

Kingdom of Cambodia
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Ministry of Health

**National Guidelines
on Management of Common and Opportunistic Infections in
HIV-infected Infants, Children and Adolescents
in Cambodia**

**4th Edition
June 2016**



National Center for HIV/AIDS, Dermatology and STD

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PREFACE

These guidelines are an important part of the National Center for HIV/AIDS, Dermatology and Sexually Transmitted Diseases (NCHADS) strategy to increase the quality of Pediatric HIV care in Cambodia. NCHADS Strategic Plan for HIV/AIDS and Sexually Transmitted Infection (STI) Prevention and Care identifies the continuous development and revision of policies and guidelines as a key strategy for achieving the objective of “improving and maintaining the quality and accessibility of care for PLHIV through extension of health facility based care services nationwide.”

This document represents the 2nd Edition of a comprehensive guideline for the prevention and treatment of HIV-related illnesses in both HIV-exposed and HIV-infected children in Cambodia. It is the result of significant contribution over a 2 year period from multiple experts both locally and internationally, and incorporates the latest knowledge in Pediatric HIV/AIDS care both regionally and globally.

During a series of technical working group meetings, staff from NCHADS, the National Pediatric Hospital, University of Health Science, Angkor Hospital for Children, UN agencies, and other NGO partners reviewed primary literature and international guidelines. Their comments, as well as clinical experience from pediatric AIDS care sites in Cambodia and elsewhere in the region, were essential to the creation of a unique document that will be useful in the Cambodian setting.

The Ministry of Health Cambodia has officially approved the National Guidelines for Management of Common and Opportunistic Infections in HIV-infected Infants, Children and Adolescents in Cambodia, and encourages pediatricians to reference the guidelines when providing HIV/AIDS care to HIV-infected infants, children and adolescents in Cambodia.

Phnom Penh, 06 August, 2016

Minister for Health *Eng Huot*



Prof. ENG HUOT
SECRETARY OF STATE

ACKNOWLEDGMENTS

The National Center for HIV/AIDS, Dermatology, and STI (NCHADS) would like to acknowledge the dedication of the members of the Pediatric AIDS Care Technical Working Group (TWG) in the revision of the 2nd Edition of the National Guidelines for Management of Common and Opportunistic Infections in HIV-infected Infants, Children and Adolescents in Cambodia. Throughout the process, they contributed high quality suggestions, enthusiasm, and hard work.

The finalization of these guidelines represents a great achievement that incorporates the latest advances in pediatric HIV/AIDS care and provides a regionally-focused, relevant guideline for use by pediatricians providing care in the field. Wherever possible, clear, feasible, and specific recommendations were agreed upon by TWG members in order to provide guidance to clinicians at a variety of sites and settings across Cambodia.

I would like to take this special occasion to thank the staff of the National Center for HIV/AIDS, Dermatology and STD (Dr. Seng Sopheap, Dr. Samreth Sovannarith, and Dr. Ngauv Bora) for coordinating the revision of these guidelines. I also want to express my gratitude to the pediatricians from the National Pediatric Hospital (Dr. Huot Chanthean and Dr. Sam Sophan), the University of Health Science (Prof. Ung Vibol), Angkor Hospital for Children (Dr. Chhraing Sengtray), Battambang Referral Hospital (Dr. Chea Peuv), FHI360 (Dr. Laurent Ferradini and Dr. Chel Sarim), Clinton Health Access Initiative (Ms. Emily Welle, Ms. Kiira Gustafson, and Dr. Herb Harwell), and UNICEF (Ms. Chin Sedtha) and Dr. Tammy Meyers, who have actively participated in revising these guidelines. Lastly, I would like to thank all partners, civil societies and PLHIV networks who have provided care, treatment and support to HIV-infected infants, children and adolescents in Cambodia.

PhnomPenh, 05 June, 2016

**Director of the National Center for
HIV/AIDS, Dermatology and STD**



Dr. Ly Penh Sun

ABBREVIATIONS AND ACRONYMS

AFB	Acid fast bacilli
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
ART	Antiretroviral therapy
ARV	Antiretroviral drug (s)
ASD	Atrial septal defect
AUC	Area under curve
AZT	Zidovudine
BCG	Bacille Calmette Guerin
BID	Twice daily
BMI	Body mass index
CBC	Complete Blood Count
CD4	CD4+ T-lymphocyte
CDC	Centers for Disease Control and Prevention
CENAT	National Centre for Tuberculosis and Leprosy Control
CMV	Cytomegalovirus
CNS	Central Nervous System
CPN+	People living with HIV networks
CrCl	Creatinine clearance
CSF	Cerebral Spinal Fluid
CT	Computed tomography
CTX	Cotrimoxazole
CXR	Chest x-ray
DIC	Disseminated intravascular coagulation
DNA	Deoxyribonucleic acid
DOT	Directly observed therapy
DST	Drug Susceptibility Testing
E	Ethambutol
EBV	Epstein Barr Virus
ECG	Electrocardiogram
EFV	Efavirenz
EPTB	Extra-pulmonary tuberculosis
FHI	Family Health International
GI	Gastrointestinal
H	Isoniazid
HAART	Highly Active Antiretroviral therapy
HIV	Human Immunodeficiency Virus
HSV	Herpes Simplex Virus
IMCI	Integrated management of childhood illness
INH	Isoniazid
IPT	Isoniazid preventive therapy
ITP	Immune thrombocytopenia
IV	Intravenous
IRIS	Immune reconstitution inflammatory syndrome
KBH	Kantha Bopha Hospital
KHANA	Khmer HIV/AIDS NGO Association
KS	Kaposi's Sarcoma
KSFH	Khmer Soviet Friendship Hospital

LDH	Lactate dehydrogenase
LFT	Liver function test
LGE	Lineal gingival erythema
LIP	Lymphoid interstitial pneumonitis
LN	Lymph node
LPV	Lopinavir
LPV/r	Lopinavir/ritonavir
Lym	Lymphocyte
MAC	<i>Mycobacterium avium</i> complex
MDR-TB	Multi drug resistant tuberculosis
MRI	Magnetic resonance imaging
MTB	<i>Mycobacterium tuberculosis</i>
NCHADS	National center for HIV/AIDS dermatology and STDs
NGT	Nasogastric Tube
NHL	Non-Hodgkin's lymphoma
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NPH	National Pediatric Hospital
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
OHL	Oral hairy leukoplakia
OI	Opportunistic infection
ORS	Oral rehydration salts
Ofx	Ofloxacin
PAS	P-aminosalicylic acid
PCP	<i>Pneumocystis jiroveci</i> pneumonia
PCNSL	Primary central nervous system lymphoma
PCR	Polymerase chain reaction
PGL	Persistent generalized lymphadenopathy
PPE	Pruritic papular eruption
PI	Protease inhibitor
PLHIV	People living with HIV
PMN	Polymorphonuclear leukocyte
PO	Per os (by mouth)
PPD	Purified protein derivative
PTB	Pulmonary tuberculosis
PTT	Partial thromboplastin time
Qd	One time daily
R	Rifampicin
RBC	Red blood cell
RNA	Ribonucleic acid
RTV	Ritonavir
SJS	Stevens Johnson syndrome
SMX	Sulfamethoxazole
STI	Sexually transmitted infection
TB	Tuberculosis
TID	3 times daily
TDF	Tenofovir disoproxil fumarate
TEN	Toxic epidermal necrolysis
TID	Three time daily
TMP	Trimethoprim
TST	Tuberculin skin test

TTP	Thrombotic thrombocytopenic purpura
UNICEF	United Nations Children's Fund
US	Ultrasound
WBC	White blood cell
WHO	World Health Organization
XDR	Extensively drug-resistant
Z	Pyrazinamide

1. INTRODUCTION

Increasingly in Cambodia, children are diagnosed with HIV and initiated on antiretroviral therapy (ART) early. They are therefore less likely to develop HIV-related morbidity, including common diseases and opportunistic infections. Nevertheless, some children may be detected late, and clinicians need to be aware of conditions that may occur in children with immunosuppression, so that these children can receive appropriate management.

Pathophysiology of HIV, transmission from mother-to-child, diagnosis and treatment of HIV in children are described in *Guidelines for Diagnosis and Antiretroviral Treatment of HIV Infection in Infants, Children and Adolescents in Cambodia*. Clinical staging of disease and especially immunological staging are no longer a priority in the decision about when to initiate ART. Nevertheless, clinical presentation may indicate whether the child has advanced disease, and the WHO staging can be used to determine this (Annex A). Following Cambodia's new ART Guidelines, children <5 years of age should be initiated on ART regardless of CD4 or clinical presentation. All children <15 years-old, regardless of CD4 count or clinical stage, should be initiated on ART. Following a decision to start ART, this should begin as soon as possible, preferably within 2 weeks.

The *Guidelines for the Management of Common and Opportunistic Infections among HIV-Infected Infants, Children and Adolescents in Cambodia* is a second edition and an important document to ensure the consistent and high quality treatment and care of HIV-infected children at all pediatric AIDS care sites in Cambodia. The guideline includes recommendations for the prevention and treatment of common HIV-associated diseases and was developed by the authors based on day-to-day experience caring for children in Cambodia, supported by the latest information from international guidelines and primary literature.

This guideline should be used as an important tool to assist pediatricians in providing high quality and standardized treatment to HIV-infected children aged less than 15 years in Cambodia.

Changes to the Guidelines For Management Of Common And Opportunistic Infections

Management guidelines for common and opportunistic infections in children with HIV have not changed much since the last version was published. These guidelines should be used as a reference for children presenting with common infections associated with HIV infection as well as opportunistic and other rare diseases manifesting in children with severe HIV infection. Information has been rearranged including:

- The section on pathogenesis of HIV Infection, Transmission, and Exposed-Infant Care has been moved to the guidelines for diagnosis and antiretroviral therapy.
- The sections on nutrition and HIV infected children and tuberculosis in HIV infected children appear in both documents because of the importance of these conditions associated with diagnosis and management of HIV.
- There is less emphasis on clinical and immunological staging because of the shift to treating children earlier regardless of clinical presentation and CD4 count.
- Guidelines for TB management and INH prophylaxis have been updated in accordance with new guidance released by WHO

- There is no longer a recommendation for prophylaxis for cryptococcal disease, and the recommendations for management of cryptococcal disease has been updated according to guidance released by WHO

2. COMMON NON-OPPORTUNISTIC ILLNESSES IN HIV-INFECTED CHILDREN

Key points

- Common childhood infections such as diarrhea, pneumonia, and upper respiratory tract infection are more frequent and more severe in HIV-infected children.
- Infection with pneumococcus, *haemophilus*, and *salmonella* species are common in HIV-infected children and may occur even in those children with a high CD4 count and on ART.
- Immunization and cotrimoxazole prophylaxis significantly decrease the frequency of invasive bacterial infections in HIV-infected children.
- Antiretroviral therapy is the most effective therapy for preventing HIV-related illness.
- Persistent fever in children with HIV infection requires a thorough evaluation.

Introduction

HIV-infected children frequently access the healthcare system with acute complaints. The most frequent presenting illnesses in these children are also common in HIV-uninfected children, and include acute gastroenteritis, upper and lower respiratory tract infections, and dermatologic complaints. The initial evaluation is identical to that of any child, and requires rapid assessment of the child's illness severity for appropriate triage and management.

Assessment for general danger signs should include asking the child's caregiver:

1. Is the child unable to drink or breastfeed?
2. Does the child vomit every meal?
3. Has the child had convulsions?
4. Has the child had urine output decreased?
5. Has the child been less playful or sleeping more than usual?
6. Has the child been less interactive with the caregiver?
7. Has the child lost weight?

Any of the above signs/symptoms may indicate life-threatening illness, and the child should be referred for inpatient evaluation and management.

Once danger signs are evaluated, critical information includes the child's prior history of any OIs or TB, assessment of the current ART regimen and adherence, and review of the most recent CD4 value. Illnesses discussed in this chapter are common even in children receiving ART with high CD4 cell count and percentage.

Fever

Introduction

Fever is a common parental concern. In most cases a thorough history and physical examination will reveal the likely source. Fever is defined as body temperature:

- >37.5°C axillary
- >38°C oral
- >38.5°C rectal

Etiology

Fever may be caused by:

- Infection: bacterial, viral, fungal, or protozoal
- Malignancy: Non-Hodgkin's lymphoma, CNS lymphoma
- Medication: CTX, ARVs
- HIV itself

In children with HIV who are on ART with a good CD4 response, the most common causes of fever are similar to children without HIV, and include upper respiratory tract infection (URI), otitis media, pharyngitis, and pneumonia. Drug-related fever must also be considered.

Children with low CD4 cell counts are at risk for opportunistic infections and AIDS defining illnesses as discussed in the following sections of this guideline. Knowledge of a child's treatment history and CD4 count is essential to developing an appropriate differential diagnosis in patients with HIV.

Assessment

- A complete history and physical examination, with attention to the oral cavity, respiratory system, abdomen, skin, lymph nodes, and neurologic system.
- Children less than 1 month of age with fever greater than 38.0 °C and no identifiable source should receive the following:
 - Complete blood count (CBC)
 - Blood and urine cultures
 - Chest radiograph
 - Lumbar puncture

Management

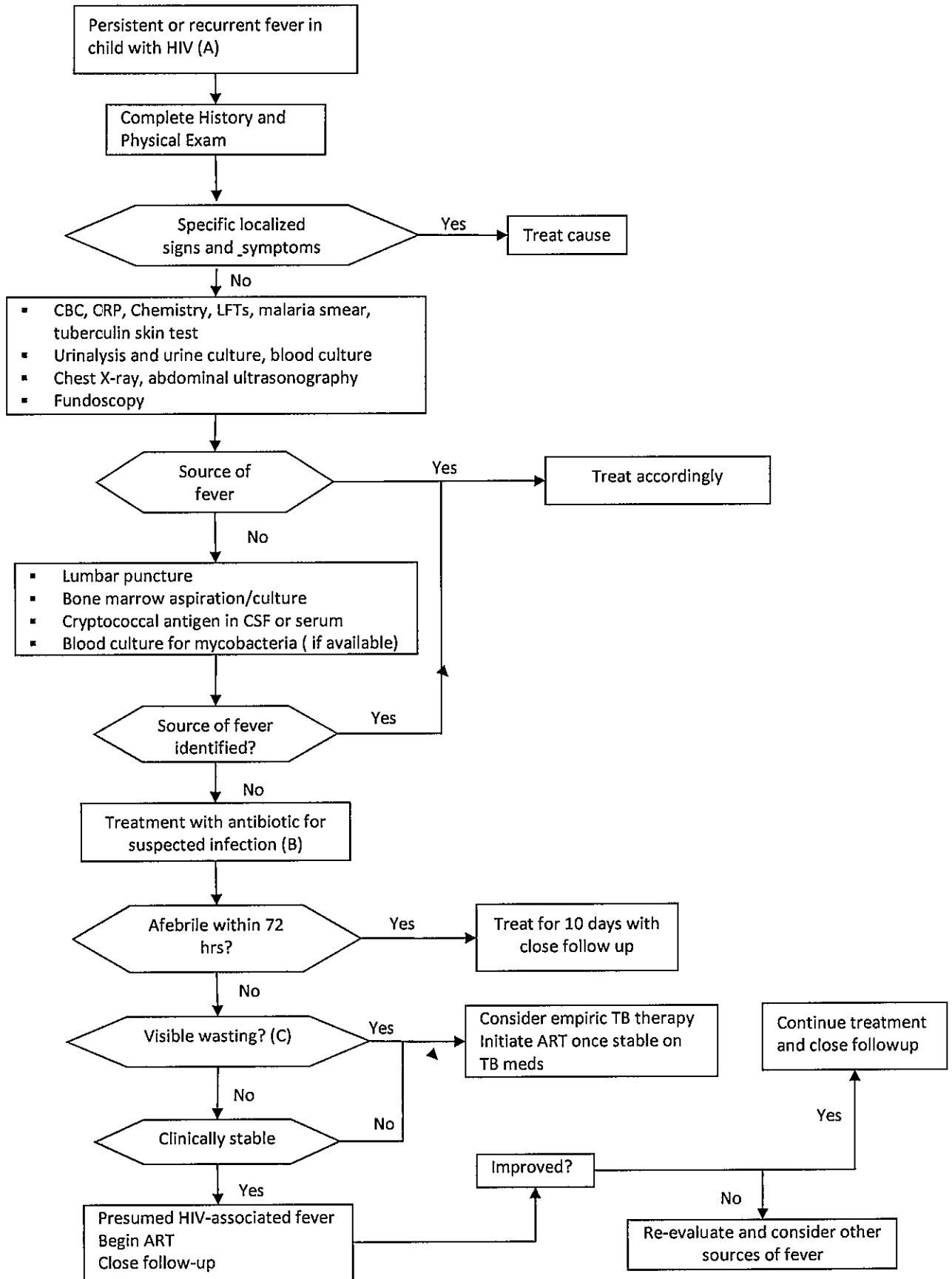
Treatment with antibiotics is indicated when:

- A source for the fever (pneumonia, otitis, urinary tract infection) is found
- A child shows signs of sepsis, which may include:
 - fast and weak pulse, *or*
 - delayed capillary refill, *or*
 - lethargy not responsive to initial fluid bolus
- Severe neutropenia (absolute neutrophil count <500) is present
- <3 months of age and febrile without a source

Persistent Fever without a source

Persistent fever without a source represents a unique challenge to clinicians, and may indicate undiagnosed infection, drug-related fever, or fever related to malignancy or HIV. Tuberculosis must be strongly considered in HIV-infected children with fever of unknown origin (≥14 days of unexplained fever). For persistent fever of ≥14 days without a source, please see algorithm below.

Figure 1. Algorithm for investigation and management of persistent fever in children with HIV infection



Annotations:

- A. Persistent fever: daily fever for ≥ 14 days
Recurrent fever: fever on the majority of days for ≥ 14 days
- B. In case of persistent high fever and bacterial infection cannot be ruled out due to inadequate diagnostic capabilities, empiric treatment with ceftriaxone 50 mg/kg daily may be considered. If the fever subsides within 72 hours but a source is not identified, 10 days of treatment should be completed.
- C. Children with HIV, persistent fever without a source, and wasting should strongly be suspected of TB and empiric therapy for TB considered.

Upper Respiratory Tract Infection**Acute Otitis Media**

- Acute otitis media is common in children with HIV infection, and refers to ear infections that have lasted for less than 14 days.
- There is pain, fever and occasionally purulent drainage.
- On physical examination, red, bulging, dull, immobile eardrum and/or pus in the ear canal.

Treatment

- Treat as an outpatient with amoxicillin for 5 days.
- Follow up after 5 days. If pain or discharge persists, treat for a further 5 days with the same antibiotic; if using amoxicillin, increase dose to 80-90 mg/kg/day divided twice daily to treat penicillin-resistant pneumococcus.

Chronic Ear Infection

- A child who has had ear drainage for longer than two weeks is considered to have chronic otitis media.
- The ear should be dried by a method known as wicking.
 - To dry the ear, roll a clean, soft, absorbent cotton cloth into a wick.
 - Place the wick in the child's ear, and remove once wet.
 - Repeat until the ear is dry.
 - Wicking should be done three times per day.
- Antibiotics are usually not effective in treating chronic ear infections, which are caused by different bacteria than acute ear infections.
- Many children with chronic otitis media DO NOT have fever. If a continued high fever is present, consider fungal or mycobacterial infection and send ear discharge for acid fast bacilli (AFB) testing and fungal stain and/or culture where available.

Mastoiditis

- Mastoiditis is a complication of otitis media.
- A child with mastoiditis will have a tender, swollen, erythematous, warm area behind the ear.
- Mastoiditis requires treatment with intravenous antibiotics and occasionally surgical drainage.
- Children with mastoiditis are at risk of developing severe bacterial meningitis and should be treated in the hospital.
- The preferred treatment is ceftriaxone 50 mg/kg IV once daily; penicillin and gentamicin may be used when ceftriaxone is not available.

Pharyngitis

- Most cases of sore throat are caused by viruses, can be treated symptomatically, and resolve in a few days.
- Antibiotics are necessary if the sore throat is caused by a throat abscess or streptococcal infection.
- A child with a throat abscess will not be able to swallow secretions, fluids, or food and should be referred to a hospital for drainage of the abscess.
- A child with a streptococcal throat infection will have tender, enlarged lymph nodes in the front of the neck and white exudate in the posterior oropharynx and/or on the tonsils.
 - All children with these symptoms require treatment for group A streptococcal infection to minimize the risk of acute rheumatic fever.
 - If the child has a streptococcal infection, treat with a single injection of weight-based benzathine penicillin or oral amoxicillin or penicillin.

Parotid Enlargement

- One of the most specific signs of HIV infection in children.
- Usually non-tender.
- Commonly found in older children, often in association with lymphoid interstitial pneumonitis (LIP).
- May be disfiguring and lead children to be teased and/or emotionally distressed.
- Occasionally can become tender from bacterial super-infection, typically staphylococcal.
- When parotids are tender and erythematous, prescribe cloxacillin and analgesics.
- Rarely, parotid abscesses may require drainage.
- Surgery is not required and parotid enlargement generally disappears on ART.

Persistent Generalized Lymphadenopathy (PGL)

- Often associated with parotid enlargement and/or hepatosplenomegaly.
- PGL is a clinical stage 1 disease and requires no treatment.
- Children with PGL should have no other evidence of systemic infection.
- Children with lymphadenopathy and fever, malnutrition, or other concerning signs of illness should be investigated for TB and other opportunistic infections or malignancies. Fine needle aspiration or lymph node biopsy is indicated particularly for isolated enlargement of a lymphnode. PGL is a diagnosis of exclusion.

HIV-associated nephropathy (HIVAN)

- Focal segmental glomerulosclerosis is the most common form of HIVAN.
- More common in Africa than Southeast Asia.
- Patients initially present with proteinuria and may develop nephrotic syndrome with edema and hypoalbuminemia.
- HIVAN can develop at various degrees of immunosuppression and is generally considered an indication for the initiation of ART.
- All children presenting with nephrotic syndrome should be considered for HIV testing.

3. ORAL MANIFESTATIONS IN HIV-INFECTED CHILDREN

Key points:

- Oral health care is an important part of HIV primary care
- All HIV-exposed and infected children should have an oral examination at every clinic visit
- Oral manifestations are common clinical findings in children with HIV infection
- Early diagnosis and management of oral manifestations is important to prevent complication and optimize nutritional status

Introduction

Oral and dental conditions are common in HIV-infected children, particularly those who are malnourished. Encouraging regular oral hygiene should be a part of routine counseling sessions. The most common oral condition in HIV-infected children is candidiasis (thrush), which is predictive of HIV infection when seen after the neonatal period. Other oral conditions can also cause difficulty with feeding and should be evaluated as outlined below. Aggressive treatment of HIV-related oral lesions can greatly improve feeding and nutritional status in HIV infected children.

Clinical manifestations

Oral candidiasis

- Oral candidiasis is frequently observed in one of the following four clinical forms:
 - erythematous (atrophic) candidiasis
 - multiple small or large patches, most often localized on the tongue and/or palate.
 - pseudomembranous candidiasis (oral thrush);
 - multiple superficial, creamy white plaques that can be easily wiped off revealing an erythematous base.
 - hyperplastic candidiasis
 - white, hyperplastic lesions that cannot be removed by scraping
 - angular cheilitis
 - erythematous fissures at the corners of the mouth, usually together with another form of oral candidiasis.
 - Superimposed vitamin deficiencies may also cause angular cheilitis.
- Oral candidiasis is often seen in conjunction with candidal diaper rash.
- Difficulty with feeding is common with oral thrush.
- When severe, esophageal candidiasis should be suspected, particularly if drooling or voice changes are present.

Oral hairy leukoplakia (OHL)

OHL presents as white, thick patches that do not wipe away and that may exhibit a “hair-like” appearance. It is usually asymptomatic but is a specific sign of HIV.

HIV-Associated Periodontal Disease

- *Lineal gingival erythema (LGE)* is characterized by the presence of a 2-3 mm red band along the marginal gingiva, associated with diffuse erythema on the attached gingiva and oral mucosa.
- *Necrotizing ulcerative gingivitis (NUG)* is more common in adults than in children. It is characterized by the presence of ulceration, sloughing, and necrosis of one or more interdental papillae, accompanied by pain, bleeding, and fetid halitosis.
- *Necrotizing ulcerative periodontitis (NUP)* is characterized by the extensive and rapid loss of soft tissue and teeth.
- *Necrotizing stomatitis* is thought to be a consequence of severe, untreated NUP. It is characterized by acute and painful ulceronecrotic lesions on the oral mucosa that expose underlying alveolar bone.

Herpes Simplex Virus (HSV) Infection

HSV infection appears as a crop of vesicles on the lips or palate. The vesicles rupture and form irregular painful ulcers. They may interfere with chewing and swallowing, resulting in decreased oral intake and dehydration.

Recurrent Aphthous Ulcers (RAUs)

- a. *Minor aphthous ulcers* are ulcers less than 5 mm in diameter covered by pseudomembrane and surrounded by an erythematous halo. They usually heal spontaneously without scarring.
- b. *Major aphthous ulcers* resemble minor aphthous ulcers, but they are fewer and larger in diameter (1-3 cm), are more painful, and may persist longer. Their presence interferes with chewing, swallowing, and speaking. Healing occurs over two to six weeks. Scarring is very common.
- c. *Herpetiform aphthous ulcers* occur as a crop of numerous small lesions (1-2 mm) disseminated on the soft palate, tonsils, tongue, and/or buccal mucosa.

Parotid Enlargement and Xerostomia

Parotid enlargement occurs as unilateral or bilateral swelling of the parotid glands. It is usually asymptomatic and may be accompanied by decreased salivary flow and dry mouth.

Human Papillomavirus (HPV) Infection

Oral warts may appear fungating, spiked, or raised with a flat surface and are not painful. The most common location is the labial and buccal mucosa. See Annex C. Occasionally, severe laryngeal disease is seen in neonates and felt to be related to inoculation of the upper respiratory tract by virus during vaginal delivery.

Treatment

Table 1. Treatment of oral lesions

Oral lesions	Treatment	Comments
Oral candidiasis	<p>Topical</p> <ul style="list-style-type: none"> • Nystatin suspension 200,000-400,000 units/day divided in 4-6 doses for 14 days. • Gentian violet 1% aqueous solution painted in the affected area q8h <p>Systemic</p> <ul style="list-style-type: none"> • Fluconazole 6 mg/kg on day 1 then 3 mg/kg daily x 7-14 days (oral) or 21 days (esophageal) <p>Prophylaxis</p> <ul style="list-style-type: none"> • Consider prophylaxis for severe/recurrent disease until established on ART • Nystatin 100,000-400,000 units PO q12h for long period • Fluconazole 3 mg/kg PO daily 	<ul style="list-style-type: none"> • Topical treatment preferred for mild oral thrush • Systemic therapy necessary for severe oral thrush interfering with feeds or for esophageal candidiasis • Amphotericin B may rarely be needed for azole-resistant infections.
Angular Cheilitis	<p>Topical</p> <ul style="list-style-type: none"> • Nystatin-triamcinolone ointment applied on the affected areas after meals and at bedtime, or • Miconazole 2% cream applied q12h on the affected areas, for 1-2 weeks • Multivitamin supplementation if evidence of malnutrition 	<ul style="list-style-type: none"> • Lesions tend to heal slowly because of the repeated opening of the mouth.
Herpes Simplex Virus (HSV) Infection	<p>Systemic</p> <ul style="list-style-type: none"> • Acyclovir 10 mg/kg PO q4h or q6h for 5-7 days • Acyclovir 10 mg/kg IV q8h for severe disease • CMV and histoplasmosis may mimic HSV in children with very low CD4; consider biopsy if lesions do not respond to IV acyclovir 	<ul style="list-style-type: none"> • Patients taking acyclovir should be instructed to drink plenty of fluids.
Lineal Gingival Erythema (LGE)	<p>Local</p> <ul style="list-style-type: none"> • Scaling and root planing • 0.12% Chlorhexidine gluconate (Periogard, Peridex) 0.5 oz q12h rinse, for 30 sec. and spit 	<ul style="list-style-type: none"> • Prophylaxis with regular brushing, flossing, and use of mouth rinses. • Treat concomitant oral thrush if present
Parotid Enlargement	<p>Systemic</p> <ul style="list-style-type: none"> • Non-steroidal anti- inflammatories • Analgesics • Antibiotics (for superinfection only, usually due to staphylococcus) 	<ul style="list-style-type: none"> • Surgical removal of the parotid gland should be avoided. • Symptoms may improve with provision of ART
Oral Hairy Leukoplakia (OHL)	<p>No treatment</p>	<ul style="list-style-type: none"> • OHL is rare in children. • Consider ART if severe symptoms

<p>Necrotizing Ulcerative Gingivitis (NUG), Necrotizing Ulcerative Periodontitis (NUP), Necrotizing Stomatitis (NS)</p>	<ul style="list-style-type: none"> • Local • Debridement of affected areas • Irrigation with povidon-iodine (10% Betadine) • 0.12% chlorhexidine gluconate (Peridex, Periogard) mouth rinse q12h • Systemic • Clindamycin 20–30 mg/kg PO q6h, for 7 days, or • Amoxicillin clavulanate (Augmentin) 40 mg/kg PO q8h, for 7 days, or • Metronidazole 15–35 mg/kg PO q8h, for 7–10 days 	<ul style="list-style-type: none"> • Prolonged use of chlorhexidine may cause staining of teeth, altered taste, and gum irritation. • Metronidazole may cause peripheral neuropathy when used for prolonged periods or with ddl, d4T
<p>Recurrent Aphthous Ulcers</p>	<ul style="list-style-type: none"> • Topical • Triamcinolone 0.1% paste applied in a thin layer q6h daily, or • Dexamethasone liquid (0.5 mg/5ml) rinse and spit • Systemic • Prednisone 2 mg/kg q6h, for 5–7 days 	<ul style="list-style-type: none"> • Major aphthous ulcers usually require systemic steroids. • Iron, vitamin B12, and folate deficiencies should be ruled out. • Dexamethasone liquid may be used for multiple ulcers or ulcers not accessible for topical application.
<p>Oral Warts</p>	<ul style="list-style-type: none"> • Topical • Podophyllin resin 25% applications q6h for long period • Cryotherapy with liquid nitrogen 	<ul style="list-style-type: none"> • Recurrence rate is high. • ART decreases recurrence.

4. DERMATOLOGIC MANIFESTATIONS IN HIV-INFECTED CHILDREN

Key points

- Skin lesions are often the first manifestation of HIV noted by patients and health professionals and occur frequently in children with HIV.
- Characteristic lesions can often provide evidence of underlying, systemic infection
- Prompt diagnosis and treatment of cutaneous manifestations can prevent complication and improve quality of life for HIV-infected persons.

Introduction

Skin disorders are common in children with HIV, and may be related to a primary dermatologic disorder, mild superficial infection, disordered inflammatory response to common antigens, or severe disseminated opportunistic infection. Table 2 lists common dermatologic manifestations in HIV-infected children.

Table 2. Causes of skin diseases in HIV

Category	Causes
Infections	<ul style="list-style-type: none"> • Varicella zoster • Herpes simplex virus • Superficial fungal infection (eg Tinea) • Disseminated fungal infection <ul style="list-style-type: none"> ○ Cryptococcosis ○ Penicilliosis ○ Histoplasmosis • Human papillomavirus • Impetigo • Mycobacterial infection • Secondary syphilis • Furunculosis • Folliculitis • Pyomyositis • Verucca planus
Neoplasia	<ul style="list-style-type: none"> • Kaposi's sarcoma • Lymphoma • Squamous and basal cell carcinoma • Sarcoma
Others	<ul style="list-style-type: none"> • Pruritic papular eruption • Seborrheic dermatitis • Drug eruptions • Vasculitis • Eczema • Psoriasis • Granuloma annulare • Thrombocytopenic purpura • Telangiectasia • Hyperpigmentation

Common cutaneous manifestations of HIV are summarized below.

Herpes simplex virus

- Stomatitis is the most common manifestation of HSV in children. See Annex B.
- Lesions are small, painful clusters of vesicles
- Diagnosis is made by clinical appearance but may be verified by viral culture where available
- Treatment of mucocutaneous HSV is with oral acyclovir 10-20 mg/kg/dose four times per day for 5-7 days
- If superinfection with staphylococcal or streptococcal species is suspected, give cloxacillin 25 mg/kg/dose q6 hours for 5-7 days

Chickenpox (primary Varicella Zoster Virus) and herpes zoster

Chickenpox

- Occurs frequently in children with HIV infection, can be severe.
- Complications include hemorrhagic skin lesions, hepatitis, pneumonia, encephalitis, bacterial superinfection, and occasionally death.
- HIV-infected children exposed to chickenpox should receive varicella zoster immune globulin (VZIG) 0.15 ml/kg within 72 hours of exposure, where available.
- Treat with acyclovir 20 mg/kg/dose (max 800mg) by mouth, administered four times per day for five days.
- Bacterial superinfection should be treated with cloxacillin 25 mg/kg/dose q6 hours for 5-7 days.

Herpes zoster (shingles)

- Painful, grouped, vesicular lesions that appear in a dermatomal pattern
- Does not cross the midline
- Complications include severe painful ulcerations, postherpetic neuralgia, and disseminated disease
- Treat with acyclovir 20 mg/kg/dose by mouth, administered four times per day for seven days.
- Treat severe disease or inability to take by mouth with acyclovir 10 mg/kg/dose intravenous (IV) every eight hours for seven days.
- Treat superinfection with cloxacillin as above.

Molluscum Contagiosum

- Commonly found in persons with advanced HIV infection and is due to a virus.
- Molluscum contagiosum lesions are pearly or flesh-colored, round papules 3-5 mm in size with a central dimple.
- In children who are ill appearing or with very low CD4 cell count, the differential diagnosis includes *cryptococcus*, *penicillium*, or *histoplasma*.
 - Serum cryptococcal antigen testing is recommended in children with possible molluscum and very low CD4 count
 - If negative, biopsy may be needed to rule-out invasive fungal infection
- Giant molluscum lesions often occur on the face when immunosuppression is severe, and can be disfiguring. See Annex B.
- Treatment includes topical therapy with phenol or liquid nitrogen cryotherapy.

- When severe or disfiguring, strongly consider initiation of ART which is the only therapy likely to prevent recurrence.

Bacterial Skin Infections

- May represent local invasion of organisms into the dermis or be manifestations of systemic infection
- Tend to be more frequent and more severe in HIV-infected children
- Children with an unusual frequency of severe skin infections should be tested for HIV.

Table 3 summarizes the bacterial causes of skin disorders seen in HIV infected children, including a brief description and suggested initial treatment.

Table 3 Causes and management of bacterial skin infections

Bacterial infection	skin	Causative organism	Description	Treatment
Folliculitis		<i>Staphylococcus aureus</i>	Inflammation, infection of the hair follicles	<ul style="list-style-type: none"> • Warm compress • Cleansing • Cloxacillin in severe cases
Cellulitis		<i>Streptococcus, Staphylococcus aureus, Haemophilus influenzae</i>	Inflammation of skin and subcutaneous tissues, characterized by edema, erythema, and pain	<ul style="list-style-type: none"> • Cloxacillin 100-200 mg/kg daily divided q6 hourly
Skin abscess		<i>Staphylococcus aureus, Haemophilus influenzae</i>	Localized collection of pus in a cavity formed by disintegration of tissue; may complicate untreated cellulitis	<ul style="list-style-type: none"> • Surgical drainage • Systemic antibiotics if cellulitis
Impetigo		<i>Staphylococcus aureus, Streptococcus</i>	Vesicles or bullae with characteristic honey-colored crusting	<ul style="list-style-type: none"> • Topical mupirocin • Cloxacillin for disseminated lesions
Furunculosis (boil)		<i>Staphylococcus aureus, Streptococcus</i>	Infection of the skin and subcutaneous tissues surrounding a hair follicle; larger than folliculitis	<ul style="list-style-type: none"> • Warm compress • Cleansing • Occasionally need drainage • Rarely requires systemic antibiotics
Paronychia		<i>Staphylococcus aureus</i>	Infection involving the folds of tissue surrounding the fingernail or toenail	<ul style="list-style-type: none"> • Surgical drainage • Cloxacillin for 5-7 days
Bacillary angiomatosis		<i>Bartonella henslae</i>	Disseminated vascular lesions that may mimic Kaposi's sarcoma	<ul style="list-style-type: none"> • Azithromycin or erythromycin • Consult expert
Staphylococcal Scalded Skin Syndrome		<i>Staphylococcus aureus</i>	Diffuse bullous lesions starting on face, most common in infants; may mimic Stevens Johnson Syndrome but without precipitating exposure and NO mucosal involvement	<ul style="list-style-type: none"> • Cloxacillin 200 mg/kg/day IV divided q6 hours • Surgical consultation • Aggressive wound care and attention to hydration status

Fungal skin infections

Fungal skin infections among people with HIV/AIDS are varied, and include both local skin infections or lesions caused by severe disseminated infection. Most common are candidiasis and dermatophytosis.

Cutaneous candidiasis:

- Found most commonly in the diaper area and skin folds. It appears as a vivid, erythematous rash with well-demarcated borders and satellite lesions.
- Treatment:
 - Topical 1% aqueous solution of gentian violet, nystatin ointment, or miconazole cream applied to lesions three times per day until 48 hours after the rash resolves.
 - If there is no response to topical treatment, systemic therapy with fluconazole 3 mg/kg/day may be rarely needed.

Dermatophytosis:

- Usually occurs as tinea corporis (ringworm) or tinea capitis. It is characterized by flat, scaling lesions with raised borders. The lesions may be very extensive and refractory to treatment in HIV-infected persons.
- Treatment:
 - Apply Whitfield's ointment (benzoic acid with salicylic acid) 2 times daily for 2 to 5 weeks on body lesions; if not successful switch to 2% miconazole cream
 - Extensive disease and tinea capitis should be treated with systemic griseofulvin, 10-15 mg/kg daily.
 - Duration of therapy depends on the location of infection
 - Tinea corporis: two to four weeks
 - Tinea capitis: four to six weeks

Scabies

- Highly contagious mite infection of the skin characterized by pruritic papular lesions found most commonly in the webs of the fingers and toes, folds of the wrist, antecubital area, and axilla.
- Infants may also have lesions on the palms and soles of the feet.
- Generalized scabies occurring in patients with advanced HIV is called Norwegian scabies and is highly contagious.
- Treatment
 - Benzyl Benzoate 25% lotion: apply over the body except head/face, leave in place 12 hours, then wash off for 2-3 consecutive days.
 - Permethrin 5% cream applied head to toe for 12 hours followed by bath is preferred where available. Toxicity is minimal, treatment effective, and it may be used in infants.
 - Pruritis can persist for 1-2 weeks due to persistent antigen in the skin even when treatment has been effective
 - In older children, 0.3% gamma-benzene hexachloride (lindane) applied from neck to toe may be used, but has been associated with neurotoxicity so is not preferred
 - Oral antihistamines may be given to relieve itching.
 - All household members should be treated along with the child, regardless of symptoms.

- All contaminated clothes and bedsheets should be washed and hung to dry in the sun.

Drug Eruptions

- Medications commonly causing drug eruptions include cotrimoxazole, penicillins, cephalosporins, dapsone, and nevirapine.
- Drug eruptions usually appear as pink to erythematous papules that run together and create a blotchy appearance.
- Other manifestations include pruritic papules (hives), mucous-membrane ulceration, scaling, and light sensitivity with abnormal pigmentation of skin or nails.
- Often an offending agent is obvious; however, in severe cases it may be necessary to discontinue ALL medications and restart one-by-one when the drug responsible is not known.
- Treatment:
 - Discontinue causative medication; if reaction is severe, DO NOT rechallenge
 - Oral antihistamine such as diphenhydramine 1 mg/kg every six hours as needed for pruritus.
 - Systemic corticosteroids are very rarely indicated; an exception includes DRESS syndrome (Drug rash, eosinophilia, and systemic symptoms including liver enzyme elevation).
 - Systemic corticosteroids HAVE NOT been shown to be beneficial in children with Stevens Johnson syndrome and their use should be avoided due to the risk of additive immunosuppression and increased risk of infection.

Seborrheic Dermatitis

Seborrheic dermatitis is characterized by dry, flaky, or scaly skin occurring on the scalp; it also may be seen on the face or in the diaper area. Older children may also have involvement of the nasolabial folds, the skin behind the ears, and the eyebrows.

Treatment:

- Selenium sulfide or ketoconazole shampoo for scalp lesions
- 1% hydrocortisone cream can be applied to the affected area three times per day but should be used sparingly on the face or diaper area as skin atrophy can occur.

Pruritic Papular Eruption

- Chronic eruption of papular lesions on the skin. See Annex B.
- May be related to disordered inflammatory response to common antigens such as those due to repeated mosquito bites.
- Itching is intense.
- Usually evenly distributed on the trunk and extremities
- May become superinfected with *Staphylococcus* or *Streptococcus* organisms
- Generally refractory to treatments other than ART; when severe, strongly consider early initiation of ART.

5. NUTRITION AND HIV-INFECTED CHILDREN

Key points

- Untreated HIV infection frequently results in nutritional deficiencies and growth failure and may be the earliest sign of HIV infection in exposed infants.
- Malnutrition associated with HIV/AIDS leads to increased rates of opportunistic infection and decreased survival.
- Monitoring of growth parameters and nutritional status is critical to ensuring good outcomes in HIV-exposed and HIV-infected infants and children.
- HIV-infected children with specific illnesses require 25-30% additional calories to prevent malnutrition.
- At the first sign of growth failure or malnutrition, children should be evaluated for opportunistic infection and treated in accordance with the *National Interim Guidelines on the Management of Acute Malnutrition*

Introduction

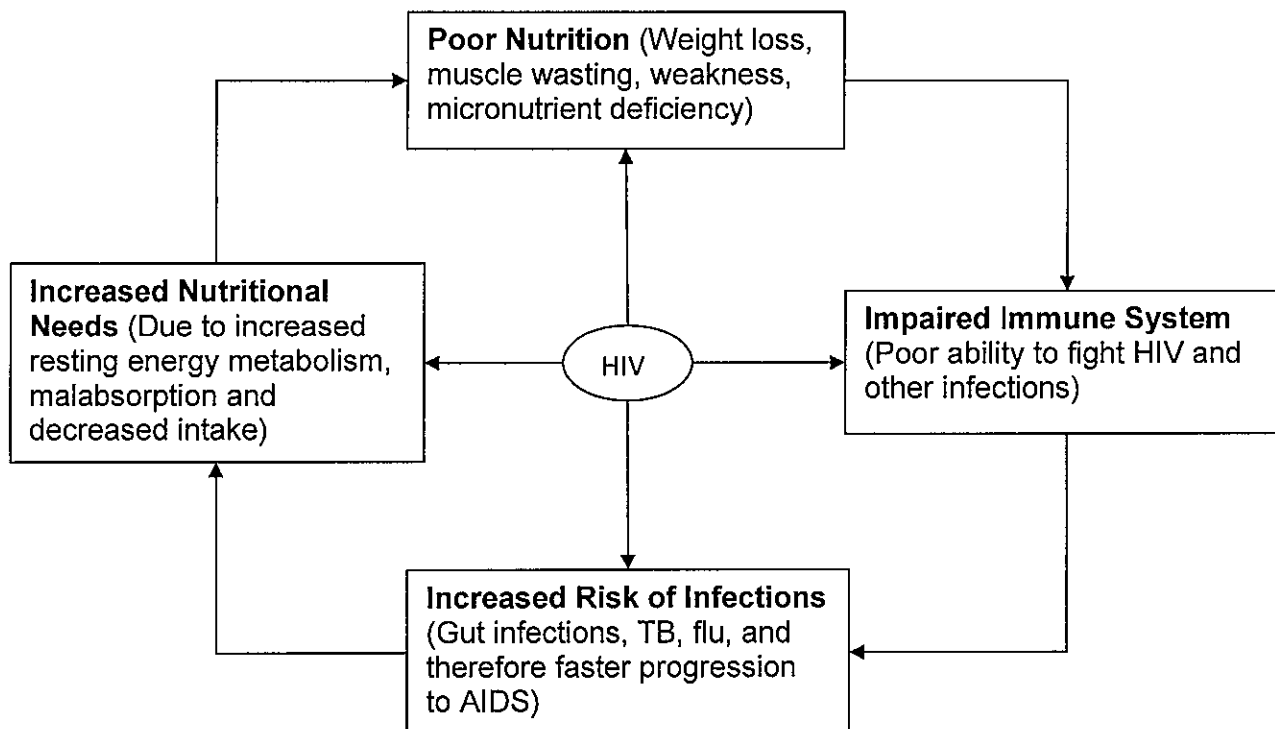
Malnutrition and inadequate growth are extremely common in HIV-infected infants and children, and is often the earliest sign of HIV-infection. This occurs due to a significant increase in metabolic needs in HIV-infected children, leading to loss of both lean (muscle) and fat body mass; once evidence of lean body mass is evident, mortality is substantial. Monitoring of sensitive indicators of growth and nutrition, including weight-for-height and mid-upper-arm-circumference, are critical to the early detection of malnutrition and should be performed at every visit. Decreasing child mortality and improving maternal health depend heavily on reducing malnutrition.

Causes of malnutrition

HIV-infected children are at increased risk of malnutrition for many reasons (See Figure 2), including:

- Decreased food intake because of anorexia associated with illness, mouth ulcers, and/or oral thrush
- Increased nutrient loss resulting from intestinal malabsorption due to infectious diarrhea and/or HIV enteropathy
- Increased metabolic rate because of recurrent bacterial infections, OIs, and HIV infection itself
- Economic issues: HIV can lead to poorer socio-economic status, especially when parents of HIV-infected children are ill; there is limited food supply; and loss of household income are common

Figure 2 Cycle of malnutrition and infection in HIV-infected children



Adapted from RCQHC and FANTA Project 2003, *Nutrition and HIV/AIDS: A Training Manual*

Nutrition assessment

Nutrition assessment should be done for all HIV-exposed and HIV-infected children at every visit, and includes the parameters listed in Box 6:

Box 1: Nutritional assessment in HIV-infected children

Nutritional assessment in HIV-infected children
<ul style="list-style-type: none"> • Weight-for-height or weight-for-length • Edema or visible wasting • Rate of weight gain and weight-for-age

The child's growth should be classified at each visit as follows:

- Normal weight gain
- Acute malnutrition

See Appendix C for WHO weight-for-length, weight-for-height, and weight-for-age growth tables.

When inadequate weight gain is noted, thorough evaluation should be performed with particular attention to ruling out TB, GI infections, neonatal sepsis, and HIV. Additional

breastfeeding and complementary feeding advice should be offered to the breastfeeding mother as deemed necessary.

Caloric supplementation in children with HIV

Children with HIV and other specific illnesses should receive 25-30% additional calories to ensure adequate weight is maintained, even in the absence of any notable malnutrition, as outlined below:

- ANY child with HIV and one of the disorders listed in Box 7 should receive 25-30% additional calories through additional household foods or nutritional supplementation.
- All children with symptoms listed in Box 7 require ART and should be prepared for treatment without delay.

Box 2: Indications for caloric supplementation to HIV infected children

Provide 25-30% additional caloric supplementation to HIV-infected children with:

- TB
- Chronic lung disease
- Chronic opportunistic infection (e.g. penicilliosis)
- Malignancy
- Persistent diarrhea (>28 days)
- Weight loss
- Poor growth

Source: WHO. Antiretroviral therapy for HIV infection in infants and children: Towards Universal Access. Recommendations for a public health approach 2010 revision

Diagnosis and evaluation of acute malnutrition

Table 4 Classification of malnutrition in children

	Mild malnutrition	Moderate malnutrition	Severe malnutrition
Symmetrical edema?	No	No	Yes
Weight-for-height	<5 th percentile or <90% of median	-2 to -3 SD below median, or 70-79% of median	Below -3 SD, or <70% of median (severe wasting)
Height-for-age		-2 to -3 SD below median, or 85-89% of median	Below -3 SD, or <85% of median (severe stunting)

Visible wasting?	No	No	Yes
Mid-upper arm circumference (age)			<ul style="list-style-type: none"> • <115 mm (≤60 months) • <129 mm (5 – 9 years) • <160mm (10 – 14 years)

Children identified as having severe acute malnutrition require outpatient therapeutic feeding. Children with severe acute malnutrition and complications as outlined below require inpatient therapeutic feeding. Treatment of complications such as diarrhea and anemia are different for children with severe acute malnutrition. All children with severe acute malnutrition should be identified and treated based on the *National Interim Guidelines on the Management of Acute Malnutrition*. HIV exposed infants should continue to receive cotrimoxazole prophylaxis and 6 monthly vitamin A supplementation and de-worming medication as outlined in the routine care and follow-up of HIV-exposed infants (see *Guidelines for Diagnosis and Antiretroviral Treatment of HIV Infection in Infants, Children and Adolescents in Cambodia*).

The presence of any medical complications (Table 5), which are significantly correlated with increased mortality, is an indication for admission. Weight-for-age is NOT a good indicator of severe malnutrition.

Table 5. Medical complications in severe malnutrition requiring inpatient care

MEDICAL COMPLICATIONS	
According to severe classifications for Integrated Management of Childhood Illness (IMCI)	
Vomiting	Intractable (empties contents of stomach)
Temperature	Fever > 101 °F (39.0°C) Hypothermia < 95 °F (35°C) under arm pit; (35.5°C rectal)
Respiration rate	≥ 50 resp/min from 6 to 12 months ≥ 40 resp/min from 1 to 5 years ≥ 30 resp/min for over 5 year olds Any chest in-drawing (for children > 6 months)
Anemia	Very pale (severe pallor), difficulty breathing
Superficial infection	Extensive skin infection requiring Intra Muscular injection treatment and follow-up monitoring
Alertness	Very weak, apathetic, unconscious Fitting/convulsions
Hydration status	Severe dehydration based primarily on recent history of diarrhea, vomiting, fever, anuria, thirst, sweating & clinical signs

OTHER INDICATIONS FOR INPATIENT MANAGEMENT
No appetite (if child is W/H <-3SD or MUAC <11.5)
Child younger than 6 months with bilateral pitting edema or visible wasting
Child older than 6 months but weighs less than 4kg
Bilateral pitting edema
Weight loss for 3 consecutive weighings Static weight for 5 consecutive weighings
Not recovered after 3 months in outpatient management of severe acute malnutrition and repeated home visits

HIV-infected children with severe acute malnutrition should be urgently evaluated at the nearest pediatric AIDS care site or admitted for inpatient care.. This may be easier to accomplish in the inpatient setting at some sites, where they should:

- Be investigated for active tuberculosis
- Receive an evaluation for oral or esophageal candidiasis, chronic intestinal infection, and disseminated fungal infection
- Begin ART if not already receiving treatment
- Be evaluated for treatment failure if receiving ART for ≥6 months
- Be assessed for immune reconstitution inflammatory syndrome (IRIS) if ART started in the prior 6 months

For treatment of severe acute malnutrition, refer to the *National Interim Guidelines on the Management of Acute Malnutrition*. Energy goals during treatment of severe malnutrition are summarized below.

Box 3: Energy goals for HIV-infected children with severe malnutrition

Energy goals for HIV-infected children with severe malnutrition
<p><i>Stabilization phase (day 1 – 7)</i></p> <ul style="list-style-type: none"> • F75, goal 100 kcal/kg/day
<p><i>Recovery phase</i></p> <ul style="list-style-type: none"> • F100 or Ready to Use Therapeutic Food (BP100) <ul style="list-style-type: none"> ○ 150 – 220 kcal/kg/day (age 6m – 5y) ○ 75 – 100 kcal/kg/day (age 6 – 9 years) ○ 60 – 90 kcal/kg/day (age 9 – 14 years)

6. HEMATOLOGIC MANIFESTATIONS OF HIV-INFECTED CHILDREN

Key Points

- Leukopenia, anemia, and thrombocytopenia are common in HIV-infected children
- Anemia can be caused by infection (particularly TB), medication, malnutrition, helminth-related iron deficiency, or HIV itself
- Neutropenic children are at increased risk of invasive bacterial and fungal infection
Idiopathic thrombocytopenic purpura (ITP) is a common cause of thrombocytopenia in HIV-infected children and usually responds to ART

Anemia

Anemia is a very common condition in HIV-infected children, as outlined below.

Table 6. Causes and etiology of anemia in HIV infection

Causes of anemia	Etiology
Poor production of red blood cells (RBCs)	HIV infection: <ul style="list-style-type: none"> ○ Anemia of chronic disease ○ HIV infection of bone marrow cells Infections: <ul style="list-style-type: none"> ○ CMV, parvovirus B19, tuberculosis Malignancy: <ul style="list-style-type: none"> ○ Lymphoma, Kaposi's sarcoma Drugs: <ul style="list-style-type: none"> ○ Cotrimoxazole, dapsone, AZT
Destruction of RBCs	Disseminated intravascular coagulation (DIC) Drug-associated hemolytic anemia <ul style="list-style-type: none"> ○ Primaquine, dapsone, cotrimoxazole
Ineffective production of RBCs	Folate and iron deficiency <ul style="list-style-type: none"> ○ Dietary ○ Intestinal malabsorption ○ Helminth-related GI bloodloss Vitamin B-12 deficiency <ul style="list-style-type: none"> ○ Intestinal malabsorption ○ Helminth infection Thalassemia

Diagnosis and treatment

- Anemia is often detected by pallor on exam or during blood examination for other indications
- Severe anemia may lead to dyspnea and fatigue
- Initial evaluation should include reticulocyte count and iron indices, where available, and malaria smear in areas where malaria is present.
- If microcytic anemia is present, initial therapy with 2mg/kg elemental iron 3 times daily with meals, along with de-worming medications, is appropriate

- Recheck CBC 3 weeks after iron supplementation; if increased by 2 g/dl, continue iron x3 more weeks. If not improved, search for other cause
- Ensure diet is adequate in iron-rich foods and vitamin C.
- When severe, profound, transfusion-dependent anemia is detected in patients with low CD4 count, strongly consider TB, Lymphoma, and chronic parvovirus B19 infection. Diagnosis of these disorders requires pathologic examination of bone marrow available only in referral centers. Treatment with IVIG is indicated in the case of chronic parvovirus B19.

Neutropenia

- Absolute neutrophil count (ANC) $<1000/\text{mm}^3$ in infants <1 year of age or $<1500/\text{mm}^3$ in children >1 year
- The risk of serious bacterial infection increases when the ANC falls below $500/\text{mm}^3$
- Severe neutropenia is rare in HIV infection and more often a late-stage event
- Neutropenia shortly after initiation of new medications is most-often drug-related

ANC= white blood cell x (percentage of segmented neutrophils + bands)

Table 7: Causes and etiology of neutropenia in HIV infection

Cause of neutropenia	Etiology
Bone marrow infiltration or infection	<ul style="list-style-type: none"> • TB, penicilliosis, mycobacterium avium complex (MAC), histoplasmosis • HIV-related bone marrow suppression • Lymphoma
Drugs	<ul style="list-style-type: none"> • AZT; rarely, 3TC, ddI, d4T • Ganciclovir, foscarnet • High-dose cotrimoxazole

Clinical presentation

- Usually patients are asymptomatic and detected incidentally
- Gram negative bacteremia becomes common as ANC falls below $500/\text{mm}^3$
- Prolonged neutropenia elevates the risk of invasive fungal infection, especially with *Aspergillus* species
- Treatment is targeted at the underlying cause:
 - Treat any OIs or TB
 - Initiate ART
 - Stop any possible offending medications
 - Consider bone marrow biopsy if 2 or more cell-lines are decreased and alternative cause is not identified

Thrombocytopenia

Platelet counts below $150,000$ cells/ mm^3 are common in HIV-infected children. However, severe thrombocytopenia ($<50,000$) is relatively rare and can have a variety of causes.

Clinical presentation

- Most patients with thrombocytopenia have no symptoms until levels are below 20,000
- Petechiae and purpura may be the only signs, often in the lower extremities
- Children may present with mucosal bleeding, particularly epistaxis

Causes

- Immune thrombocytopenia (ITP) is an autoimmune disorder caused by anti-platelet antibodies which lead to platelet removal from the bloodstream in the spleen. On blood smear, giant platelets are usually seen and there is NO evidence of leukemia. ITP may be treated with intravenous immune globulin (IVIG), but is likely to recur unless ART is initiated.
- Thrombotic thrombocytopenic purpura (TTP) is a very rare HIV-related disorder which is frequently fatal. Patients with TTP have fever, acute renal failure, hemolytic anemia, and mental status change in addition to low platelets and purpuric rash. This is easily mistaken for disseminated intravascular coagulation (DIC), but the prothrombin time and partial thromboplastin time will be in the normal ranges. Treatment for TTP requires urgent plasma exchange until platelet count and lactate dehydrogenase (LDH) are normal.
- Infection of platelet progenitor cells by HIV may also contribute to chronic thrombocytopenia, which improves with ART.
- Medication-related thrombocytopenia is rare but can occur with high-dose cloxacillin, vancomycin, and cotrimoxazole.

7. HIV-ASSOCIATED MALIGNANCIES IN CHILDREN

Key points

- HIV-infected patients are at increased risk of malignancy, particularly lymphoma
- HIV-associated malignancy should be considered when fever and cytopenias are present
- Primary central nervous system (CNS) lymphoma is a large B-cell variant affecting only the CNS and is frequently fatal
- Treatment with ART is recommended in all HIV-infected patients with malignancy
- Chemotherapy is rarely available in many resource-limited settings

Non-Hodgkin's Lymphoma (NHL)

HIV infected children most commonly develop Burkitt's (small non-cleaved cell) lymphoma and immunoblastic (large cell) lymphoma. Burkitt's lymphoma is related to infection with EBV-virus and progresses very rapidly, but is less common than large cell lymphoma.

Clinical presentation

Symptoms of lymphoma can be highly variable, depending on what organ system is most involved. Most patients will present with fever and lymphadenopathy, but fatigue, weight loss, and night sweats are also common. Lymphoma is frequently misdiagnosed as TB but fails to improve with TB medications. Lymphoma should be in the differential in any patient with fever and lymphadenopathy who does not have an alternative explanation for their symptoms, especially if splenomegaly or any cytopenias are present.

Table 8: Site-dependent symptoms of NHL

Mediastinal or Pharyngeal tumor <ul style="list-style-type: none"> • Tachypnea • Nasal flaring • Stridor • Localized decrease in breath sounds • Dry cough 	Abdominal tumor <ul style="list-style-type: none"> • Abdominal distension • Ascites • Palpable abdominal mass • Jaundice • Pain
Central nervous system disease <ul style="list-style-type: none"> • Headache • Vomiting • Visual disturbances • Gait instability • Cranial nerve palsies • Hemiparesies • Seizures 	Maxillofacial tumor <ul style="list-style-type: none"> • Jaw mass • Numbness of the chin (peripheral facial nerve compression) • Asymmetric facial expression

Diagnosis

Definitive diagnosis of NHL is made through biopsy of affected tissue, usually lymph node or bone marrow. Any child suspected of lymphoma should have biopsy of abnormal tissue to evaluate for lymphoma and to rule out TB or invasive fungal infection.

Treatment

Treatment of NHL requires specialty care in a referral center with access to pediatric oncology specialists and chemotherapy. NHL is a clinical stage 4 disease and requires early initiation of ART for optimal outcome.

Primary CNS Lymphoma

- Primary CNS lymphoma (PCNSL) is a subtype of NHL that is limited to the brain tissue.
- PCNSL is much more common in HIV-infected children than in uninfected children.
- The differential diagnosis of CNS lymphoma includes toxoplasmosis, tuberculoma, and cryptococcoma.
- Unlike adults with HIV, where toxoplasmosis is the most common cause of a brain mass, PCNSL is the most common cause of an isolated brain mass in HIV-infected children.
- PCNSL should be suspected in any HIV-infected child with neurologic abnormalities accompanied by ring-enhancing mass lesions on a computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain.
- Epstein Barr Virus (EBV) virus is often detectable in the cerebral spinal fluid (CSF) of patients with PCNSL in laboratories where advanced PCR techniques are available.

Diagnosis

- Characteristic ring-enhancing CT lesions in the brain; may be single or multiple, whereas toxoplasmosis almost always presents with multiple lesions.
- Cytology of CSF showing moderate lymphocytic pleocytosis and elevated protein with EBV+ PCR where available
- Failure to improve after empiric treatment for toxoplasmosis
- Brain biopsy is required for definitive diagnosis

Treatment

- Urgent transfer to a referral center with access to pediatric oncology services.
- Treatment for PCNSL involves either the use of whole-brain radiation or high-dose methotrexate along with early initiation of ART.
- Prognosis remains poor for this tumor.

Kaposi's Sarcoma

Kaposi's sarcoma is a vascular tumor caused by infection with Human Herpes Virus-8, and is extremely rare in Southeast Asia. Children with this malignancy present with raised, purple lesions on the palate and extremities. Treatment is with either local or systemic chemotherapy and ART.

8. RESPIRATORY MANIFESTATIONS IN HIV-INFECTED CHILDREN

Key Points

- Pneumonia is the leading cause of hospital admissions and death in HIV-infected children.
- Recurrent episodes of pneumonia may suggest immune suppression, TB, foreign body aspiration, bronchiectasis, and/or lymphoid interstitial pneumonitis.
- HIV-exposed or infected infants <12 months of age with severe pneumonia should receive empiric treatment for *Pneumocystis jiroveci* pneumonia (PCP) until HIV is ruled-out or another cause is clearly found.
- PCP in an infant is most common at 4 – 6 months of age and may be the first AIDS-defining condition in the child. A high index of suspicion is required to diagnose PCP in children without known HIV-exposure.
- All HIV-exposed children should receive prophylaxis against PCP from 6 weeks of age until it is established that the child is not HIV-infected.
- Lymphoid interstitial pneumonitis (LIP) is seen in 40% of children with perinatally acquired HIV and is often mistaken for miliary TB.

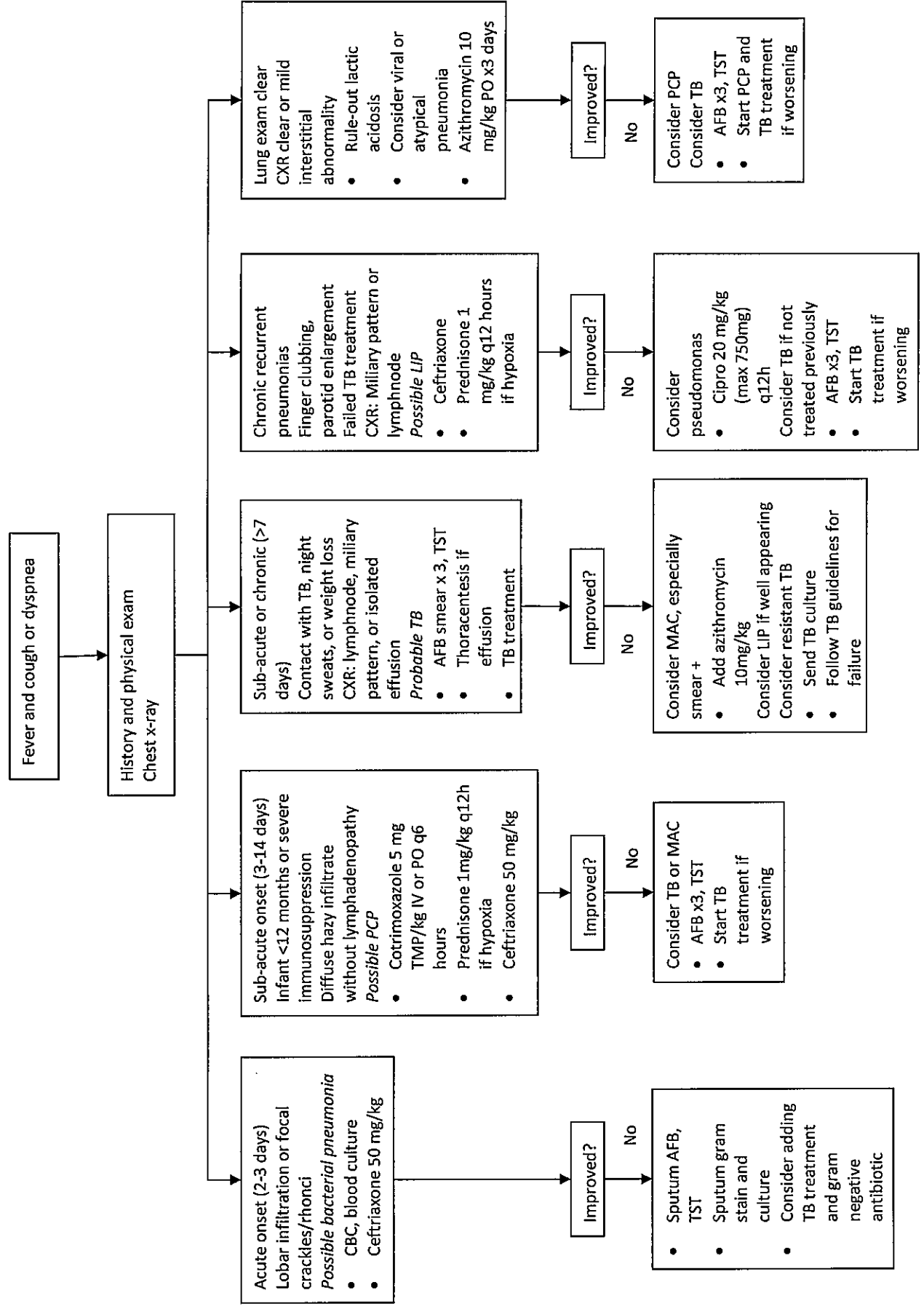
Introduction

Pneumonia (including PCP) and chronic lung disease contribute heavily to the high-mortality in HIV-infected children prior to the initiation of ART. Accurate diagnosis of pulmonary conditions is difficult in Cambodia due to limitations on accurate diagnostic tests, and empiric treatment for several diseases is often necessary. Common conditions in HIV-infected children in Cambodia are:

- Bacterial pneumonia
- Tuberculosis
- Lymphoid interstitial pneumonitis (LIP)
- Bronchiectasis
- Viral pneumonitis
- Pneumocystis pneumonia (PCP)

See Figure 3 for a suggested approach to respiratory complaints in children with HIV.

Figure 3: Evaluation of respiratory complaints in children with HIV



Bacterial Pneumonia

Common bacterial causes of pneumonia in HIV-infected children include:

- *Streptococcus pneumoniae*
- *H. influenzae*
- *Klebsiella*
- *Staphylococcus aureus*
- Gram negative bacilli
- Melioidosis

Recurrent bacterial pneumonia (≥ 3 episodes in one year) suggests immune suppression, and should be investigated further to exclude other conditions such as tuberculosis, foreign body, bronchiectasis, LIP, and fungal pneumonia. In Southeast Asia, lung infection with *Burkholderia pseudomallei*, or melioidosis, is a common cause of severe recurrent pneumonia. In Thailand this bacteria is responsible for 20% of all community-acquired septicemias.

Clinical Presentation

Clinical presentation of pneumonia includes the following:

- History of acute onset fever, cough, and fast breathing
 - Retractions, cyanosis, and lethargy may be present in severe pneumonia
- On auscultation one may hear crackles, decreased breath sounds, or bronchial breathing
- When pulse oximetry is available, results usually show persistent hypoxia ($O_2 < 95\%$).

Investigations

- An increased white blood cell count may be present
- Bacteremia is common in HIV-infected patients with pneumonia
 - Send blood cultures where possible
- Chest x-ray where available
- A blood smear for malaria in malaria-endemic areas

Treatment

Outpatient Management (mild pneumonia)

The management of pneumonia should follow recommended IMCI guidelines.

- Oral amoxicillin 50 mg/kg/day divided 3 times daily for 5 days.
- A child with mild pneumonia that is allergic to penicillin may be given a macrolide antibiotic (erythromycin, azithromycin, or clarithromycin), or if older than 7 years, doxycycline.
- If a child is already on CTX prophylaxis, CTX should not be used to treat pneumonia unless PCP is suspected (see below).
- Follow-up in 3-4 days.

Severe Pneumonia

Severe pneumonia should be managed in a hospital or other inpatient facility.

Supportive Care

- Use supplemental oxygen when a child presents with chest indrawing, cyanosis, and/or hypoxia ($< 92\%$).
- Correct severe anemia ($Hb < 7$ g/dL) by transfusion with packed red blood cells.

- Ensure adequate oral hydration and monitor fluid input and output (I/O chart). NG feeding and/or IV hydration will be necessary in severe cases.
- Provide paracetamol for fever and pain.
- Provide Vitamin A supplementation if the child has not received vitamin A in the last 3 months

Specific Therapy

- Use IV ampicillin plus gentamicin if cephalosporins are not available and there is a high level of resistance to chloramphenicol.
 - Ampicillin dose: 200 mg/kg/day divided q6 hours
 - Gentamicin dose: 7 mg/kg once, then 5 mg/kg once daily
- Add IV cloxacillin 200 mg/kg/day divided q6 hours when staphylococcal pneumonia is suspected:
 - Pneumatoceles on chest xray
 - *Staphylococcus aureus* in blood culture
 - Severe pneumonia not responding to the usual therapy
 - Heavy presence of *S. aureus* in sputum gram stain or culture

Other Considerations

- Any HIV-exposed or infected child less than 1 year of age with severe pneumonia should receive empiric therapy for PCP until another cause is found or HIV is ruled-out.
- Children with bronchiectasis are frequently colonized with *Pseudomonas* species; add gentamicin or ceftazidime in these cases, based on local susceptibility patterns

Pneumocystis jiroveci pneumonia (PCP)

Introduction

PCP is a common cause of death in HIV-infected infants, particularly between 4 – 6 months of age. Cotrimoxazole dramatically decreases the incidence of PCP, but up to 25% of infants with PCP develop illness despite prophylaxis. **PCP should be suspected in any HIV-exposed or infected infant with severe pneumonia and treatment started without delay.**

Epidemiology

- Pneumocystis:
 - Based on genetic characteristics pneumocystis can be classified as a fungus
 - The species *carinii* infects rats
 - The species *jiroveci* infects human → PCP (PneumoCystis Pneumonia)
- CD4 cell counts **ARE NOT** a good indicator of risk for PCP in children <1 year of age
 - Many infants with PCP have %CD4+ >25%

Clinical Manifestations

- Fever, tachypnea, dyspnea, and cough
- Abrupt or insidious onset with non-specific symptoms including poor feeding or weight loss
- Lung sounds may be clear or with soft crackles
- Hypoxia often out-of-proportion to exam, with room-air O2 levels frequently below 85%

Diagnosis

- Diagnosis of PCP in Cambodia is usually made on clinical grounds on the basis of abnormal chest x-ray with typical interstitial infiltrates, hypoxia, and a response to PCP therapy.
- Treatment MUST NOT be delayed as definitive diagnosis is rarely possible
- If PCP is in the differential diagnosis, it should be treated immediately
- Chest radiographs may show bilateral diffuse parenchymal infiltrates with 'ground-grass' or reticulogranular appearance, **but may be normal.**
- Definitive diagnosis is difficult in children. The organism can be demonstrated in pulmonary tissues or fluids by silver or fluorescent antibody staining where available, collected as follows:
 - induced sputum analysis (nebulized 3% hypertonic saline), *or*
 - bronchoscopy with bronchoalveolar lavage

Differential Diagnosis

- Bacterial pneumonia
- Viral pneumonia (particularly CMV)
- Pulmonary tuberculosis
- Disseminated *Mycobacterium avium* complex
- Lymphoid interstitial pneumonitis (in children over 1 year of age)
- Atypical pneumonia (*Mycoplasma*, *Chlamydia*, *Legionella*)

Treatment

- Cotrimoxazole 15-20/75-100 mg/kg/day, 3-4 divided doses IV for 21 days. **Note that this dose is much higher than prophylactic cotrimoxazole.**
 - Change to oral therapy at the same dose once improved and taking PO
 - Some experts add clindamycin 30 – 40 mg/kg/day divided q8 hours for severe disease
- Pentamidine isothionate (4 mg/kg/day once daily, IV 60–90 min):
 - An alternative for intolerance to cotrimoxazole, or clinical treatment failure after 5–7 days of cotrimoxazole therapy.
 - With clinical improvement after 7–10 days of intravenous therapy with pentamidine, an oral regimen (e.g., atovaquone) might be considered to complete a 21-day course.
 - Adverse drug reaction: renal toxicity, severe hypotension (particularly if infused rapidly), prolonged QT, cardiac arrhythmias.
- Atovaquone 30-40 mg/kg/d, 2 divided doses with fatty food (3-24 months, 45 mg); data limited for children.
 - Adverse reactions: skin rashes (10%–15%), nausea, and diarrhea can occur.
- Others treatments in adults:
 - Clindamycin/primaquine: data for children are not available
 - Dapsone/trimethoprim: data on toxicity and efficacy among children are not available.

Corticosteroids

- Indication:
 - Room-air PaO₂ value of <70 mmHg, or alveolar-arterial gradient of >35 mmHg
 - When blood gas not available: O₂ saturation <90%
- Doses:
 - Prednisone
 - D1-5: 1mg/kg/12h (max 40mg/12h)
 - D6-10: 0.5 mg/12h (max 40mg/24h)
 - D11-21: 0.5 mg/24h (max 20mg/24h)

Methylprednisolone iv

- D1-7: 1 mg/kg/6h
- D8-9: 1 mg/kg/12h
- D10-11: 0.5 mg/kg/12h
- D12-16: 1 mg/kg/24h
- D17-21: 0.5 mg/kg/24h

Cotrimoxazole Prophylaxis

All children diagnosed with PCP should begin cotrimoxazole prophylaxis as soon as treatment-dose cotrimoxazole has been completed, and should continue through the age of 5 years regardless of immune reconstitution on ART.

See *Guidelines for the Management of Common and Opportunistic Infections among HIV-Infected Infants, Children and Adolescents in Cambodia* for further discussion on CTX prophylaxis

Lymphoid Interstitial Pneumonitis (LIP)

Lymphoid interstitial pneumonitis (LIP) is common in children but rare in adults and usually occurs in children more than 2 years of age. LIP may occur in up to 40% of HIV-infected children, and is often mistaken for miliary TB because of the diffuse nodular pattern on chest x-ray along with mediastinal lymphadenopathy.

Pathogenesis

A possible explanation for LIP includes co-infection of the lungs by HIV and Epstein Barr Virus (EBV), leading to immune stimulation with lymphoid infiltration and chronic inflammation.

Clinical Symptoms

LIP should be considered in patients with:

- Good general condition despite respiratory distress
- Chronic/recurrent cough
- Parotid enlargement, generalized lymphadenopathy, and/or hepatosplenomegaly
- Finger clubbing
- Poor response to TB therapy
- Terminally chronic lung disease with hypoxia
- Children with recurrent pneumonia, often in the same lobar distribution

Chest xray findings in LIP include:

- Diffuse bilateral reticulonodular infiltrates that appear similar to miliary TB, but nodules are usually slightly larger
- Bilateral hilar or mediastinal lymph node enlargement may be present
- Dense lobar infiltrates may occasionally be seen
- Bronchiectasis is present in many children with LIP

Management

- LIP is an indication for ART, which should begin without delay

- Prednisone 2 mg/kg/day for severe exacerbation, tapered over several weeks as symptoms improve
 - Add cotrimoxazole prophylaxis for duration of steroid therapy if no other indications exist
- Oxygen during episodes of hypoxia <88%
- Bronchodilators
- Treat superimposed bacterial pneumonia and consider pseudomonas if no improvement on standard antibiotics
- Chest physiotherapy may benefit children with bronchial plugging due to mucoid secretions

Bronchiectasis

Bronchiectasis may occur as a complication of severe or recurrent pneumonia, TB, or LIP. Airways in the lung become damaged, lose elasticity, and dilate abnormally, leading to impaired secretion clearance and risk for further infection.

Epidemiology

Bronchiectasis occurs in over 15% of children with HIV in some series, with median age at diagnosis of 7.5 years. Predisposing conditions include LIP, chronic pneumonia, and recurrent pneumonias.

Clinical Presentation

Children with bronchiectasis typically have a history of recurrent hospitalizations or treatments for pneumonia with only partial improvement. Consider bronchiectasis in children with:

- Chronic cough
- Copious purulent sputum
- Digital clubbing
- Recurrent pneumonia

Diagnosis

- Severe bronchiectasis is often visible on CXR; computed tomography (CT) is more sensitive but not usually necessary
- Diagnosis of acute exacerbations should include sputum gram stain and culture where available, because pseudomonas and other resistant bacteria are common

Treatment

- Initiate ART and cotrimoxazole prophylaxis
- Chest physiotherapy
- Consider the addition of an anti-pseudomonal antibiotic (ceftazidime or ciprofloxacin) for severe exacerbations
- Bronchodilators for wheezing

Prevention

Prevention of bronchiectasis involves early and aggressive diagnosis and treatment of pulmonary infections and ART. Cotrimoxazole prophylaxis can reduce the frequency of bacterial pneumonia and may play a role in preventing bronchiectasis. Any child with recurrent bacterial infections should be considered for indefinite cotrimoxazole prophylaxis.

9. TUBERCULOSIS IN HIV-INFECTED CHILDREN

Key Points

- Tuberculosis(TB) is the leading cause of death in HIV infected patients
- Cambodia has a high incidence of TB
- Children with HIV must be screened for symptoms of active TB at every visit
- Diagnosing TB in children is difficult and should follow the *National Clinical Guideline for the Management of TB/HIV Co-infection* and the *National Guidelines for the Diagnosis and Treatment of TB in Children*
- Treatment regimens for TB depend on the site of infection and should follow the *National Clinical Guideline for the Management of TB/HIV Co-infection* and the *National Guidelines for the Diagnosis and Treatment of TB in Children*
- HIV-infected children with no clinical signs of TB should receive 6 months of isoniazid preventive therapy dosed at 10 mg/kg daily

Epidemiology

Mycobacterium tuberculosis is now the most common cause of death in HIV-infected individuals worldwide. Because patients with HIV are particularly susceptible to TB, tuberculosis rates have risen rapidly, fueled by the HIV epidemic. Cambodia is a high burden TB country with the highest incidence in the Western Pacific Region, estimated at 442 cases/100,000 populations in 2014. Nearly 50% of cases remain undetected per year.

Table 9 shows the effect of HIV infection on lifetime risk of an *M. tuberculosis* infected individual developing TB.

Table 9: Lifetime risk of active TB with and without HIV

HIV status	Lifetime risk of developing TB
Negative	5-10%
Positive	50%

Clinical Manifestations of tuberculosis in children

The symptoms of active tuberculosis in young children are non-specific, and often include weight loss, fever, and failure to thrive. In immunocompetent children, the presentations of TB vary predictably by age, with miliary disease and meningitis common among infants, focal infiltrate with mediastinal lymphadenopathy common in ages 1 – 5 years, and adult-type cavitation or pleural effusion common over 10 years of age.

The clinical presentation of TB among children with HIV depends on the CD4 cell count and age. In children with severe immunosuppression, TB can present acutely with rapid dissemination and meningitis. Up to 15% of HIV-infected children with TB present with cough of less than 2 weeks duration. In children on ART with high CD4 counts, TB often presents as it would in the HIV-uninfected child.

TB is difficult to diagnose in HIV-infected children because:

- Symptoms of TB might be due to other diseases
- The tuberculin skin test is often negative in HIV-infected children with TB
- Other causes of respiratory disease and abnormal chest x-ray are common in children with HIV
- Children with HIV often have more than one infection at the same time
- Children with HIV very often become sick with TB after exposure

No clinical prediction rule can accurately diagnose TB. Therefore, TB should always be considered in children with any of the following:

- 1) Contact with an adult or older child with smear-positive PTB
- 2) Failure to thrive or weight loss
- 3) Current cough
- 4) Current fever
- 5) Enlarged cervical lymph nodes

The symptoms most suggestive of tuberculosis in children include:

- Continuous cough of >2 weeks duration
- New loss of weight or failure to thrive
- Persistent fever for >2 weeks duration
- Painless enlarged lymph nodes in the neck

However, tuberculosis can cause many different clinical manifestations as summarized in Box 9.

Box 4: Clinical manifestations of tuberculosis

- | |
|--|
| <ul style="list-style-type: none"> • Gibbus deformity (angulation) of the spine • Serositis (Pleural, pericardial, and/or peritoneal effusions) • Meningitis and coma • Joint or bone swelling or deformity • Unexplained abdominal mass or ascites • Isolated pericarditis (not associated with poly-serositis) • Chest x-ray findings including: <ul style="list-style-type: none"> ○ Miliary pattern ○ Hilar or mediastinal lymph node enlargement ○ Airway compression by lymph nodes causing segmental hyperinflation or collapse ○ Chronic parenchymal infiltrate not improving after antibiotic treatment ○ Isolated unilateral pleural effusion |
|--|

Diagnosis of active TB disease

Obtaining a smear or culture-proven diagnosis of TB disease among children is very difficult. Children with TB disease rarely produce sputum and typically have a low bacterial load. Acid-fast stains of early morning gastric aspirates are positive in 0-20 % of children with TB, and in children with extrapulmonary TB, acid-fast stains of samples such as pleural fluid, CSF, and joint fluid are usually negative. Similarly,

tuberculin skin testing (TST) may be used to aid in the diagnosis but is positive in a minority of children. **There is no single test that can rule-out TB.**

A definitive diagnosis of TB disease requires isolation of *M. tuberculosis* in culture from expectorated sputum, gastric fluid, lymph node fine-needle aspiration (FNA), or other site. TB culture is an important part of the evaluation of HIV-infected children suspected of tuberculosis, and should be obtained whenever possible.

TB is very likely when 2 of the following occur and treatment for TB should begin without delay:

- 1) History of TB exposure *or* positive tuberculin skin test (TST), *and either*
- 2) Symptoms suggestive of TB, *or*
- 3) Abnormal chest x-ray suggestive of TB

Children who do not meet the definition of TB should receive treatment with antibiotics as appropriate, along with sputum AFB evaluation and very close follow-up. Symptoms suggestive of TB that do not improve with antibiotics should usually prompt treatment of tuberculosis in HIV-infected children.

Treatment Regimens

2 months RHZE / 4 months RH for new cases:

- Smear positive pulmonary TB (PTB)
- Smear negative PTB and extrapulmonary TB (EPTB) with the following:
 - extensive lung parenchymal involvement
 - pericarditis, peritonitis, bilateral or extensive pleural effusion
 - Gastrointestinal or genitourinary TB
- TB/HIV patients

TB dosing recommendations for children were amended by WHO in 2009 and are summarized below.

Table 10. Recommended doses for TB medication in children

Drug	Daily dosage in mg/kg (range)	Maximum dose/day
Rifampicin (R)	15 (10-20)	600 mg
Isoniazid (H)	10 (7-15)	300 mg
Pyrazinamide (Z)	35 (30-40)	2 g
Ethambutol (E)	20 (15-25)	1 g
Streptomycin (S)	15 (12-18)	1 g

For currently available fixed dose combination (FDC) formulations for TB treatment and dosing recommendations for Cambodia, please refer to the *National Guidelines for Diagnosis and Treatment of TB in Children*.

Additional considerations for HIV-infected children

- Pyridoxine supplementation during TB treatment should always be given as follows:

- Age <5 years, 12.5 mg daily
- Age ≥5 years, 25 mg daily
- Children with active TB should be given cotrimoxazole prophylaxis for the duration of TB therapy, regardless of the CD4 count.

Common side-effects of TB medications

Table 11. Management of anti-tuberculosis drug side-effects

Side-effects	Drug(s) probably Responsible	Management
<u>Minor side effects</u>		
Anorexia, nausea, abdominal pain	Rifampicin	Give tablets last thing at night or with food
Joint pain	Pyrazinamide	Give aspirin or nonsteroidal anti-inflammatory drug
Burning sensation in feet	Isoniazid	Increase pyridoxine to 50-75 mg daily
Orange/red urine	Rifampicin	reassurance
<u>Severe side effects</u>		
Deafness	Streptomycin	Stop streptomycin, give ethambutol instead
Dizziness, vertigo, or nystagmus	Streptomycin	Stop streptomycin, give ethambutol instead
Jaundice	Most anti-TB drugs	Stop all anti-TB drugs until jaundice resolves
Vomiting and confusion (consider drug-included liver failure if jaundice present)	Most anti-TB drugs	Stop all anti-TB drugs, urgent liver function tests
Visual impairment	Ethambutol	Stop ethambutol
Shock, purpura, acute renal failure	Rifampicin	Stop rifampicin

*If TB treatment regimen must be modified because of side effects, consult with TB treatment expert.

Severe forms of tuberculosis

Miliary TB

- Miliary TB is defined as disseminated TB infection
- Disseminated infection is common among infants and HIV-infected children with severe immunosuppression
- Evaluation may reveal a miliary chest x-ray pattern or choroidal tubercles on fundoscopy
- Mycobacterial blood and bone marrow cultures may be positive (where available)
- Lumbar puncture will show CNS involvement in over 1/3 of cases
- Treatment is the same as for TB meningitis and should follow the *National Clinical Guideline for the Management of TB/HIV Co-infection* and the *National Guidelines for the Diagnosis and Treatment of TB in Children*

- Steroids are not usually indicated in the routine management of miliary TB unless signs or symptoms of TB meningitis are present
- TB treatment 2 RHZS/4 RH

TB Meningitis

- Infection of the CNS by *M. tuberculosis*. Characterized by 3 distinct stages.
 1. Prodromal stage: symptoms are vague and include drowsiness, mild fever, convulsion, vomiting and headache.
 2. Transitional stage: manifestation of raised intracranial pressure and meningeal irritation
 3. Terminal stage: paralysis and coma
- Lumbar puncture usually shows the following:
 - CSF pressure is raised
 - CSF WBC count 10-500/mm³ with predominance of lymphocytes
 - Protein usually very elevated and glucose very low
 - Rarely, bacilli in CSF smear

Treatment is as follows:

- 2 RHZS/ 10 RH
- Prednisone 2-4 mg/kg (max 60mg) daily x 28 days then tapered over 2 weeks
 - Can use dexamethasone 0.6 mg/kg in place of prednisone
- For children intolerant of streptomycin, replace with ethionamide 20 mg/kg daily
 - Ethionamide has excellent CNS penetration, is available in an oral form, and is safe in small infants

Failure to improve on TB therapy

Children without HIV infection generally show improvement within 2 weeks of initiating pulmonary TB treatment, with decreased fever and cough. Those with abdominal, CNS, or other forms of extra-pulmonary TB may have slower responses. Children with smear-positive PTB should convert to smear negative by week 8.

Slow or inadequate response to treatment in HIV-infected patients may be due to:

- Another untreated infection or malignancy superimposed on TB, such as:
 - Penicilliosis
 - Histoplasmosis
 - MAC
 - Lymphoma
- Incorrect diagnosis of TB in patients with smear-negative disease
- Disseminated smear-positive MAC, since AFB smear without culture does not distinguish between the two organisms
- Immune reconstitution inflammatory syndrome
- Multi-drug resistant (MDR) tuberculosis

Patients with untreated infections such as penicilliosis or histoplasmosis usually continue to worsen on treatment, while those with IRIS, MAC, or MDR TB may have an initial period of improvement, followed by incomplete response or new worsening symptoms.

It is very hard to distinguish between the above problems clinically. IRIS is the most common cause of worsening after initial improvement on TB treatment; however, the other diagnoses above must be excluded before IRIS can be assumed.

Patients with failure to respond after 8 weeks of treatment should be investigated as follows:

- Repeat sputum smear *with culture*, if possible
 - Will distinguish between MAC and TB
 - Will allow drug susceptibility testing to rule-out MDR TB
- Send sputum for giemsa stain to evaluate for fungal pneumonia, particularly penicilliosis
- Send blood culture
 - *Penicillium* and *Histoplasma* may grow in routine blood culture media
 - Where available, send mycobacterial blood culture
- Check serum cryptococcal antigen where available
- If possible, aspiration of accessible lymph nodes for AFB and fungal staining and to rule-out lymphoma
- Consider adding azithromycin 10 mg/kg for the treatment of MAC if:
 - Smear positive after 2 months, *or*
 - Elevated ALT, alkaline phosphatase, *or* LDH, *or*
 - Continued depression of 2 cell-lines on CBC
 - For example, continued leukopenia and anemia
- Add amphotericin B 0.7 mg daily for empiric treatment for penicilliosis if clinically worsening and the above workup cannot be done due to limited capacity
 - Patients who do not improve after 2 weeks of amphotericin B are unlikely to have penicilliosis
- Suspect MDR TB in:
 - Patients exposed to a case of MDR TB
 - Patient with a history of past TB treatment, particularly if incomplete
 - Suspected poor compliance with self-administered medications
 - Treatment relapse, especially if category II
 - For management of suspected MDR TB, refer to the *National Guidelines for MDR TB management*
 - Patients who are clinically worsening may need addition of 3 new TB drugs for MDR treatment. Discuss with an expert.
- Consider IRIS in patients with continued fever and/or worsening lymphadenopathy who otherwise appear well, particularly when ART was started in prior 6 months
 - These patients usually will have shown good weight gain and appear clinically stable
 - Where possible, repeat CD4 testing usually shows a significant increase after ART

Immune reconstitution inflammatory syndrome (IRIS)

Patients who begin treatment with ART usually have rapid recovery of immune function. When the immune system begins to strongly fight infection, symptoms can worsen even when the infection is adequately treated. This is referred to as immune reconstitution inflammatory syndrome. IRIS usually occurs 2 – 8 weeks after starting ART, but may be seen up to one year after starting ART.

TB is the most common cause of IRIS, which occurs in up to one third of patients who start ART shortly after TB diagnosis. Other common causes include *Cryptococcus*, CMV, MAC, and PCP.

Two types of IRIS are summarized below:

- Paradoxical IRIS
 - Symptoms of infection improve with treatment, then worsen when ART is started

- Usually occurs when ART is started *after* OI treatment
 - Patients with TB often have worsening lung infiltrates and lymphadenopathy and may appear to be failing treatment
 - Evaluation for other possible causes of worsening such as treatment failure or undiagnosed infection is required, and IRIS diagnosed only if no untreated infections are present
 - ART should be continued
 - If symptoms are severe, 1-2 mg/kg/day of prednisone may be given for several weeks to minimize symptoms
- Unmasking IRIS
 - ART is begun in a patient with no symptoms of infection
 - TB or another OI develops several weeks *after* starting ART
 - This is usually due to pre-existing infection that was asymptomatic
 - Treatment for the underlying OI should be started immediately
 - ART should be continued
 - If symptoms are severe, 1-2 mg/kg/day of prednisone may be given for several weeks once OI treatment has been started

Isoniazid preventive therapy (IPT)

Children living with HIV should be screened for TB at the OI/ART clinic during their initial visit, prior to initiating ART and at every follow-up visit thereafter. Symptom screening should take place regardless of TB treatment history. Counselors, nurses or doctors should screen children living with HIV for the following five symptoms or conditions:

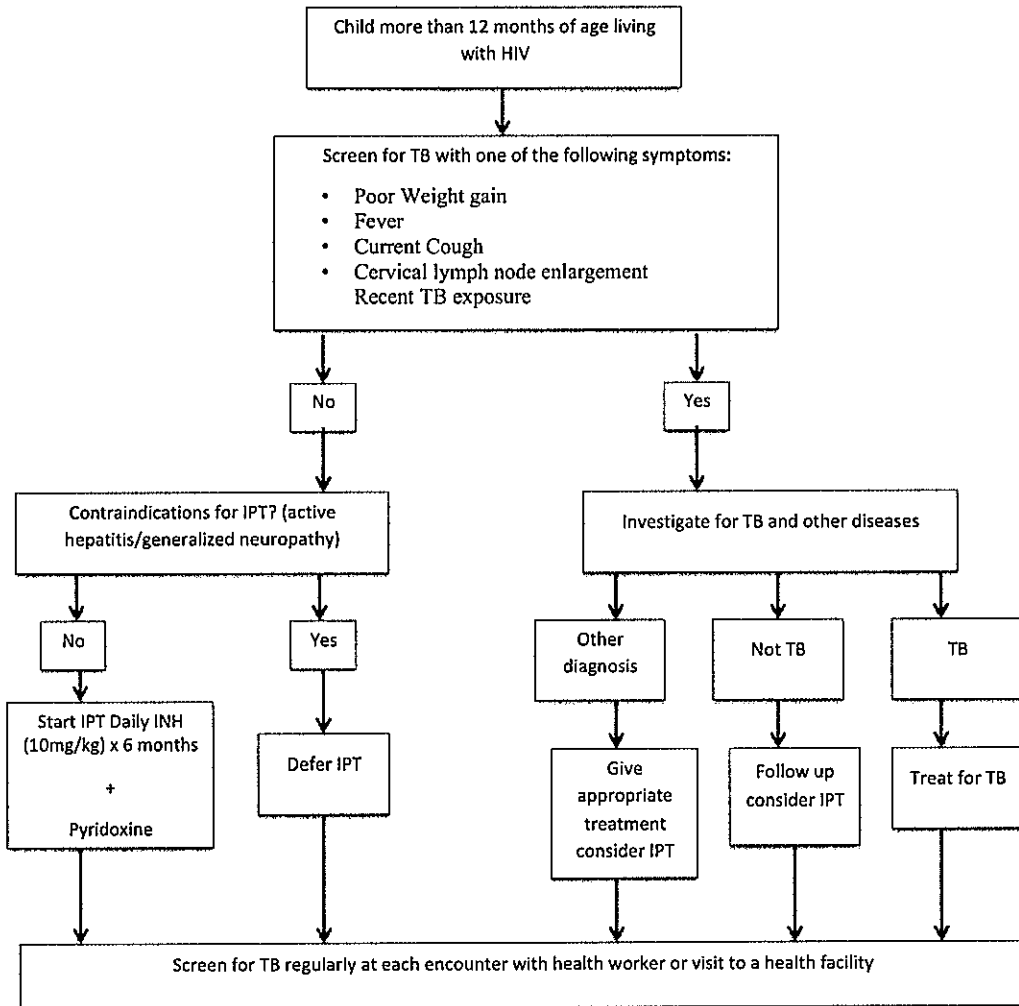
- Living with active TB patients or ex-patients
- Failure to thrive
- Fever
- Current cough
- Enlarged cervical lymph nodes

If children living with HIV have none of these symptoms, they are considered unlikely to have active TB and those over 12 months of age are eligible for IPT (See Figure 5). In addition, children less than 12 months old with a household TB contact and all children living with HIV after a successful completion of TB disease treatment should receive IPT. However, IPT should not be started in case of the following contraindications:

- Active hepatitis (acute or chronic) with ALT ≥ 2 N
- Symptoms of peripheral neuropathy

Figure 4. Isoniazid preventive therapy in children

Figure 4: Isoniazid preventive therapy in children



IPT should not be started in case of the following contraindications:

- Active hepatitis (acute or chronic) with ALT ≥ 2 N
- Symptoms of peripheral neuropathy

Pyridoxine dose x 6 months:

- Age <5 years, 12.5 mg daily
- Age ≥ 5 years, 25 mg daily

BCG immunization

- BCG is an immunization of live mycobacteria derived from *M. bovis*
- BCG reduces the risk of disseminated TB in immunocompetent infants and young children
- Children born to HIV-infected mothers should receive BCG vaccination at birth per the routine vaccination guidelines
- BCG vaccine should be withheld in the following circumstances:
 - Newborns with neonatal sepsis or fever
 - Newborns strongly suspected of having symptomatic HIV
 - Newborns who will be placed on isoniazid preventive therapy (IPT) because of active TB exposure in the home

- Isoniazid kills the vaccine organisms, so BCG will not be effective in this case
- BCG may be given once IPT has been completed and HIV testing is negative

BCG complications

- Infants with HIV may rarely develop severe localized or systemic BCG infection
 - This usually occurs as a presentation of IRIS shortly after ART initiation
 - Signs and symptoms include:
 - Abscess or ulceration at the vaccination site
 - Lymphadenitis in the axilla, supraclavicular area, and neck on the same side as BCG vaccination
 - Disseminated BCG
 - Bone infection
 - Erythema nodosum, iritis, or lupus vulgaris
 - Mild localized infection does not require treatment
 - Severe localized infection or abscess should be drained and systemic anti-BCG therapy given
 - Investigate disseminated BCG with chest x-ray, gastric aspirates, and abdominal ultrasound as indicated by symptoms
 - Treatment of proven disseminated BCG is 6 months of RHE, which should be given by an expert in TB treatment
 - Without culture it may be difficult to distinguish disseminated BCG from local BCG with severe TB. Consider a regimen of 2RHZE/4RHE to treat both infections if the diagnosis is uncertain.

10. NEUROLOGIC MANIFESTATIONS IN HIV-INFECTED CHILDREN

Key points

- Central nervous system (CNS) abnormalities are common in children with HIV
- HIV encephalopathy results from direct invasion of the CNS by HIV and presents as developmental delay, inadequate growth of head circumference, and/or motor abnormalities
- HIV encephalopathy should be treated with ART
- Seizure in patients with HIV may indicate CNS infection or malignancy and should be evaluated with brain imaging and CSF analysis
- Patients with HIV and severe immunosuppression are at high risk of CNS opportunistic infection and CNS lymphoma
- Cryptococcal meningitis is more common in adults than children, but is readily diagnosed by CSF analysis
- Children with ring-enhancing brain lesions should receive empiric treatment for toxoplasmosis and/or tuberculosis; if no improvement occurs within 14 days, CNS lymphoma should be suspected.

Overview

The nervous system is a frequent target of HIV infection, and the consequences of nervous-system involvement in HIV infection are serious. Nervous system involvement typically occurs in conjunction with profound immunosuppression, but may be the first evidence of HIV infection in some children. These abnormalities are a result of direct effects of HIV virus on the brain and nervous tissue, invasion of the CNS by opportunistic infections, or HIV-associated CNS malignancy.

Neurologic disorders in children with HIV are varied and include:

- encephalopathy
- meningitis and meningoencephalitis
- peripheral neuropathy
- myelopathy (disorders of the spinal cord)
- focal cerebral mass lesions due to infection or malignancy
- cerebral vasculitis

HIV Encephalopathy

Children infected with HIV at a young age are infected at a time when the brain is in its most important stages of development. Failure to achieve age-related developmental milestones is often the first evidence of HIV encephalopathy in infants, and may lead to permanent disability if not recognized early and treated aggressively with ART. For this reason, it is critical to perform developmental assessment and measure head circumference at every visit in HIV-exposed infants.

Epidemiology

Encephalopathy is a common and severe complication of HIV infection in children that has been reported to occur in over 20% of perinatally HIV-infected children with a median age at diagnosis of approximately 1 ½ years.

Diagnosis

Diagnosis is clinical and depends on the presence of two or more of the following for at least 2 months:

- Failure to attain or loss of developmental milestones or loss of intellectual ability
- Impaired brain growth or acquired microcephaly
- Acquired symmetrical motor deficit manifested by two or more of the following: paresis, pathologic reflexes, ataxia, or gait disturbances
- Cerebrospinal fluid is normal or has non-specific findings and CT scan shows diffuse brain atrophy.

Seizures may occur in children with HIV encephalopathy. Any child with HIV and seizure or focal neurologic deficit should receive CT scanning of the brain with contrast followed by CSF analysis to exclude CNS lymphoma, toxoplasmosis, tuberculosis, and cryptococcal meningitis before determining that a child has HIV encephalopathy. See figures 7 and 8.

Treatment

HIV encephalopathy is a stage 4 condition and should be treated with immediate antiretroviral therapy. Many children with encephalopathy will continue to have mild neurocognitive deficits even after successful provision of ART. The most common complication is spasticity of the lower extremities. Physical therapy, stretching exercises, bracing, and other devices may be necessary to preserve flexibility and ability to walk and achieve independence.

Prevention

Detection of HIV during pregnancy, provision of PMTCT, and early infant diagnosis and treatment are the primary prevention of HIV encephalopathy in children.

Seizures

Seizures are a sign of disordered electrical activity in the brain, and may be a result of high fever, epilepsy, or opportunistic infection/malignancy. Causes of seizure in patients with HIV are listed below:

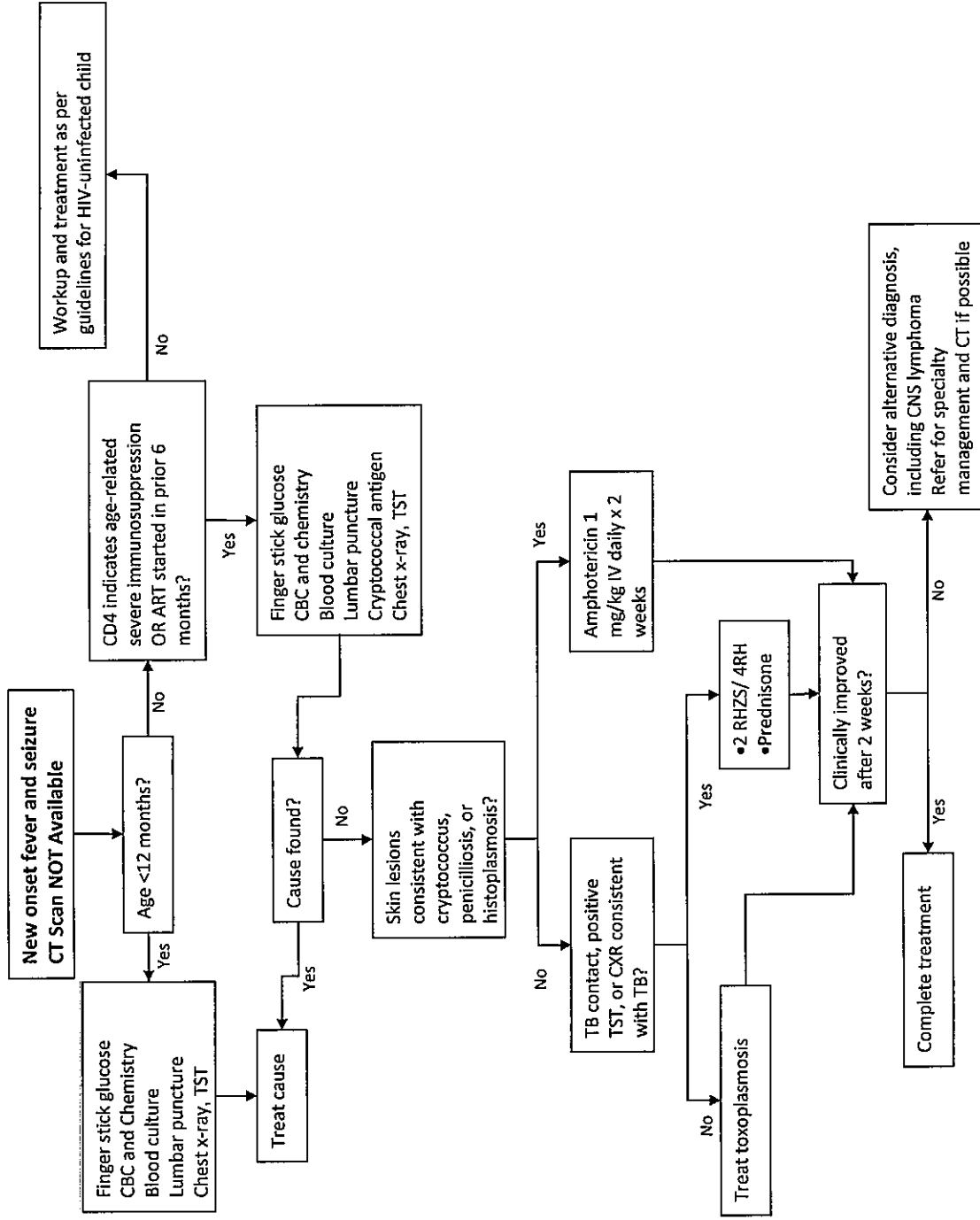
- Space-occupying lesions, including toxoplasmosis, tuberculoma, fungal infection, and lymphoma
- Meningitis or meningoencephalitis (cryptococcal, TB, bacterial, viral)
- Cerebral malaria
- Febrile convulsions (age 6 months – 5 years)
- Metabolic disturbances (e.g. hypoglycemia)
- Epilepsy

HIV infected children with severe immunosuppression and new-onset seizures require an extensive workup for CNS-related infection or malignancy, and should be evaluated in a referral center with expertise in this situation.

See Figures 6 and 7 for the evaluation of new seizures in children with HIV. New focal neurologic deficit and fever should be evaluated using the same algorithms.

Many anti-epileptic agents interact with ARVs, which may result in either abnormally low or high serum concentrations of the anti-seizure drug. Valproate is the preferred agent in children with seizures who are receiving ART.

Figure 5: Workup of seizure and fever when CT scan is NOT available*



* Use fluconazole 12 mg/kg if amphotericin B is not available

Infections of the Central Nervous System (CNS)

Infections of the CNS are common in HIV-infected children. As immunosuppression becomes more severe, the likelihood of an unusual opportunistic infection such as *Cryptococcus* or *Toxoplasma* increases. Most children over 12 months of age with CNS infection will present with fever and signs of either meningitis, focal neurologic deficit, altered mental status, and/or seizure. New onset neurologic symptoms in an HIV-infected child with severe immunosuppression are often life threatening, and should be considered an emergency requiring thorough evaluation as outlined below.

Bacterial meningitis

- The presentation of bacterial meningitis in HIV infected infants and children is similar to that in HIV uninfected patients, and should be diagnosed and treated in accordance with the *National Clinical and Therapeutic Guidelines for Referral Hospitals*.
- Children under 12 months of age or with severe immunosuppression may have more non-specific presentations with minimal meningismus.
- Bacterial meningitis should be suspected in any febrile HIV patient with either headache, meningismus, vision-changes, or altered mental status.
- Cerebral malaria should be considered in regions where malaria is present
- Early therapy improves mortality; do not delay antibiotics and/or anti-malarials if LP cannot be urgently performed

Cryptococcal meningitis

- *Cryptococcus neoformans* is the most common life-threatening fungal infection in patients with AIDS. It occurs most often in HIV-positive adults with CD4 <100, but is occasionally seen in children over 6 years of age.
- Fever and headache are the usual initial symptoms; neck stiffness, cranial nerve palsy, and altered mental status are late findings.
- Symptoms may be present for many weeks before dramatically worsening.
- CT scans are usually normal in patients with cryptococcal meningitis.
- Consider the diagnosis even in children receiving fluconazole prophylaxis.

Evaluation

- All children suspected of cryptococcal meningitis require the following:
 - CBC, chemistry, LFT
 - Blood culture
 - CSF evaluation for:
 - Opening pressure
 - CSF Gram stain and culture
 - India (Chinese) ink stain
 - Cryptococcal antigen (where available)
 - Ophthalmologic exam
 - Chest xray
 - If lumbar puncture fails, cryptococcal antigen testing of the blood

See Table 21 for typical CSF findings in cryptococcal meningitis.

Treatment:

Induction therapy

- Amphotericin B, 1mg/kg/d IV diluted in 5% glucose infused by slow drip over 4 hrs x 2 weeks, followed by fluconazole consolidation therapy
 - Pre-emptive fluids to minimise renal toxicity¹
 - If creatinine doubles, decrease dose to 0.7 mg/kg/day
 - If creatinine continues to rise despite lower dose, change to fluconazole 12 mg/kg/day
 - If amphotericin B not available, initiate treatment with fluconazole 12 mg/kg/day
- If opening pressure during initial lumbar puncture is >20 cm CSF:
 - Remove CSF until pressure is reduced to below 20 cm *or* to 50% of initial opening pressure, whichever is higher
 - Repeat daily lumbar puncture and remove fluid as above until opening pressure remains below 20 cm CSF
 - Do NOT use steroids or diuretics to decrease intracranial pressure
 - Consider delaying ART initiation until after induction therapy is complete in children with elevated intracranial pressure
- Where culture is available, repeat lumbar puncture on day 14 to ensure CSF is sterile prior to stopping amphotericin B

Consolidation therapy

- Fluconazole 10-12 mg/kg x 8 weeks, *followed by*
- Secondary prophylaxis with fluconazole 6mg/kg/day (maximum 200mg), continued until age ≥5 years and CD4 >100 cells/mm³ for >6 months on adherent ART

Primary Prophylaxis:

- See Chapter 1 for guidelines on fluconazole primary prophylaxis.

Tuberculous meningitis

(see section on TB)

¹ One litre of normal saline solution with one ampoule (20 mmol) of KCL at 10-15 ml/ kg over 2-4 hours before each controlled infusion of amphotericin B (other intravenous rehydration solutions that contain potassium can be used eg. Darrow's or Ringer's Lactate solutions)

Monitor :

- Serum potassium and creatinine (baseline and twice weekly), especially in the second week of amphotericin B administration.
- Haemoglobin (baseline and weekly)
- Daily weight, input/output
- hypokalaemia remains uncorrected, double magnesium oral supplementation

If creatinine increases by >2 fold from baseline value, either temporary omission of an amphotericin B dose, or increase pre-hydration to one litre 8 hourly. Once improved, restart at 0.7 mg/kg/day and consider alternate day amphotericin B. If creatinine remains elevated, discontinue amphotericin and continue with fluconazole at 1200mg/day. Monitor creatinine daily.

From: WHO Rapid advice: diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. December 2011

Table 12 CSF Findings in HIV-infected patients with CNS disease

Disease	Appearance	Opening Pressure	WBC/mm ³	Protein	Glucose	Microscopy
TB meningitis	Clear or slightly yellow	Increased	25-1000 Lym>PMN	0.5 – 5 g/L	10-45 mmol/L	AFB (rarely positive)
Cryptococcal meningitis	Clear or slightly yellow	Increased	<800 Lym>PMN	Increased but <5 g/L	Slightly decreased	India Ink+ (90%) Crypt Ag+ (98%)
Bacterial Meningitis	Cloudy or purulent	Increased	25-10,000 PMNs	0.5-15g/L	0-45 mmol/L	Bacteria on gram stain 60-90% sensitivity
Viral Meningitis	Clear	Normal	20-300 Lym>PMN	0.5 – 1.5 g/L	Normal	Negative
Toxoplasmosis	Normal	Increased	Normal	Normal or increased	Normal	Normal
HIV encephalopathy	Normal	Normal	<50, Lym>PMN	Increased but <2 g/L	Normal	Normal

Adapted from *Clinical HIV/AIDS Care Guideline for resource poor settings, MSF, 2006*

Toxoplasma encephalitis

Epidemiology

- Parasitic infection of the brain caused by *Toxoplasma gondii*
- The frequency of toxoplasmosis in Southeast Asia appears to be lower than many other regions in the world
- Toxoplasmosis is probably rare in Cambodia but is difficult to diagnose
- Children with possible toxoplasmosis should be empirically treated until they improve or another diagnosis is confirmed

Clinical manifestations

- Cerebral toxoplasmosis evolves quickly with the time from onset to presentation usually a few days
- Most often the disease presents with:
 - focal neurologic dysfunction, *and/or*
 - new seizures, *plus*
 - fever and headache or altered level of alertness

Diagnosis:

- CT scan (if available) shows the presence of mass lesions, which demonstrate ring enhancement after injection of contrast material. Ring-enhancing lesions in patients with HIV are usually either toxoplasmosis, CNS lymphoma or TB.
- Ophthalmologic exam should be performed; toxoplasmosis lesions are white exudates on the retina with minimal associated hemorrhage
- Definitive diagnosis of ring-enhancing brain lesions requires biopsy, which is not widely available
- Patients with HIV and ring-enhancing brain lesions should receive empiric therapy for toxoplasmosis unless another diagnosis has been definitively established
- If clinical or radiographic improvement is not seen within 14 days of starting treatment, the diagnosis of toxoplasmosis is unlikely

Treatment:

- Preferred (where available):
 - Pyrimethamine loading dose 2mg/kg/day (max 50mg) for 3 days then maintenance 1 mg/kg/d (max 25 mg), plus

- Sulfadiazine 100 mg/kg/day divided qid, plus
- Folinic acid 5-20 mg 3 times weekly
- All for 6 weeks
- 2nd line therapy:
 - High dose cotrimoxazole (10-15/50-75 mg/kg daily) for 6 weeks, then cotrimoxazole secondary prophylaxis as below
- Consider the addition of dexamethasone 0.6mg/kg/day for clinical evidence of mass effect
 - Taper steroids over several weeks as tolerated

Primary prophylaxis:

- Cotrimoxazole 6/30 mg/kg/day per the indications in Chapter 1.

Secondary prophylaxis

- In patients with prior toxoplasmosis, cotrimoxazole may be discontinued when age ≥ 5 years *and* CD4 >350 cells/mm³ for >6 months on adherent ART

Viral encephalitis

Viral encephalitis may be caused by a wide-variety of agents, including CMV, HSV, enteroviruses, and Japanese encephalitis virus. Encephalitis is defined as evidence of inflammation of the brain or meninges by CSF analysis or MRI imaging *and* alteration in mood, personality, or mental status. Suspect viral meningitis in patient with:

- Fever
- Altered personality or level of consciousness
- Lumbar puncture with mild lymphocytic pleocytosis and protein elevation with normal glucose

Further evaluation

- If retinal exam reveals evidence of CMV retinitis, CMV encephalitis is likely
 - CMV encephalitis occurs with severe immunosuppression
 - Treatment for CMV encephalitis (IV ganciclovir and foscarnet) is not widely available in Cambodia
 - Refer to a center with experience treating CMV disease in children with HIV
- Children with suspected viral encephalitis should receive acyclovir 10 mg/kg IV every 8 hours for 21 days (where available) for treatment of HSV and varicella unless an alternative diagnosis is confirmed
 - Neonates should receive 20 mg/kg IV every 8 hours
 - Where PCR is available, treatment may be discontinued earlier if negative
 - HSV lesions are rarely present in children with HSV encephalitis but provide supportive evidence when seen
- CT scan will be normal in patients with viral encephalitis
 - MRI is necessary to see the inflammation caused by these agents but not widely available

Stroke

Strokes are occasionally seen in children with advanced HIV disease or HIV encephalopathy. HIV produces inflammation of blood vessels, including those in the brain. Arteriovenous malformations (AVMs) are known to increase the risk of stroke in the context of HIV infection. Children with HIV and evidence of acute cerebral infarct should receive the following:

- CT scan of the brain with and without contrast, whenever possible
- CBC, chemistry, LFTs, coagulation studies

- Blood culture to rule-out endocarditis or bacteremic/fungemic meningitis
- Echocardiogram to rule-out ASD or endocardial source of emboli such as valvular vegetation or mitral stenosis resulting in left atrial clot
- Chest xray to search for evidence of tuberculosis
- Lumbar puncture if fever or if above workup negative
- When CT imaging is not available, children with severe immunosuppression should receive empiric treatment as outlined in Figure 7 unless an alternative diagnosis is confirmed

Peripheral neuropathy

- Causes of peripheral neuropathy in children with HIV infection include:
 - HIV-related autoimmune effects
 - Vitamin deficiencies
 - CMV-related polyradiculoneuropathy
- Symptoms of peripheral neuropathy range from mild numbness or tingling to debilitating pain.
- Children with peripheral neuropathy should be provided with multivitamin supplementation and ART.
- Children receiving d4T should be changed to AZT when neuropathy is noted, as severe medication-related neuropathy is not always reversible.
- Children receiving 2nd line ART with ddi should be referred to an expert for ART adjustment.

11. GASTROINTESTINAL MANIFESTATIONS IN HIV-INFECTED CHILDREN

Key Points

- Patients with diarrhea or vomiting should be monitored carefully for signs and symptoms of dehydration
- Oral-rehydration fluids should be used when possible for patients with dehydration
- Acute watery diarrhea should be treated with supportive measures
- Bloody diarrhea (dysentery) requires empiric antibiotic therapy
- All children with acute diarrhea should receive 10 – 14 days of zinc supplementation
- Chronic diarrhea may be due to opportunistic infection, HIV-enteropathy, vitamin deficiency, or osmotic causes and carries a high mortality
- ART should be initiated in all HIV-infected children with chronic diarrhea

Diagnosis and treatment of dehydration

Acute gastroenteritis usually presents with fever, nausea, vomiting, and diarrhea. Mortality is high in HIV-infected patients, primarily related to severe volume loss.

Hydration status can be accurately assessed by physical examination, and should be immediately determined and corrected in children presenting with these symptoms. Hydration status can be classified as follows:

Table 13. Classification of dehydration

	Mild dehydration	Moderate dehydration	Severe dehydration
Older child	3% (30 ml/kg)	6% (60 ml/kg)	9% (90 ml/kg)
Infant	5% (50 ml/kg)	10% (100 ml/kg)	15% (150 ml/kg)
Skin turgor	Normal	Tenting	None
Skin (touch)	Normal	Dry	Clammy
Buccal mucosal/lips	Moist	Dry	Parched/cracked
Eyes	Normal	Deep set	Sunken
Tears	Present	Reduced	Absent
Fontanelle	Flat	Soft	Sunken
CNS	Consolable	Irritable	Lethargic/obtunded
Pulse rate	Normal	Slightly increased	Increased
Pulse quality	Normal	Weak	Feeble/impalpable
Blood pressure	Normal	Normal	Low
Capillary refill	Normal	~2 seconds	~3 seconds
Urine output	Normal	decreased	Anuric

Adapted from Johns Hopkins Hospital's The Harriet Lane Handbook (2002). Clinical observation in Dehydration.

Once the degree of volume depletion has been determined, replacement hydration should occur in accordance with pre-existing IMCI guidelines as outlined below.

Table 14. Rehydration

Indication	Route	Fluid choice	Dose*
Plan A:	Oral	ORS (oral rehydration)	Children <2 years: 50-100 ml after each loose stool

Prevention of dehydration in the setting of diarrhea.		salts) solution+	Children 2-10 years: 100-200 ml after each loose stool. Children > 10 years and adults: as much fluid as desired after each loose stool.
No current dehydration			
Plan B: Mild to moderate dehydration	Oral	ORS solution	Children < 2 years: 5 ml every 1-2 minutes by spoon. Total volume over 4 hours should equal about 75 ml x weight (kg) Children > 2 years and adults: 5-10 ml, every 5-10 minutes, increase amount as tolerated. Total volume over 4 hours should be equal about 75 ml x weight (kg)
Plan C: Severe dehydration	Intravenous	LR, Normal saline (0.9% NaCl)	Infants: 30 ml/kg for 1 hour+, then 70 ml/kg over 5 hours (total of 100 ml/kg over 6 hours) Older children and adults: 30 ml/kg over 30m, then 70ml/kg over 2.5 hours (total of 100 ml/kg over 3 hours)
Plan C: Severe dehydration	Nasogastric (only if IV therapy is not available)	ORS	20 ml/kg/h* for 6 hours (total of 120 ml/kg)
Plan C: Severe dehydration	Oral (only if alert and when IV/NG are not possible)	ORS	Children < 2 years: 5 ml/minute by spoon. Children > 2 years and adults: 20 ml/kg/h for 6 hours (total of 120 ml/kg)

*Decrease the rate if there is vomiting or abdominal distension

+Repeat once if the radial pulse is still very weak or not detectable

Acute Diarrhea

Diarrhea is defined as an excessive loss of fluid and electrolytes in the stool resulting in three or more loose stools in a 24-hour period. Acute diarrhea persists for up to 14 days, while chronic or persistent diarrhea continues for two weeks or longer. The principles of management of acute diarrhea in HIV-infected children are the same as in other children and should follow IMCI guidelines.

Children should be admitted to inpatient care if:

- <1 month of age
- Malnourished
- Convulsions
- Persistent vomiting
- Very painful abdomen
- Bloody diarrhea and <12 months of age

- Severe dehydration

Watery diarrhea

- Acute watery diarrhea may be due to the following:
 - Rotavirus, norwalk virus, adenoviruses, enteroviruses
 - Enterotoxigenic *E. coli*
 - *Vibrio cholerae* (during an outbreak)
- Acute watery diarrhea *should not* routinely be treated with antibiotics
- **Provide children with 20 mg/day of elemental zinc supplementation for 10-14 days during all acute diarrheal episodes**
 - Give 10 mg/day elemental zinc for infants under 6 months old
- Provide mother or caregiver with oral rehydration salts for home use until diarrhea stops
- Follow-up in 2-3 days, or earlier if symptoms worsen

Bloody diarrhea

- Dysentery, or bloody diarrhea, may be caused by:
 - Shigella
 - Typhoid and non-typhoidal salmonella
 - Yersinia, campylobacter, enterohemorrhagic and enteroinvasive *E. coli*, and the parasite *Entamoeba histolytica*.
- Dysentery may be accompanied by systemic symptoms such as fever and an elevated white blood cell count
- Send stool for microscopy and culture, where available
 - If an organism is identified, ensure antibiotic regimen selected below is appropriate when culture result returns
- Provide antibiotics as follows:
 - Ciprofloxacin 15 mg/kg PO q 12 hours x 3 days, *OR*
 - Azithromycin 10 mg/kg PO daily x 3 days, *OR*
 - Ceftriaxone 50 mg/kg IV daily (hospitalized patients)
- Provide children with 20 mg/day of elemental zinc supplementation for 10-14 days during all acute diarrheal episodes
 - Give 10 mg/day elemental zinc for infants under 6 months old
- Provide mother or caregiver oral rehydration salts for home use until diarrhea stops
- Follow up in 2-3 days, or earlier if symptoms worsen

Chronic diarrhea

- Chronic diarrhea that persists for >28 days carries a 10-fold increased risk of mortality in HIV-infected patients
- Start ART as soon as possible if not currently receiving treatment
- Parasites such as giardia, cryptosporidium, and isospora all can cause chronic diarrhea in HIV-infected patients
- Other causes of chronic diarrhea may include:
 - HIV enteropathy
 - Vitamin deficiencies (zinc, niacin)
 - MAC, CMV, or TB infection of the intestine
 - Rarely, GI lymphoma or Kaposi's sarcoma
- Send stool for microscopy (for ova and parasites) and culture
 - If an organism is identified, treat as per Table 24 below.

- Consider empiric treatment for giardia with metronidazole 7.5 mg/kg/dose q 8 hours x 10 days
- Provide children with 20 mg/day of zinc supplementation for 10-14 days
 - 10 mg/day for infants under 6 months old
- Give an age-appropriate dose of vitamin A, unless given in prior 1 month
- If malnourished, provide multivitamin supplement daily
- Provide mother or caregiver oral rehydration salts for home use until diarrhea stops
- Figure 8 outlines the approach to an HIV infected child with chronic diarrhea

Figure 7: Approach to the child with chronic diarrhea

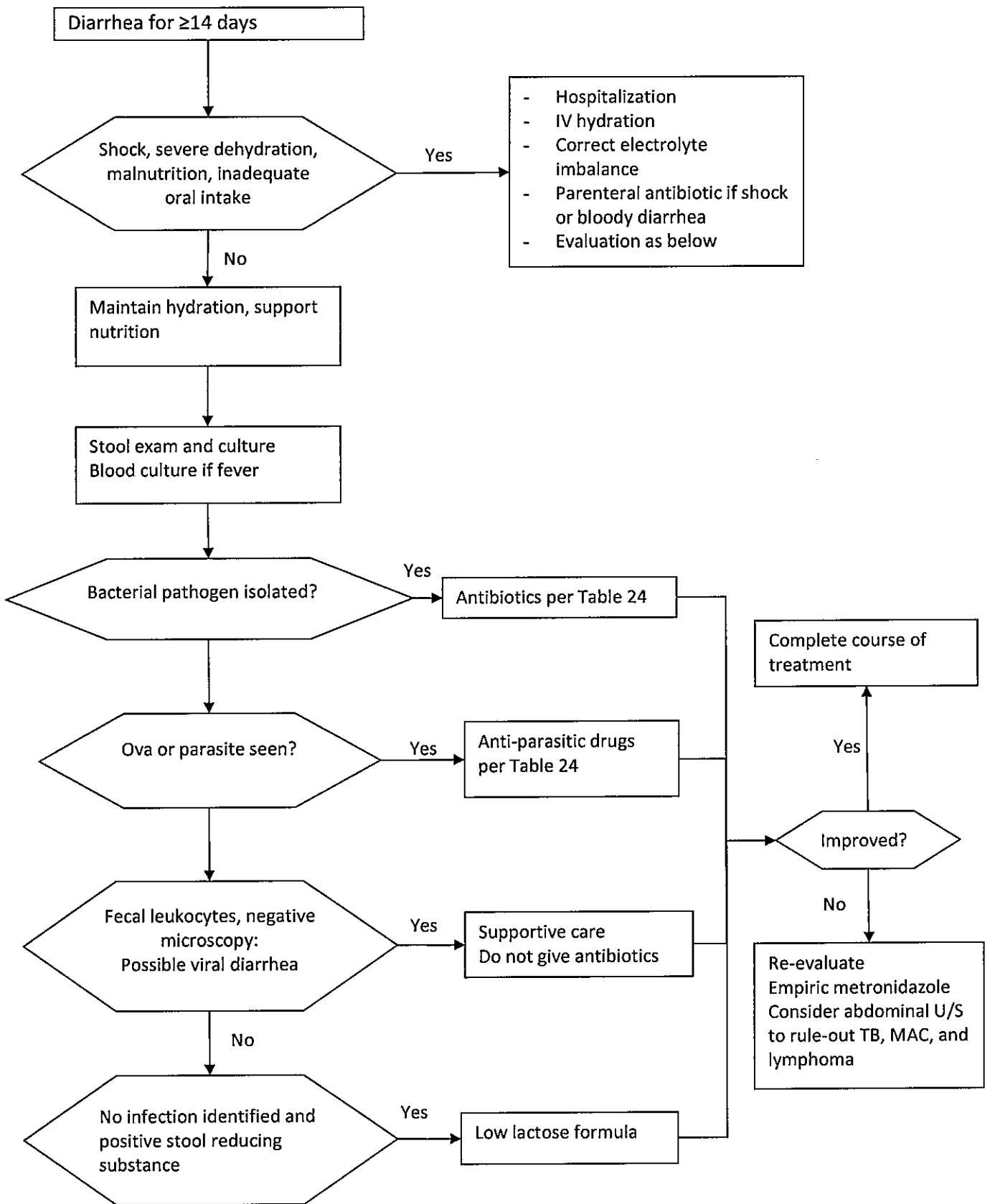


Table 15. Treatment of diarrhea

Etiology	Treatment
<u>Bacteria:</u>	
<i>Salmonella</i> (non-typhoidal)	Ciprofloxacin 15mg/kg PO twice daily for 3-7 days
<i>Salmonella typhi</i>	Ceftriaxone 50-75mg/kg OD, IV for 7 days Or Ciprofloxacin for 15mg/kg PO BID for 7 days
<i>Shigella</i>	Ciprofloxacin 15mg/kg PO BID for 3 days
<i>Escherichia coli</i>	No antibiotic
<i>Campylobacter jejuni</i>	Erythromycin 10mg/kg PO QID for 5 days Or Ciprofloxacin 15 mg/kg PO BID for 5 days
Cholera	Erythromycin 20mg/kg/dose, 4 times daily for 3 days
<i>Mycobacterium avium</i> Complex	Clarithromycin 15mg/kg/day Bid Or Azithromycin 10mg/kg OD PLUS Ethambutol 15-25 mg/kg OD PLUS Rifabutin 10-20mg/kg OD Or Ciprofloxacin 20-30mg/kg OD
Tuberculosis	2RHZE/4RH
<i>Yersinia enterocolitica</i>	TMP-SMZ (TMP 8mg/kg/day) divided BID for 5 days.
<u>Protozoa:</u>	
<i>Cryptosporidium</i>	No therapy proven efficacious Spontaneous resolution may occur after ART Azithromycin 10mg/kg OD for 1 day, FOLLOWED BY 5 mg/kg OD for 9 days may be useful If no response, azithromycin 10mg/kg OD for 2 weeks may be tried
<i>Isospora belli</i>	TMP-SMZ (TMP 5mg/kg/dose) qid for 10 days then bid for 3 weeks.
<i>Giardia lamblia</i>	Metronidazole 20mg/kg/day PO divided tid for 10 days
<i>Entamoeba histolytica</i>	Metronidazole 35-50mg/kg/day PO divided tid for 10 days
<i>Microsporidia</i>	Albendazole 20mg/kg/day bid x 4 weeks
<i>Cyclospora</i>	TMP-SMZ (TMP 5mg/kg/dose) qid for 10 days then bid for 3 weeks

Viral Hepatitis

Signs and symptoms of acute viral hepatitis may include:

- Nausea and vomiting
- Loss of appetite
- Right upper quadrant abdominal pain
- Jaundice

- Pruritus
- Dark urine
- Pale grey stools

Any of the hepatitis viruses can cause acute symptomatic hepatitis, although hepatitis A more commonly causes acute disease than hepatitis B or C. Acute viral hepatitis is difficult to distinguish from severe medication-related hepatitis, and children on hepatotoxic drugs may need to have medications held briefly while a diagnosis is pursued.

HIV-infected children with suspected acute viral hepatitis should receive the following:

- CBC, chemistry, LFTs, and prothrombin time
- Blood culture if fever is present
- Discontinuation of any hepatotoxic drugs
- Testing for hepatitis B surface antigen, hepatitis A IgM, and hepatitis C antibodies
- Ultrasound of the right upper quadrant if severe pain, high fever, or continued upward trending of serum transaminase levels
- Follow the usual algorithms for restarting hepatotoxic medications once serum transaminase levels fall

Hepatitis A and E viruses:

- Spread by oral-fecal route, often through contaminated food
- Rarely may progress to fulminant liver failure
- Acute hepatitis A can be diagnosed by serum IgM antibody testing
- Symptoms usually persist for several weeks and gradually resolve with supportive care

Hepatitis B virus (HBV)

- Frequently acquired at the time of birth via mother-to-child transmission
- Horizontal transmission in early childhood accounts for a large number of infections
- Most children become chronic carriers and show no signs of infection for many years
- Acute flares of chronic hepatitis B can occur in mid-to-late childhood and be mistaken for acute infection
- Hepatitis B is now part of the routine vaccine schedule in Cambodia
- All children with HIV should receive screening for chronic hepatitis B at the time of diagnosis if available
- Adolescents ≥ 12 years of age with HBV-HIV coinfection should receive ART containing a tenofovir and lamivudine or emtricitabine backbone (see the *National Guidelines on the use of Pediatric Antiretroviral Therapy*)
- Children with chronic HBV should be monitored carefully for toxicity when hepatotoxic drugs are administered

Hepatitis C virus (HCV)

- Co-infection with HIV is common among IV drug abusers and men who have sex with men
- Perinatal transmission of hepatitis C is ~10% among women who are co-infected with HIV
- All HIV infected children should be screened for hepatitis C with hepatitis C antibody testing if available
- New drugs such as sofosbuvir have not yet been approved for use in children.
- **Therefore, HCV treatment is not recommended for HIV co-infected children at this time.**

- Children with chronic HCV should be monitored carefully for toxicity when hepatotoxic drugs are administered

12. OTHER SYSTEMIC OPPORTUNISTIC INFECTIONS

Key points

- Disseminated *Mycobacterium avium* complex occurs in children with severe immunosuppression and presents as non-specific fever, weight loss, anemia, and elevated liver enzymes
- Disseminated MAC and tuberculosis are often indistinguishable
- *Penicillium marneffe* is endemic in Southeast Asia and causes disseminated fungal infection in severely immunosuppressed hosts
- Characteristic skin lesions may indicate disseminated penicilliosis
- Histoplasmosis has been reported in Cambodia and causes disseminated infection with skin lesions similar to those of *Penicillium*
- Itraconazole is the azole of choice for treatment of penicilliosis and histoplasmosis
- CMV frequently causes retinitis in children with very low CD4 counts and may worsen rapidly when ART is initiated
- Children with CMV retinitis should receive intraocular or systemic ganciclovir to preserve vision while being immune-reconstituted on ART
- Annex D summarises common opportunistic infections occurring in children and management of these conditions

Disseminated *Mycobacterium avium* complex (MAC)

Epidemiology

M. avium and *M. Intracellulare* comprise the *Mycobacterium avium* complex. They are ubiquitous in the environment and disseminated infection results from recent infection rather than reactivation. It is thought to be rare in infants.

Disseminated MAC becomes more likely when the CD4 count falls below the following age-related thresholds:

- Children <12 months: <750 cells/mm³
- Children 12-24 months: <500 cells/mm³
- Children 2 – 5 years: <75 cells/mm³
- Children ≥6 years: <50 cells/mm³

Clinical presentation

- Respiratory symptoms are uncommon among HIV-infected children with disseminated MAC, and isolated pulmonary disease is rare.
- Persistent or recurrent fever
- Weight loss or failure to gain weight
- Sweats, fatigue
- Persistent diarrhea or recurrent abdominal pain
- Lymphadenopathy, hepatomegaly, and splenomegaly

Diagnosis

- Anemia, leukopenia, and thrombocytopenia often indicate bone-marrow infection
- Elevations in alkaline phosphatase and lactate dehydrogenase are common but non-specific.
- Identification in the stool may or may not indicate infection as MAC can colonise the epithelial lining of the GI tract without causing invasive disease

- Microscopy (without culture) does not differentiate between MAC and TB
- Definitive diagnosis requires isolation in mycobacterial culture from a sterile site, including blood, bone marrow, lymph node aspiration, tissue, or urine
- See annex E for workup of MAC and other systemic OIs

Treatment

- At least two drugs should be used to avoid emergence of resistance
 - Azithromycin 10mg/kg PO daily, or Clarithromycin 15 mg/kg PO bid *and*
 - Ethambutol 15 mg/kg PO daily, +/-
 - Rifampicin 15 mg/kg PO daily (use azithromycin if adding rifampicin)
- Ciprofloxacin or amikacin may be effective for cases failing to respond to standard therapy
- Treatment should be given for 12 months, followed by secondary prophylaxis
- TB and MAC appear very similar. In settings where TB culture is not available, treat tuberculosis first. In cases with poor improvement, empiric therapy for MAC should be considered, and azithromycin 10 mg/kg PO daily may be added to the TB regimen.
- ART should be started in all patients as soon as tolerated within 2 weeks of TB or MAC diagnosis.

Primary and Secondary Prophylaxis

- Based on available data, routine primary prophylaxis of MAC is not recommended at this time
- Children with a history of disseminated MAC should receive treatment for 12 months, followed by secondary prophylaxis with azithromycin 5 mg/kg PO daily and ethambutol 15 mg/kg PO daily
- Once established on ART and CD4 cell counts are greater than the thresholds listed above for >6 months, secondary prophylaxis may be discontinued

Penicilliosis

Epidemiology

- Penicilliosis is an invasive fungal disease cause by the organism *Penicillium marneffe* which is endemic in Southeast Asia
 - Highest prevalence in Northern Thailand
- CD4 counts in adults below 100 cells/mm³ increase the risk of infection; age related thresholds for children <5 years are not known

Clinical Manifestations

- Usually presents as disseminated disease with fever, anemia, weight loss, lymphadenopathy, pneumonia, and/or hepatosplenomegaly
- Papular, umbilicated or ulcerating skin lesions are common and may be mistaken for *Molluscum contagiosum* or *Cryptococcus* (See Annex C)
- CNS disease with brain abscess has been reported

Investigations

- Pancytopenia, elevated liver enzymes, and high alkaline phosphatase
- Nodular or cavitary lesions on chest xray, may be confused with TB
- Fungal identification from blood culture, skin lesions, lymph node, or bone marrow aspirate is definitive

Treatment

- Amphotericin B 0.7 mg/kg IV daily for at least 2 weeks, *followed by*
- Itraconazole 5 mg/kg PO twice daily for 10 weeks
 - Liquid formulation is preferred
- After treatment is complete, secondary prophylaxis should continue as below
- Fluconazole is minimally active against *Penicillium*; failure rates of 64% have been reported
 - Use amphotericin B until itraconazole can be procured
 - Fluconazole 8 mg/kg PO twice daily may be attempted until amphotericin B or itraconazole can be obtained

Secondary prophylaxis

- Itraconazole 5 mg/kg PO daily should be given until immune restoration occurs.
 - Efficacy of fluconazole prophylaxis is unknown, may be attempted at 6-12 mg/kg/day
- Secondary prophylaxis may be discontinued if:
 - >5 years of age
 - >12 weeks of antifungal treatment
 - Immunological restoration with CD4 >150 cells/mm³ after 6 months of adherent ART

Histoplasmosis

Epidemiology

- Histoplasmosis is caused by infection with the dimorphic fungus *Histoplasma capsulatum*
- CD4 counts in adults below 150 cells/mm³ increase the risk of histoplasmosis; age related thresholds for children <5 years are not well established
- The overall incidence of histoplasmosis in children has not been systematically examined but appeared to be low even in the pre-HAART era
- Histoplasmosis has been reported in Cambodia but appears to be rare

Clinical manifestations

- Acute pulmonary histoplasmosis:
 - Cough, fever, malaise, chills, myalgia, anorexia and chest pain
- Disseminated histoplasmosis:
 - Prolonged fever
 - Weight loss, failure to thrive
 - Hepatosplenomegaly, lymphadenopathy
 - Large oral ulcerations
 - Discrete fungating or umbilicated skin papules or masses
 - Respiratory symptoms with cough, respiratory distress

Investigations

- Pancytopenia, elevated transaminases, and very elevated LDH may be seen
- Chest xray may show miliary pattern similar to TB
- Isolation of the fungus using culture is diagnostic but rarely available
- Histopathologic identification of yeast forms in white blood cells and macrophages in Giemsa stained smears from blood, bone marrow or BAL

- Silver staining of tissue biopsies may reveal yeast forms

Treatment

- Amphotericin B 1 mg/kg/day IV for at least 2 weeks, *followed by*
- Fluconazole* 6-8 mg/kg daily x 12 months (maintenance phase)
- Children with Histoplasmosis meningitis:
 - Amphotericin B therapy should be continued 12-16 weeks followed by maintenance therapy.
- Non-hospitalized patients may be treated with fluconazole* 5-6 mg/kg twice daily without amphotericin B induction therapy

*Where available, itraconazole liquid (2-5 mg/kg PO twice daily) should replace fluconazole in the above treatment regimens due to improved potency and clinical outcomes.

Maintenance Phase:

- Fluconazole 6 mg/kg PO daily x 12 months
 - Itraconazole 2-5 mg PO twice daily should be used in place of fluconazole, where available
- Maintenance therapy can be stopped if:
 - >5 years of age
 - >12 months of antifungal treatment
 - Immunological restoration with CD4 >15% and >150 cells/mm³ after 6 months of adherent ART
- Maintenance therapy should be restarted in children with history of histoplasmosis if the CD4 count falls below the thresholds above

Cytomegalovirus (CMV) Infection

- A common virus which causes disease in advanced HIV infection
- Most commonly causes retinitis but can infect any organ
- May present as colitis, esophagitis, encephalitis, hepatitis, cholangitis, pneumonia, cutaneous ulcerations, or prolonged fever

Epidemiology

- Prior to the availability of ART, 20-30% of adult patients with CD4 <100 cells/mm³ could be expected to develop CMV retinitis over a one year period
- Rare in the ART-era
- Suspect in newly-diagnosed patients with visual abnormalities and very low CD4 counts, and in patients developing visual abnormalities soon after starting ART, when it can present as an IRIS reaction

Clinical Manifestations

- Most common presentation is as retinitis with visual "floaters," photophobia (light sensitivity), and visual field defects. Pain and redness of the eye are absent.
- Non-ocular presentations of CMV infection account for only about 20% of cases with symptoms dependent on organ system involved.

Diagnosis

- CMV retinitis can be detected on retinal exam as large white perivascular exudates with or without associated hemorrhage.

- Consider annual ophthalmologic screening in patients with CD4 cell counts below 100 cells/mm³
- Experienced ophthalmologists can distinguish CMV retinitis lesions from cotton-wool spots, toxoplasmosis, acute retinal necrosis, and progressive outer retinal necrosis. The latter two diseases are related to herpes viruses and should be treated with acyclovir.
- Diagnosis at other organ sites requires tissue biopsy and histopathologic identification of characteristic inclusions and positive immunoperoxidase staining.
- Diagnosis of CNS disease is made by PCR testing of CSF, where available. MRI scanning may show characteristic periventricular or sacral nerve root enhancement.

Treatment

- Treatment of CMV retinitis consists of intraocular ganciclovir administered by an ophthalmologist trained in intra-ocular injection. Children with CMV retinitis should be urgently referred to a specialist with experience treating CMV retinitis.
- Systemic therapy has the advantage of fewer relapses and prevention of infection in other organ systems but is not widely available.

Prevention

- Routine antiviral prophylaxis of CMV disease is not recommended
- Early initiation of ART and early detection of retinal lesions in children with CD4 cell counts <100 cells/mm³ should be attempted whenever possible

REFERENCES

Baylor International Pediatric AIDS Initiative, HIV curriculum for the health professional, 2007.

Bun Navy et al. The first reported cases of disseminated histoplasmosis in Cambodia, complicated by multiple opportunistic infections. *Southeast Asian J Trop Med Public Health*. 2005, 36:1272.

Centers for Disease Control and Prevention. Guidelines for Prevention and Treatment of Opportunistic Infections among HIV-Exposed and HIV-infected Children. *MMWR* 2009;58 (RR-11):1-166.

Crowe SM, Carlin JB, et al. Predictive value of CD4 lymphocyte numbers for the development of opportunistic infection and malignancies in HIV-infected persons. *JAIDS* 1991; 4:770-776.

Gallant JE, et al. Incidence and natural history of cytomegalovirus disease in patients with advanced immunodeficiency disease treated with Zidovudine. *J Infect Dis* 1992; 166: 1223-27.

Guidelines for the Management of HIV in Children. National Department of Health, South Africa. 2nd Edition, 2010.

Guidelines for HIV/AIDS Diagnosis and Treatment. Ministry of Health, Vietnam. 2009

Handbook on paediatric AIDS in Africa. African Network for the Care of Children Affected by AIDS. 2004.

Lynen, L et al. Clinical HIV/AIDS Care Guideline for Resource Poor Settings. *Medicins Sans Frontieres*, 2006.

Marais BJ, Graham SM, Cotton MF, Beyers N. Diagnostic and Management Challenges for Childhood Tuberculosis in the Era of HIV. *Journal of Infectious Diseases*, 2007, 196 (Suppl 1), S76-S85..

National Interim Guidelines for the Management of Acute Malnutrition
Cambodia December 2011

The PIH Guide to the Community-Based Treatment of HIV in Resource-Poor Settings. Partners In Health Program in Infectious Disease and Social Change, Harvard Medical School. Second Edition, 2006.

Wheat L. et al. Practice guidelines for the management of patients with histoplasmosis. *Infectious Diseases Society of America*. *Clin Infect Dis* 2007; 45:807–25.

World Health Organisation Guidance for national tuberculosis programmes on the management of tuberculosis in children 2nd edition 2014

World Health Organization. Guidelines on Cotrimoxazole Prophylaxis for HIV-related Infections among Children, Adolescents, and Adults: Recommendations for a public health approach. 2006.

World Health Organization. Pocket Book of Hospital Care for Children: Guidelines for the Management of Common Illnesses with Limited Resources, 2005.

WHO Rapid advice: diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children 2011

World Health Organization. TB/HIV: a clinical manual, 2004.

ANNEXES

Annex A: WHO Clinical Staging of HIV/AIDS for Children with Confirmed HIV Infection

Stage 1

- Asymptomatic
- Persistent generalized lymphadenopathy

Stage 2

- Unexplained* persistent hepatosplenomegaly
- Papular pruritic eruptions
- Extensive wart virus infection
- Extensive molluscum contagiosum
- Fungal nail infections
- Recurrent oral ulcerations
- Unexplained persistent parotid enlargement
- Lineal gingival erythema
- Herpes zoster
- Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis or tonsillitis)

Stage 3

- Unexplained* moderate malnutrition not adequately responding to standard therapy
- Unexplained* persistent diarrhoea (14 days or more)
- Unexplained* persistent fever (above 37.5°C intermittent or constant, for longer than one month)
- Persistent oral candidiasis (after first 6-8 weeks of life)
- Oral hairy leukoplakia
- Acute necrotizing ulcerative gingivitis or periodontitis
- Lymph node tuberculosis
- Pulmonary tuberculosis
- Severe recurrent bacterial pneumonia
- Symptomatic lymphoid interstitial pneumonitis
- Chronic HIV-associated lung disease including bronchiectasis
- Unexplained* anaemia (<8.g/dl), neutropaenia (<0.5 x 10⁹ per liter) and/or chronic thrombocytopaenia (<50 x 10⁹ per liter)

Stage 4

- Unexplained* severe wasting, stunting or severe malnutrition not responding to standard therapy
- Pneumocystis pneumonia
- Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection or meningitis but excluding pneumonia)

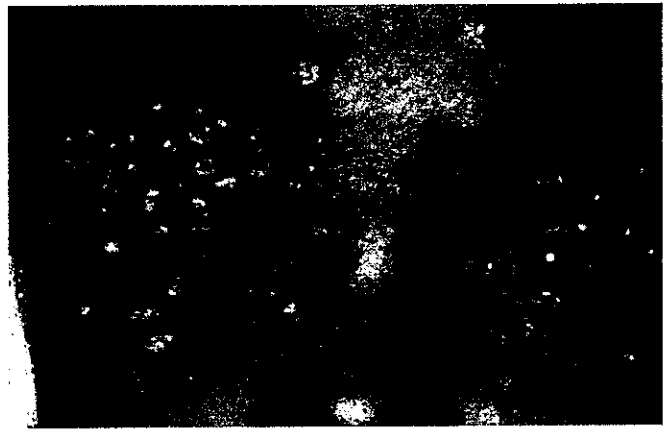
- Chronic herpes simplex infection (orolabial or cutaneous of more than one month's duration or visceral at any site)
- Extrapulmonary tuberculosis
- Kaposi sarcoma
- Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
- Central nervous system toxoplasmosis (after one month of life)
- HIV encephalopathy
- Cytomegalovirus infection: retinitis or cytomegalovirus infection affecting another organ, with onset at age older than one month
- Extrapulmonary cryptococcosis (including meningitis)
- Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis, penicilliosis)
- Chronic cryptosporidiosis
- Chronic isosporiasis
- Disseminated non-tuberculous mycobacterial infection
- Cerebral or B-cell non-Hodgkin lymphoma
- Progressive multifocal leukoencephalopathy
- Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

* - Unexplained refers to where the condition is not explained by other causes such as tuberculosis or cryptosporidiosis

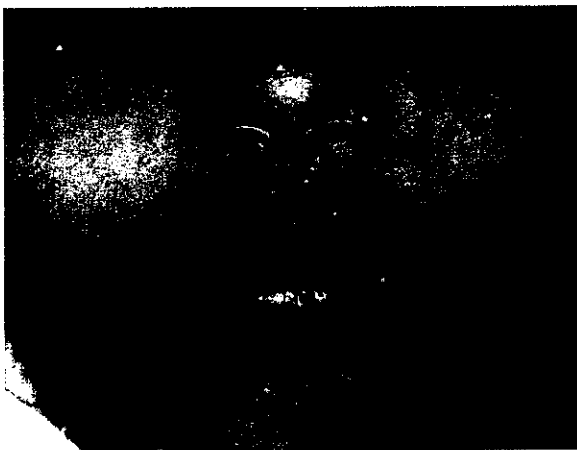
Annex B: Photos of Oral and Skin lesions in HIV-infected Children



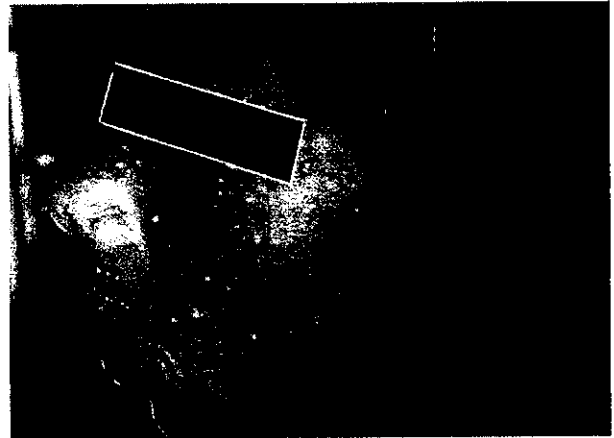
Pruritic Papular Eruption



Molluscum Contagiosum with Giant Molluscum



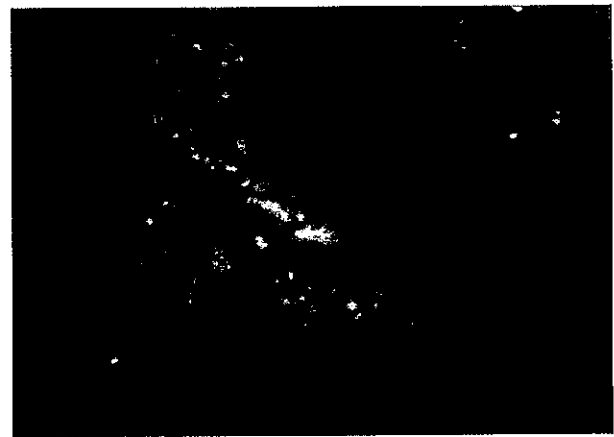
Cryptococcosis



Penicilliosis



Herpes Simplex Virus



Oral Human Papilloma Virus

Images courtesy of: AIDS Images Library
www.aidsimages.ch

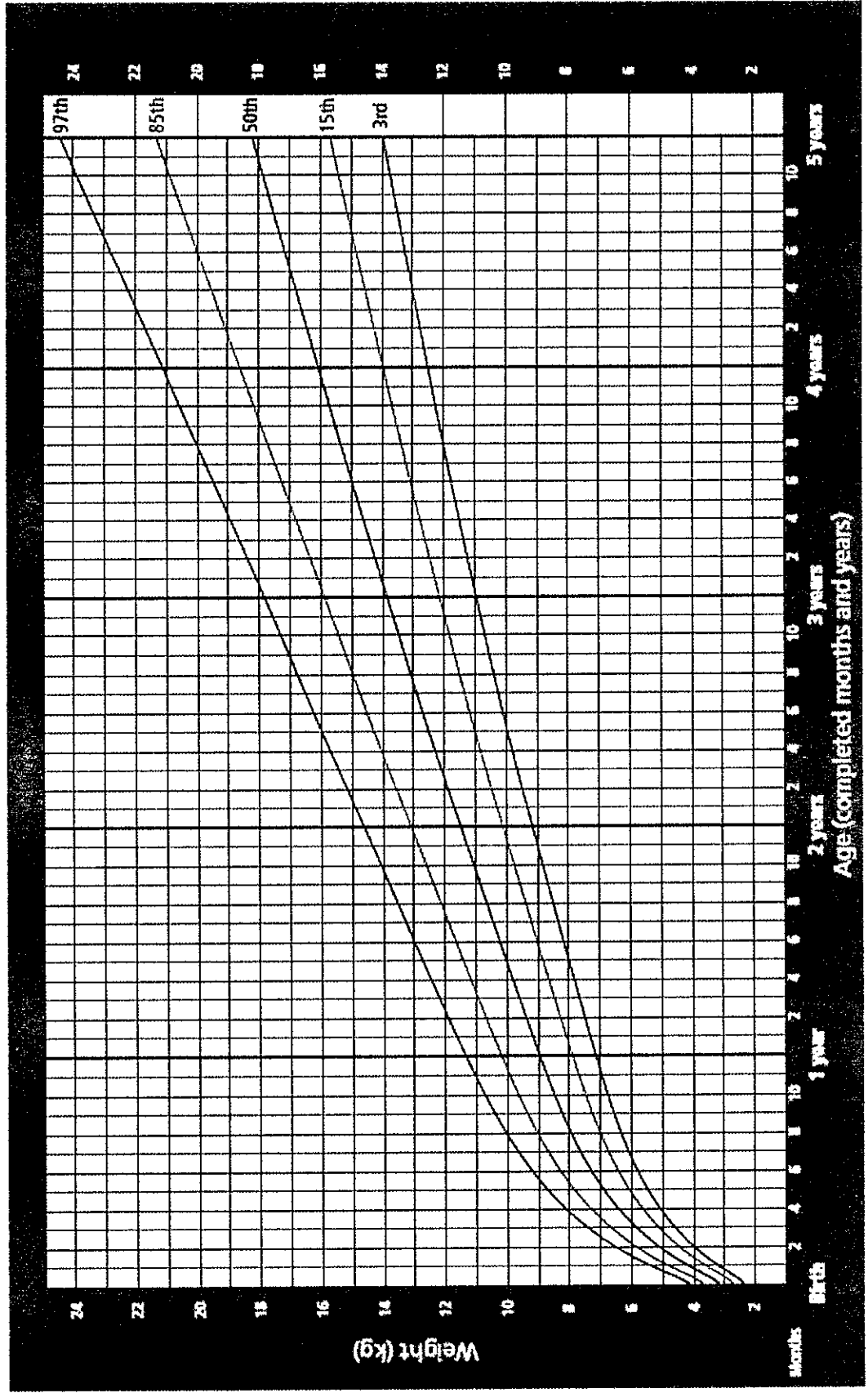
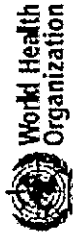
Annex C: WHO growth monitoring tables and charts

WHO Child Growth Standards 2006. Weight for Length (up to 87 cm)								
GIRLS				length (cm)	BOYS			
weight (kg)	weight (kg)	weight (kg)	weight (kg)		weight (kg)	weight (kg)	weight (kg)	weight (kg)
-3SD	-2SD	-1 SD	media n		media n	-1 SD	-2SD	-3 SD
3.1	3.4	3.7	4.0	53.0	4.0	3.7	3.4	3.1
3.3	3.6	3.9	4.3	54.0	4.3	3.9	3.6	3.3
3.5	3.8	4.2	4.5	55.0	4.5	4.2	3.8	3.6
3.7	4.0	4.4	4.8	56.0	4.8	4.4	4.1	3.8
3.9	4.3	4.6	5.1	57.0	5.1	4.7	4.3	4.0
4.1	4.5	4.9	5.4	58.0	5.4	5.0	4.6	4.3
4.3	4.7	5.1	5.6	59.0	5.7	5.3	4.8	4.5
4.5	4.9	5.4	5.9	60.0	6.0	5.5	5.1	4.7
4.7	5.1	5.6	6.1	61.0	6.3	5.8	5.3	4.9
4.9	5.3	5.8	6.4	62.0	6.5	6.0	5.6	5.1
5.1	5.5	6.0	6.6	63.0	6.8	6.2	5.8	5.3
5.3	5.7	6.3	6.9	64.0	7.0	6.5	6.0	5.5
5.5	5.9	6.5	7.1	65.0	7.3	6.7	6.2	5.7
5.6	6.1	6.7	7.3	66.0	7.5	6.9	6.4	5.9
5.8	6.3	6.9	7.5	67.0	7.7	7.1	6.6	6.1
6.0	6.5	7.1	7.7	68.0	8.0	7.3	6.8	6.3
6.1	6.7	7.3	8.0	69.0	8.2	7.6	7.0	6.5
6.3	6.9	7.5	8.2	70.0	8.4	7.8	7.2	6.6
6.5	7.0	7.7	8.4	71.0	8.6	8.0	7.4	6.8
6.6	7.2	7.8	8.6	72.0	8.9	8.2	7.6	7.0
6.8	7.4	8.0	8.8	73.0	9.1	8.4	7.7	7.2
6.9	7.5	8.2	9.0	74.0	9.3	8.6	7.9	7.3
7.1	7.7	8.4	9.1	75.0	9.5	8.8	8.1	7.5
7.2	7.8	8.5	9.3	76.0	9.7	8.9	8.3	7.6
7.4	8.0	8.7	9.5	77.0	9.9	9.1	8.4	7.8
7.5	8.2	8.9	9.7	78.0	10.1	9.3	8.6	7.9
7.7	8.3	9.1	9.9	79.0	10.3	9.5	8.7	8.1
7.8	8.5	9.2	10.1	80.0	10.4	9.6	8.9	8.2
8.0	8.7	9.4	10.3	81.0	10.6	9.8	9.1	8.4
8.1	8.8	9.6	10.5	82.0	10.8	10.0	9.2	8.5
8.3	9.0	9.8	10.7	83.0	11.0	10.2	9.4	8.7
8.5	9.2	10.1	11.0	84.0	11.3	10.4	9.6	8.9
8.7	9.4	10.3	11.2	85.0	11.5	10.6	9.8	9.1
8.9	9.7	10.5	11.5	86.0	11.7	10.8	10.0	9.3

WHO Child Growth Standards 2006 Weight for Height								
GIRLS				Height (cm)	BOYS			
weight (kg)	weight (kg)	weight (kg)	weight (kg)		weight (kg)	weight (kg)	weight (kg)	weight (kg)
-3 SD	-2 SD	-1 SD	media n		media n	-1 SD	-2 SD	-3 SD
9.2	10.0	10.9	11.9	87.0	12.2	11.2	10.4	9.6
9.4	10.2	11.1	12.1	88.0	12.4	11.5	10.6	9.8
9.6	10.4	11.4	12.4	89.0	12.6	11.7	10.8	10.0
9.8	10.6	11.6	12.6	90.0	12.9	11.9	11.0	10.2
10.0	10.9	11.8	12.9	91.0	13.1	12.1	11.2	10.4
10.2	11.1	12.0	13.1	92.0	13.4	12.3	11.4	10.6
10.4	11.3	12.3	13.4	93.0	13.6	12.6	11.6	10.8
10.6	11.5	12.5	13.6	94.0	13.8	12.8	11.8	11.0
10.8	11.7	12.7	13.9	95.0	14.1	13.0	12.0	11.1
10.9	11.9	12.9	14.1	96.0	14.3	13.2	12.2	11.3
11.1	12.1	13.2	14.4	97.0	14.6	13.4	12.4	11.5
11.3	12.3	13.4	14.7	98.0	14.8	13.7	12.6	11.7
11.5	12.5	13.7	14.9	99.0	15.0	13.9	12.9	11.9
11.7	12.8	13.9	15.2	100.0	15.2	14.2	13.1	12.1
12.0	13.0	14.2	15.5	101.0	15.5	14.4	13.3	12.3
12.2	13.3	14.5	15.8	102.0	15.8	14.7	13.6	12.5
12.4	13.5	14.7	16.1	103.0	16.1	14.9	13.8	12.8
12.6	13.8	15.0	16.4	104.0	16.4	15.2	14.0	13.0
12.9	14.0	15.3	16.8	105.0	16.7	15.5	14.3	13.2
13.1	14.3	15.6	17.1	106.0	17.0	15.8	14.5	13.4
13.4	14.6	15.9	17.5	107.0	17.3	16.1	14.8	13.7
13.7	14.9	16.3	17.8	108.0	17.7	16.4	15.1	13.9
13.9	15.2	16.6	18.2	109.0	18.0	16.7	15.3	14.1
14.2	15.5	17.0	18.6	110.0	18.5	17.0	15.6	14.4
14.5	15.8	17.3	19.0	111.0	18.9	17.3	15.9	14.6
14.8	16.2	17.7	19.4	112.0	19.2	17.6	16.2	14.9
15.1	16.5	18.0	19.8	113.0	19.6	18.0	16.5	15.2
15.4	16.8	18.4	20.2	114.0	20.0	18.3	16.8	15.4
15.7	17.2	18.8	20.7	115.0	20.4	18.6	17.1	15.7
16.0	17.5	19.2	21.1	116.0	20.8	19.0	17.4	16.0
16.3	17.8	19.6	21.5	117.0	21.2	19.3	17.7	16.2
16.6	18.2	19.9	22.0	118.0	21.6	19.7	18.0	16.5
16.9	18.5	20.3	22.4	119.0	22.0	20.0	18.3	16.8
17.3	18.9	20.7	22.8	120.0	22.4	20.4	18.6	17.1

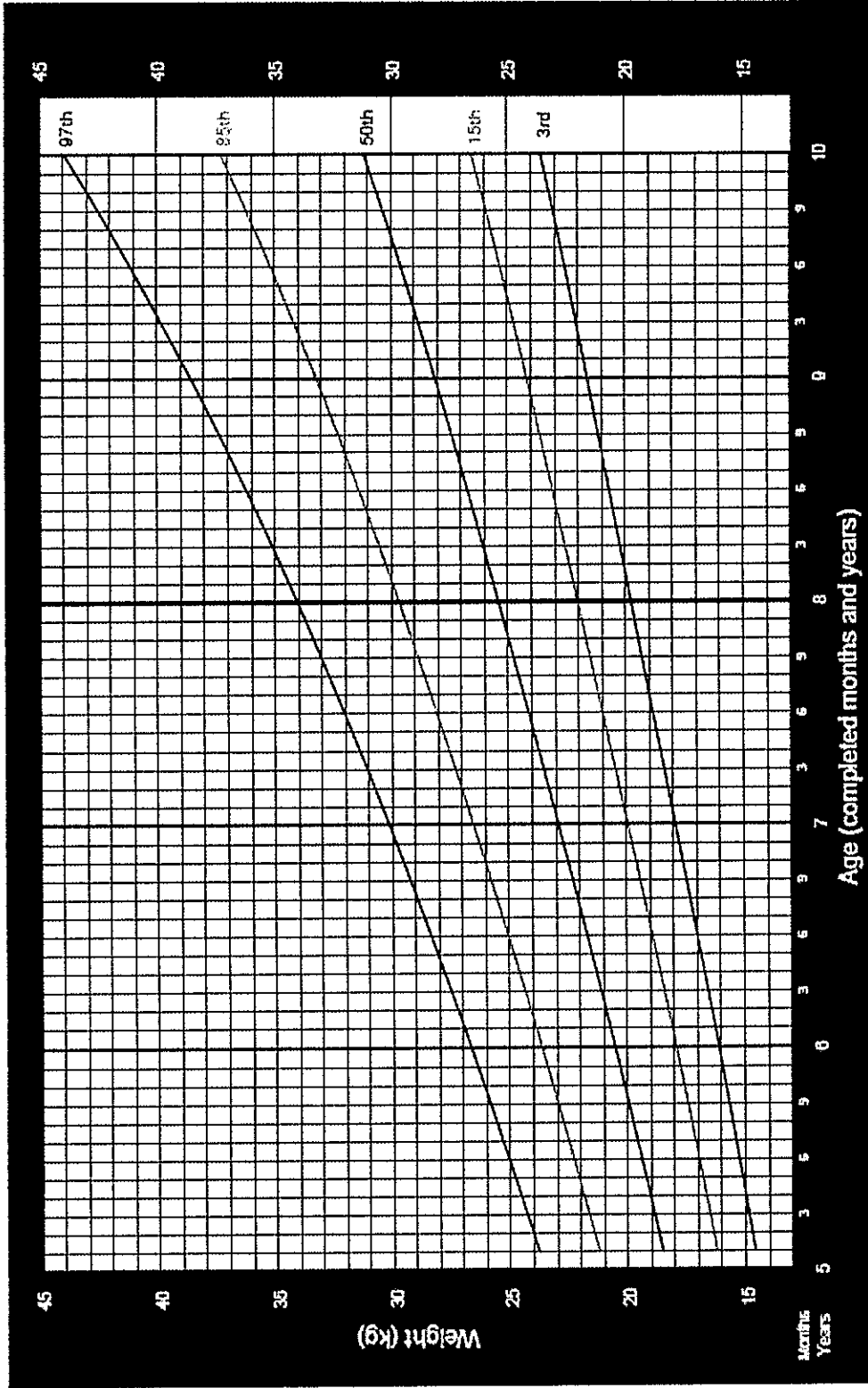
Weight-for-age GIRLS

Birth to 5 years (percentiles)



Weight-for-age BOYS

5 to 10 years (percentiles)



2007 WHO Reference

Annex D: Table of Opportunistic Infection Symptoms, Diagnosis, and Treatment

Symptoms		Workup		Treatment																				
Mycobacterial Diseases																								
Tuberculosis	<ul style="list-style-type: none"> • Continuous cough of >2 weeks duration • New loss of weight or failure to thrive • Persistent fever for >2 weeks duration • Painless enlarged lymph nodes in the neck 	<ul style="list-style-type: none"> • History of TB contact? • Chest x-ray, TST • Symptom directed: <ul style="list-style-type: none"> ○ Abdominal U/S ○ Lumbar puncture ○ Retina exam ○ Tissue aspirate: <ul style="list-style-type: none"> ▪ Lymph node ▪ Bone/joint ▪ Bone marrow 	<ul style="list-style-type: none"> • All forms of TB other than TB meningitis or osteoarticular TB: <ul style="list-style-type: none"> ○ 2 RHZE/ 4 RH • TB meningitis/osteoarticular TB: <ul style="list-style-type: none"> ○ 2 RHZS/ 4 – 10 RH ○ Prednisone 2 mg/kg x28d. if TB meningitis • Consider adding azithromycin 10 mg/kg daily if CD4 below age-related MAC threshold 	<table border="1"> <thead> <tr> <th>Drug</th> <th>Daily dosage in mg/kg (range)</th> <th>Maximum dose/day</th> </tr> </thead> <tbody> <tr> <td>Rifampicin (R)</td> <td>15 (10-20)</td> <td>600 mg</td> </tr> <tr> <td>Isoniazid (H)</td> <td>10 (7-15)</td> <td>300 mg</td> </tr> <tr> <td>Pyrazinamide (Z)</td> <td>35 (30-40)</td> <td>2 g</td> </tr> <tr> <td>Ethambutol (E)</td> <td>20 (15-25)</td> <td>1 g</td> </tr> <tr> <td>Streptomycin (S)</td> <td>15 (12-18)</td> <td>1 g</td> </tr> </tbody> </table>	Drug	Daily dosage in mg/kg (range)	Maximum dose/day	Rifampicin (R)	15 (10-20)	600 mg	Isoniazid (H)	10 (7-15)	300 mg	Pyrazinamide (Z)	35 (30-40)	2 g	Ethambutol (E)	20 (15-25)	1 g	Streptomycin (S)	15 (12-18)	1 g		
Drug	Daily dosage in mg/kg (range)	Maximum dose/day																						
Rifampicin (R)	15 (10-20)	600 mg																						
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Pyrazinamide (Z)	35 (30-40)	2 g																						
Ethambutol (E)	20 (15-25)	1 g																						
Streptomycin (S)	15 (12-18)	1 g																						
BCG infection	<ul style="list-style-type: none"> • Abscess or ulceration at the vaccination site • Lymphadenitis in the axilla, supraclavicular area, or neck on same side as BCG vaccination • Disseminated BCG 	<ul style="list-style-type: none"> • Chest x-ray • Lymph node aspirate • Retina exam • Culture is important to distinguish from TB 	<ul style="list-style-type: none"> • 6 RHE <ul style="list-style-type: none"> ○ Ensure dosed at weight-based upper limit (higher than usual for TB) 																					

	<ul style="list-style-type: none"> ○ Fever, weight loss ● Bone infection ● Erythema nodosum, iritis, lupus vulgaris 		<ul style="list-style-type: none"> ○ Consider 2 RHZE/ 4 RHE to treat BCG and TB if diagnosis uncertain and culture not available
<i>Mycobacterium avium</i> complex	<ul style="list-style-type: none"> ● Persistent or recurrent fever ● Weight loss/Failure to thrive ● Sweats, fatigue ● Persistent diarrhea or recurrent abdominal pain ● Lymphadenopathy, hepatomegaly, and splenomegaly 	<ul style="list-style-type: none"> ● CBC and LFTs <ul style="list-style-type: none"> ○ Pancytopenia, high alkaline phosphatase ● Lymph node aspirate for smear and culture ● Bone marrow aspirate 	<ul style="list-style-type: none"> ● Azithromycin 10mg/kg PO daily, and ● Ethambutol 15 mg/kg PO daily, +/- ● Rifampicin 15 mg/kg PO daily ● All x 12 months, then ● Azithromycin 5 mg/kg and ethambutol 15 mg/kg daily until CD4 above age-related cutoff on ART ● Age-related CD4 risk for MAC: <ul style="list-style-type: none"> ○ <12 months: <750 cells/mm³ ○ 12-24 months: <500 cells/mm³ ○ 2 – 5 years: <75 cells/mm³ ○ ≥6 years: <50 cells/mm³
Fungal Diseases			
Cryptococcal meningitis	<ul style="list-style-type: none"> ● Fever and headache ● Vision change ● Neck stiffness, cranial nerve palsy (late stages) ● Usually age >6 years and CD4 <100 cells/ mm³ 	<ul style="list-style-type: none"> ● CBC, chemistry, LFT ● Blood culture ● CSF evaluation for: <ul style="list-style-type: none"> ○ Opening pressure ○ CSF Gram stain and culture ○ India (Chinese) ink stain 	<ul style="list-style-type: none"> ● Pre-emptive fluids ● Amphotericin B 1 mg/kg IV daily x 2 weeks, then ● Fluconazole 12 mg/kg PO daily x 8 weeks, then ● Fluconazole 6mg/kg/day (maximum 200mg) until age ≥5 years and CD4

		<ul style="list-style-type: none"> ○ Cryptococcal antigen ● Ophthalmologic exam ● Chest xray 	<p>>100 cells/mm³ for >6 months on adherent ART</p> <ul style="list-style-type: none"> ● If opening pressure >20 cm CSF: <ul style="list-style-type: none"> ○ Remove CSF until below 20 cm or 50% of initial opening pressure ○ Repeat daily until opening pressure below 20 cm CSF ○ Do NOT use steroids or diuretics to decrease intracranial pressure ○ Consider delaying ART until after induction therapy is complete
<p>Histoplasmosis</p>	<ul style="list-style-type: none"> ● Acute pulmonary histoplasmosis: <ul style="list-style-type: none"> ○ Cough, fever, malaise, chills, myalgia, anorexia and chest pain ● Disseminated histoplasmosis: <ul style="list-style-type: none"> ○ Prolonged fever ○ Weight loss, failure to thrive ○ Hepatosplenomegaly, lymphadenopathy ○ Large oral ulcerations ○ Discrete fungating or umbilicated skin papules or masses ○ Respiratory symptoms with cough, respiratory distress 	<ul style="list-style-type: none"> ● Pancytopenia, elevated transaminases, and very elevated LDH ● Chest xray may show miliary pattern ● Sometimes can see yeast on peripheral blood smear ● Isolation of the fungus from blood, skin lesion, or bone marrow using culture is diagnostic ● Silver staining of tissue biopsies may reveal yeast forms 	<ul style="list-style-type: none"> ● Amphotericin B 1 mg/kg/day IV for at least 2 weeks, <i>followed by</i> ● Itraconazole 5 mg/kg PO twice daily or Fluconazole 6-8 mg/kg daily x 12 months ● Non-hospitalized patients may be treated with itraconazole or fluconazole without amphotericin B ● Therapy can be stopped if: <ul style="list-style-type: none"> ○ >5 years of age ○ >12 months of antifungal treatment ○ CD4 >15% and >150 cells/mm³ after 6 months of adherent ART

			<ul style="list-style-type: none"> Restart itraconazole or fluconazole in if the CD4 count falls below the thresholds above
Penicilliosis	<ul style="list-style-type: none"> Disseminated disease with fever, anemia, weight loss, lymphadenopathy, pneumonia, and/or hepatosplenomegaly Papular, umbilicated or ulcerating skin lesions are common and may be mistaken for Molluscum contagiosum or <i>Cryptococcus</i> CNS disease with brain abscess has been reported 	<ul style="list-style-type: none"> Pancytopenia, elevated liver enzymes, high alkaline phosphatase Nodular or cavitary lesions on chest xray, may be confused with TB Fungal identification from blood culture, skin lesions, lymph node, or bone marrow aspirate 	<ul style="list-style-type: none"> Amphotericin B 0.7 mg/kg IV daily for at least 2 weeks, followed by Itraconazole 5 mg/kg PO twice daily for 10 weeks Use fluconazole 8 mg/kg PO twice daily if itraconazole is not available Itraconazole 5 mg/kg PO daily should be given until immune restoration occurs. Secondary prophylaxis may be discontinued if: <ul style="list-style-type: none"> >5 years of age >12 weeks of antifungal treatment Immunological restoration with CD4 >150 cells/mm³ after 6 months of ART
<i>Pneumocystis jiroveci</i> pneumonia (PCP)	<ul style="list-style-type: none"> Fever, tachypnea, dyspnea, and cough, usually infant 2 – 6 months <ul style="list-style-type: none"> CD4 does not determine risk in infants Abrupt or slow onset Poor feeding or weight loss 	<ul style="list-style-type: none"> CXR: bilateral hazy, 'ground-glass', granular, or normal. Lung sounds often only mildly abnormal LDH usually elevated 	<ul style="list-style-type: none"> Cotrimoxazole 15-20/75-100 mg/kg/day, 3-4 divided doses IV for 21 days. <ul style="list-style-type: none"> May add clindamycin 30 – 40 mg/kg/day divided q8 hours for severe disease

	<ul style="list-style-type: none"> • Hypoxia often severe, room-air O2 below 85% common 	<ul style="list-style-type: none"> • Sputum silver stain or DFA where available 	<p><u>Corticosteroids</u></p> <ul style="list-style-type: none"> • Indication: <ul style="list-style-type: none"> ○ PaO2 <70 mmHg, alveolar-arterial gradient >35 mmHg, or O2 saturation <90% • Initial doses: <ul style="list-style-type: none"> ○ Prednisone 1mg/kg/12h (max 40mg/12h) ○ Methylprednisolone iv 1 mg/kg/6h
Parasitic Diseases			
Toxoplasmosis	<ul style="list-style-type: none"> • Acute onset over <1 week • Focal neurologic dysfunction, <i>and/or</i> • New seizures, <i>plus</i> • Fever and headache or altered level of alertness 	<ul style="list-style-type: none"> • CT with contrast shows ring-enhancing brain lesions • Retina exam may show white exudates • Toxoplasma IgG antibody usually positive (where available) • Empiric treatment usually necessary 	<ul style="list-style-type: none"> • Preferred: <ul style="list-style-type: none"> ○ Pyrimethamine loading dose 2mg/kg/day (max 50mg) for 3 days then maintenance 1 mg/kg/d (max 25 mg), plus ○ Sulfadiazine 100 mg/kg/day divided qid, plus ○ Folic acid 5-20 mg 3 times weekly ○ All for 6 weeks • 2nd line therapy: <ul style="list-style-type: none"> ○ High dose cotrimoxazole (10-15/50-75 mg/kg daily) for 6 weeks

				<ul style="list-style-type: none"> Dexamethasone 0.6mg/kg/day for clinical evidence of mass effect or edema on CT Cotrimoxazole prophylaxis after treatment
Viral Diseases				
CMV	<ul style="list-style-type: none"> Acute painless vision loss CD4 usually very low Often shortly after starting ART Disseminated disease: <ul style="list-style-type: none"> Cough and wheezing Clinical hepatitis Diarrhea, often bloody Pancytopenia Encephalitis 	<ul style="list-style-type: none"> Retina exam with perivascular exudates Pancytopenia on CBC Elevated ALT, LDH, and alkaline phosphatase Definitive diagnosis of disseminated disease requires biopsy or PCR 	<ul style="list-style-type: none"> Intra-ocular ganciclovir injections for retinitis Ganciclovir IV (where available) for disseminated or CNS disease ART 	