 (8):1274-80. doi: 10.1002/pbc.24516.
2. Saka B, Mouhari-Toure A, Wateba IM et al. AIDS related Kaposi sarcoma: 103 cases in dermatology in Lomé (Togo). Med Sante Trop. 2013; 23(1):109-11. doi: 10.1684/mst.2013.0145.
3. Oladokun RE, Kolude B, Ogun GO et al. Kaposi sarcoma in HIV positive Nigerian Children: A case series. World J AIDS 2011; 1(3), 63-69.
4. Yanik EL, Tamburro K, Eron JJ et al. Recent cancer incidence trends in an observational clinical cohort of HIV-infected patients in the US, 2000 to 2011. Infect Agent Cancer 2013; 8(1):18.
5. Chagaluka G, Stanley C, Banda K et al. Kaposi's sarcoma in children: an open randomised trial of vincristine, oral etoposide and a combination of vincristine and bleomycin. Eur J Cancer. 2014; 50(8):1472-81. doi: 10.1016/j.ejca.2014.02.019.

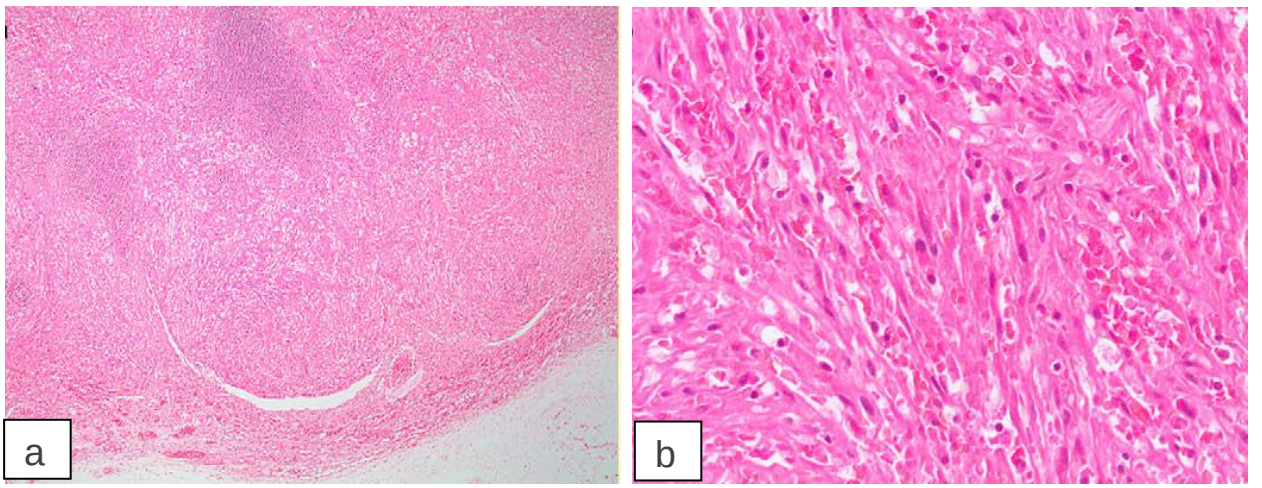


Figure 161a and b: (a) almost complete replacement of the nodal tissue by (b) a proliferation of spindle cells with slit-like vascular spaces. (Courtesy: Dr. Komala Pillay. Paediatric pathologist, Red Cross Children's Hospital, Cape Town).

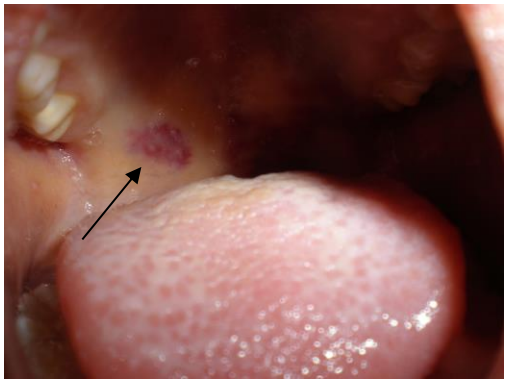


Figure 162: Kaposi sarcoma lesion (black arrow).

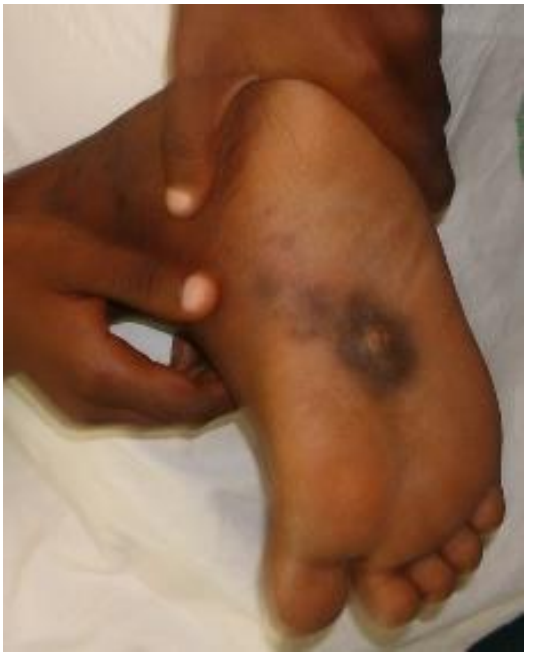


Figure 163: Kaposi sarcoma on the sole of the right foot.

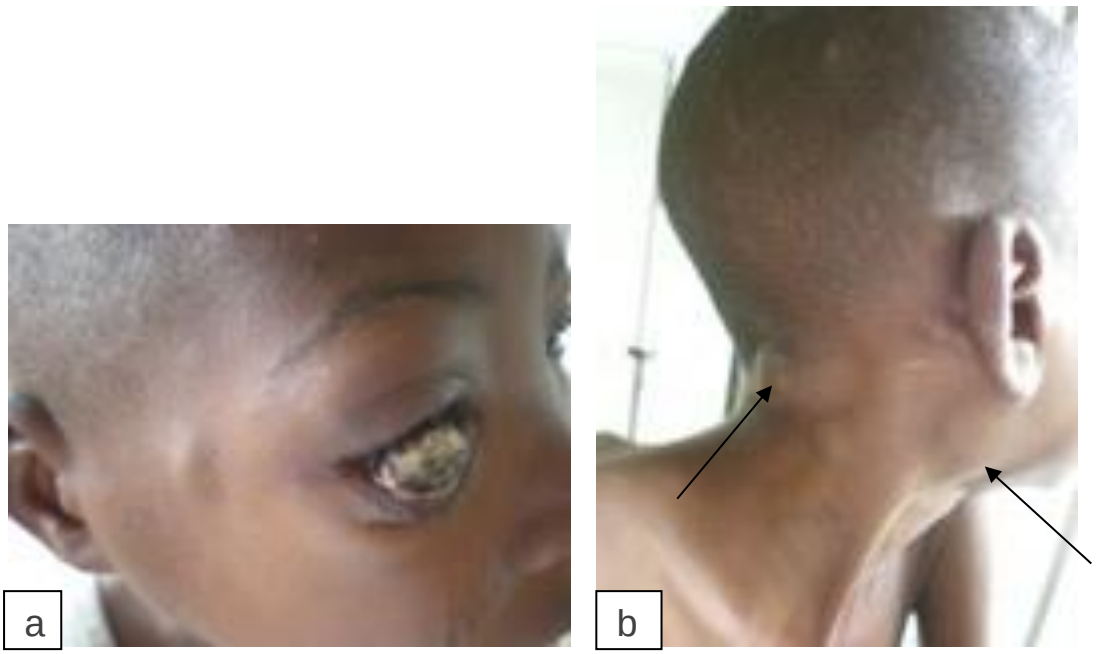
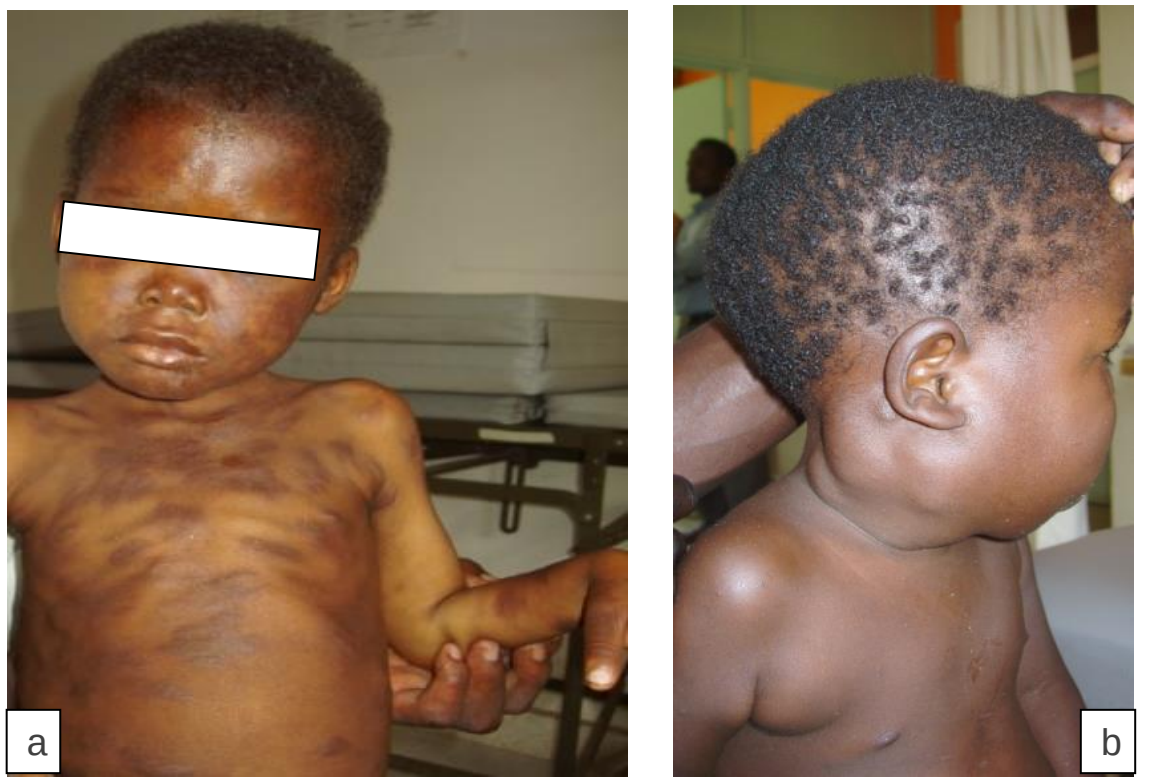


Figure 164a and b: Fungating eye tumour and lymph node in an 8 year old child with late diagnosis of HIV. Histology confirmed the lesion to be Kaposi sarcoma.



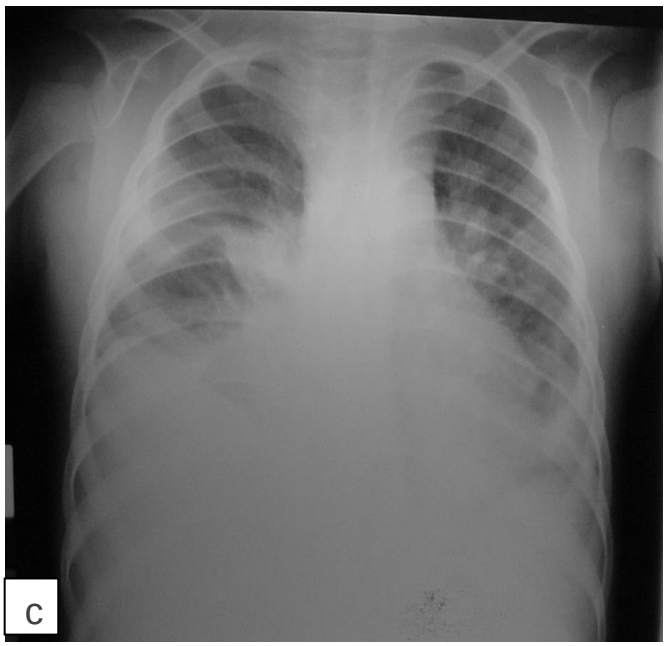


Figure 165a, b and c: Kaposi sarcoma involving the skin, lymph nodes and lungs (Courtesy of Dr George Chagaluka, Queen Elizabeth Central Hospital, Malawi).

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.

Further reading

1. Sungari P, Santilli V, Cotugno N et al. Raising awareness of non-Hodgkin lymphoma in HIV-infected adolescents: report of 2 cases in the HAART era. J Pediatr Hematol Oncol. 2013 Apr;35 (3):e134-7. doi: 10.1097/MPH.0b013e318282cef5.
2. Shiels MS, Engels EA, Linet MS, Clarke CA, Li J, Hall HI, Hartge P, Morton LM. The Epidemic of Non-Hodgkin Lymphoma in the United States: Disentangling the Effect of HIV, 1992-2009. Cancer Epidemiol Biomarkers Prev. 2013; 22(6):1069-78.
3. Carreira H, Lorenzoni C, Carrilho C et al. Spectrum of pediatric cancers in Mozambique: an analysis of hospital and population-based data. Pediatr Hematol Oncol. 2014; 31(6):498-508.
4. Davidson A, Wainwright RD, Stones DK et al. Malignancies in South African children with HIV. J Pediatr Hematol Oncol. 2014; 36 (2):111-7.

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

1. Smith K, Kuhn L, Coovadia A et al. Immune reconstitution inflammatory syndrome among HIV-infected South African infants initiating antiretroviral therapy. AIDS. 2009; 23 (9):1097-107.
2. Gkentzi D, Tebruegge M, Tudor-Williams G et al. Incidence, spectrum and outcome of immune reconstitution syndrome in HIV-infected children after initiation of antiretroviral therapy. Pediatr Infect Dis J. 2014; 33(9):953-8.
3. Link-Gelles R, Moultrie H, Sawry S et al. Tuberculosis Immune Reconstitution Inflammatory Syndrome in children initiating Antiretroviral Therapy for HIV infection: A systematic literature review. Pediatr Infect Dis J. 2014; 33(5):499-503.

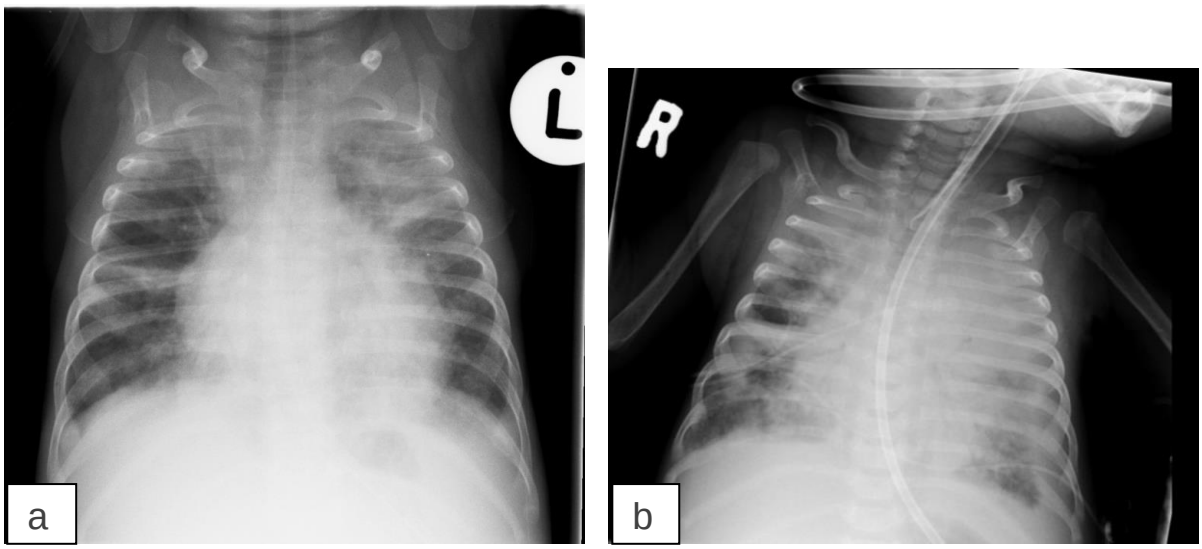


Figure 166a and b: (a) CXR taken pre-ART in a 4 month old child newly diagnosed with HIV infection. Xray shows: Multifocal airspace disease involving both upper lobes, right middle lobe, left lingular and left lower lobe. (b) CXR, 5 weeks post-ART initiation in the same child as above. He had been readmitted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

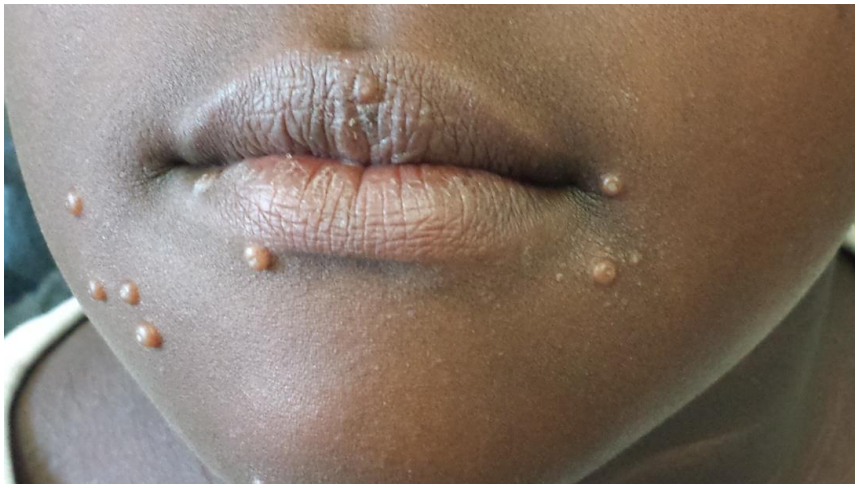


Figure 167: Molluscum contagiosum following antiretroviral therapy.

Appendix I

Who Clinical Staging of HIV for Infants and Children with Established HIV Infection

Clinical stage 1

Asymptomatic

Persistent generalized lymphadenopathy

Clinical stage 2

Unexplained persistent hepatosplenomegaly

Papular pruritic eruptions

Extensive wart virus infection

Extensive molluscum contagiosum

Recurrent oral ulcerations

Unexplained persistent parotid enlargement

Lineal gingival erythema

Herpes zoster

Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis)

Fungal nail infections

Clinical stage 3

Unexplained moderate malnutrition not adequately responding to standard therapy

Unexplained persistent diarrhoea (14 days or more)

Unexplained persistent fever (above 37.5 ºC, intermittent or constant, for longer than one month)

Persistent oral candidiasis (after first 6 weeks of life)

Oral hairy leukoplakia

Acute necrotizing ulcerative gingivitis/periodontitis

Lymph node TB

Pulmonary TB

Severe recurrent bacterial pneumonia

Symptomatic lymphoid interstitial pneumonitis

Chronic HIV-associated lung disease including bronchiectasis

Unexplained anaemia (<8.0 g/dl), neutropenia (<0.5 x $10^9/L^3$) or chronic thrombocytopenia (<50 x $10^9/ L^3$)

Clinical stage 4

Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy

Pneumocystis pneumonia

Recurrent severe bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)

Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration, or visceral at any site)

Extrapulmonary TB

Kaposi sarcoma

Oesophageal candidiasis (or Candida of trachea, bronchi or lungs)

Central nervous system toxoplasmosis (after the neonatal period)

HIV encephalopathy

Cytomegalovirus (CMV) infection; retinitis or CMV infection affecting another organ, with onset at age over 1 month

Extrapulmonary cryptococcosis (including meningitis)

Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis)

Chronic cryptosporidiosis (with diarrhoea)

Chronic isosporiasis

Disseminated non-tuberculous mycobacteria infection

Cerebral or B cell non-Hodgkin lymphoma

Progressive multifocal leukoencephalopathy

HIV-associated cardiomyopathy or nephropathy

(i) Unexplained refers to where the condition is not explained by other causes.

(ii) Some additional specific conditions can be included in regional classifications (e.g. penicilliosis in Asia, HIV associated rectovaginal fistula in Africa).

Source: World Health Organisation. WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. 2007. Http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf?ua=1.