Kingdom of Cambodia
Nation Religion King

Ministry of Health

Guidelines for the Prevention and Treatment of Opportunistic Infections among HIV-exposed and HIV-infected Children in Cambodia

1st Edition
June 2011

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 1st 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 the NCHADS, the National Pediatric Hospital, Angkor Hospital for Children, 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 the Prevention and Treatment of Opportunistic Infections among HIV-exposed and HIV-infected Children in Cambodia, and encourages pediatricians to reference the guidelines when providing HIV/AIDS care to HIV-exposed and HIV-infected children.

Phnom Penh, 07/06/ 2011

Prof. ENG HUOT
SECRETARY OF STATE

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The National Center for HIV/AIDS, Dermatology, and Sexually Transmitted Diseases (NCHADS) would like to acknowledge the dedication of the members of the Pediatric AIDS Care Technical Working Group in the revision of the National Guidelines for the Use of Pediatric Antiretroviral Therapy in Cambodia. Throughout the process, they contributed high quality suggestions, enthusiasm, and hard work.

The process of revising these guidelines represents continued achievement in providing high-quality pediatric HIV/AIDS care to HIV-infected children in Cambodia, and ensures the treatment provided incorporates the latest knowledge in the field.

I would like to take this special occasion to thank the staff of NCHADS (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 (Professor Chhour Y Meng, Dr. Kdan Yuvatha, Dr. Ung Vibol, and Dr. Sam Sophan), Angkor Hospital for Children (Dr. Soeung Seitaboth), Battambang Referral Hospital (Dr. Chea Peuv), Family Health International (Dr. Laurent Ferradini), Clinton Health Access Initiative (Ms. Magdalena Barr-Dichiara and Ms. Cabrie Kearns), and the United Nations Children's Fund (UNICEF) and Brown University, USA (Ms. Penelope Campbell and Dr. Benjamin Westley), who have actively participated in revising these guidelines. Lastly, I would like thank to all partners, civil societies and partners who have provided care, treatment and support to HIV-infected children in Cambodia.

Phnom Penh, 16 June, 2011

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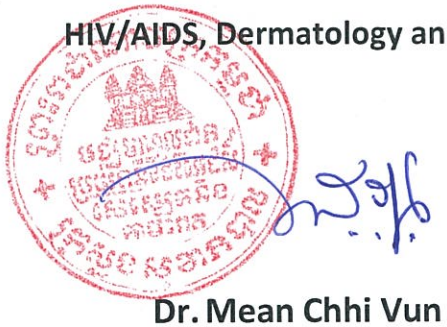

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ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
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
BID	Twice daily
BMI	Body mass index
CBC	Complete Blood Count
CD4	CD4+ T-lymphocyte
CMV	Cytomegalovirus
CNS	Central Nervous System
CrCl	Creatinine clearance
CSF	Cerebral Spinal Fluid
CTX	Cotrimoxazole
CXR	Chest x-ray
D4T	Stavudine
ddI	Didanosine
DIC	Disseminated intravascular coagulation
DOT	Directly observed therapy
DST	Drug Susceptibility Testing
E	Ethambutol
EBV	Epstein Barr Virus
ECG	Electrocardiogram
EFV	Efavirenz
EPTB	Extra-pulmonary tuberculosis
H	Isoniazid
HAART	Highly Active Antiretroviral therapy
HIV	Human Immunodeficiency Virus
HSV	Herpes Simplex Virus
IDV	Indinavir
INH	Isoniazid
ITP	Immune thrombocytopenia
IPT	Isoniazid preventive therapy
IRIS	Immune reconstitution inflammatory syndrome
KS	Kaposi's Sarcoma
LDH	Lactate dehydrogenase
LFT	Liver function test
LGE	Lineal gingival erythema
LN	Lymph node
LPV	Lopinavir
LPV/r	Lopinavir/ritonavir
Lym	Lymphocyte
MAC	*Mycobacterium avium* complex

MDR-TB	Multi drug resistant tuberculosis
MTB	*Mycobacterium tuberculosis*
NCHADS	National center for HIV/AIDS dermatology and STIs
NGT	Nasogastric Tube
NHL	Non-Hodgkin's lymphoma
NNRTI	Non-nucleoside reverse transcriptase inhibitor
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	*Pneumocystis jiroveci* pneumonia
PGL	Persistent generalized lymphadenopathy
PPE	Pruritic papular eruption
PI	Protease inhibitor
PLWA	People living with AIDS
PMN	Polymorphonuclear leukocyte
PO	Per os
PPD	Purified protein derivative
PTB	Pulmonary tuberculosis
PTT	Partial thromboplastin time
Qd	One time daily
R	Rifampicin
RBC	Red blood cell
RTV	Ritonavir
SJS	Stevens Johnson syndrome
SMX	Sulfamethoxazole
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
US	Ultrasound
WBC	White blood cell
WHO	World Health Organization
XDR	Extensively drug-resistant
Z	Pyrazinamide

INTRODUCTION

Through concerted efforts of all stakeholders, Cambodia has been successful in bringing down the prevalence of HIV infection among the general population aged 15-49 years from 2% in 1998 to 0.7% in 2010. It is estimated that there are 56,200 people currently living with HIV (PLHIV), and among these 3,881 are children aged 0 – 14 years who are receiving ART. Despite declining HIV prevalence, the need for HIV/AIDS treatment and care is expected to remain high due to improved mortality on ART and the natural course of HIV infection in those not yet qualifying for treatment. The majority of children with HIV are infected at birth, allowing early identification and treatment to prevent opportunistic infection. The appropriate follow-up and administration of cotrimoxazole prophylaxis to HIV-exposed infants is a critical component of OI/ART care, but opportunistic infections continue to be seen in HIV-infected children with unknown exposure history or inability to access interventions for PMTCT.

Since 2003, NCHADS has been implementing a Continuum of Care (CoC) framework, which is a comprehensive care, treatment and support system for people living with HIV/AIDS. Through September 2010, NCHADS has expanded HIV/AIDS care and treatment services to 52 sites for adults and 32 sites for children in 20 provinces. In order to better meet the needs of children with HIV infection, NCHADS convened a series of meetings of key stakeholders consisting of medical doctors from government, private, NGO, and academic institutions to develop a comprehensive guideline on the treatment of opportunistic infections among HIV-exposed and HIV-infected children in Cambodia.

The National Guidelines for the Treatment of Opportunistic Infections among HIV-Exposed and HIV-Infected Children in Cambodia is the first 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.

CHAPTER 1

HIV INFECTION, TRANSMISSION, AND EXPOSED-INFANT CARE

Key points:

- HIV is an RNA virus that is converted to DNA and incorporated into the host genome
- HIV cannot be cured and must be managed as a chronic illness
- Transmission to children generally occurs through mother to child transmission (MTCT) but may also occur during sexual abuse, through unsafe injections/infusions, and rarely through the pre-mastication of food
- MTCT can be significantly reduced by appropriate administration of ARV medications to the mother and infant
- All HIV-exposed infants require HIV testing at 6 weeks of age, at 6 weeks after cessation of breastfeeding, and if any signs/symptoms of HIV occur
- All HIV-exposed infants require cotrimoxazole prophylaxis from 6 weeks of age until HIV has been ruled-out
- Infection from unintended exposures can be minimized by the use of ARVs for post-exposure prophylaxis (PEP

1.1 Basics of HIV infection

HIV is an RNA virus that is able to enter cells in the body that possess a CD4 receptor. These cells include lymphocytes, monocytes, and macrophages, which help to coordinate the response of the immune system to infection. When the virus infects CD4 cells, it is converted to DNA by viral reverse transcriptase and inserted into the host genome, at which time the infection becomes incurable. New virus particles are made by the host cells, which are then packaged and released. Because CD4 cells are necessary for the immune system to function, the level of CD4 cells in the blood serves as a marker for the degree of functioning of the immune system. As more cells are infected the immune system become weaker and eventually illness occurs. Table 1 shows the CD4 levels that correlate with immune function at various ages.

Table 1: CD4 count and degree of immunosuppression

	<12 months	12-35 months	36-59 months	>5 years
No significant immunosuppression	>35%	>30%	>25%	>500 cells/mm^3
Mild immunosuppression	30-35%	25-29%	20-24%	350-500 cells/mm^3
Advanced immunosuppression	25-29%	20-24%	15-19%	200-349 cells/mm^3
Severe immunosuppression	<25%	<20%	<15%	<200 cells/mm^3

1.2 HIV transmission and PMTCT

HIV may be transmitted by blood or certain bodily fluids in the following ways:

- Vertical transmission from mother to child during pregnancy, delivery, or breastmilk (MTCT) accounts for the vast majority of pediatric infections
- Sexual abuse

- Consensual sex among adolescents
- Unsafe therapeutic injections or infusions
- Blood transfusion (prior to the era of universal screening)
- Accidental needle stick injury contaminated with HIV-infected blood

Certain risk-factors increase the likelihood of HIV transmission from mother to child, as outlined in Table 2.

Table 2: Risk factors for mother-to-child transmission of HIV

Maternal factors	Infant factors
High Viral load	Prematurity
Low CD4 count	Use of fetal scalp electrode monitoring
Advanced AIDS	Receipt of mixed feedings
Chorioamnionitis	Breastfeeding
Prolonged rupture of membranes	Mouth lesions
Cracked or bleeding nipples while breastfeeding	Receipt of pre-chewed foods

Mother to child transmission can be greatly reduced by the provision of ART to the HIV-infected mother during pregnancy and delivery, with continued ART through the duration of breastfeeding. Without intervention, ~1/3 of infants will become HIV-infected. With proper regimens for PMTCT, <5% of infants are expected to become infected. Policy in Cambodia is currently to treat all identified HIV-infected mothers with ART from 14 weeks gestation through the period of breastfeeding. Infants are to receive 6 weeks of daily AZT or nevirapine, and breastfeeding for up to 12 months is preferred. In rare instances, transmission of HIV from parent to child has been documented in cases where food is pre-chewed by an infected parent and then fed to a child; parents should be informed not to pre-chew food for their children. See the *National Guidelines for the Prevention of Mother to Child Transmission* for details of the currently recommended regimens.

<u>Breastfeeding infants whose mothers are NOT on ART</u>.
In some situations where HIV was diagnosed late in pregnancy, mothers may not yet be receiving ART but may be breastfeeding. In this case, infants must receive once-daily NVP liquid through the duration of breastfeeding. Dosing of NVP to be used in this situation is shown in Table 3.

Table 3: Nevirapine prophylaxis dosing for breastfeeding infants

Nevirapine (NVP) For PMTCT and Breastfeeding Prophylaxis ONLY	
Formulation	10 mg/ml liquid
Weight/age	
1st 6 weeks of age, weight <2.5 kg	10 mg (1 ml) once daily
1st 6 weeks of age, weight >2.5 kg	15 mg (1.5 ml) once daily
Age 6 weeks to 6 months	20 mg (2 ml) once daily
Age 6 – 9 months	30 mg (3 ml) once daily
Age 9 months to end of breastfeeding	40 mg (4 ml) once daily

1.3 Core components of HIV-exposed infant care

Core components in the follow-up of HIV-exposed infants include:

- Counseling on appropriate feeding practices, with emphasis on avoidance of mixed-feeding
- Routine immunization, vitamin A supplementation, and deworming according to the standard schedule for non HIV-infected children
- Support from home-based care services for completion of prescribed PMTCT medication
- Initiation of cotrimoxazole prophylaxis and DNA PCR #1 testing at 6 weeks of age, with repeat testing 6 weeks after cessation of all breastfeeding

1.4 Recommendations for infant and child feeding

Breastfeeding

Birth to six months of age:

- **All women, irrespective of HIV status**, are encouraged to exclusively breastfeed their infants for the first six months of life. Exclusive breastfeeding means giving infants **only** breast milk. Infants should not receive any other food or drink, not even water, during the six months of exclusive breastfeeding. Mixed feeding increases the risk of HIV transmission.
- **All HIV-infected mothers taking maternal triple ARV prophylaxis** should continue their ARV drugs until one week after complete cessation of breastfeeding, to prevent HIV transmission through breast milk. HIV-infected women on ART should continue their drugs throughout the breastfeeding period and lifelong thereafter for their own health.

After six months of age:

- **HIV-negative mothers and women of unknown HIV status** should introduce complementary foods and continue to breastfeed for up to 24 months or longer.
- **HIV-infected mothers whose infants ARE NOT HIV-infected (HIV-DNA PCR test negative),** or are of unknown HIV status, should introduce appropriate complementary foods after 6 months and continue breastfeeding for up to 12 months[1]. Mothers should continue to take maternal triple ARV prophylaxis (or ART) throughout the breastfeeding period.
- **HIV-infected mothers whose infants ARE HIV-infected (HIV-DNA PCR test positive**), are strongly encouraged to exclusively breastfeed for the first six months of life and then to continue breastfeeding with the addition of complementary foods, as recommended for the general population, up to 24 months or longer.

Important: Stopping breastfeeding abruptly is not advisable because it is associated with adverse consequences for the infant such as growth failure and increased prevalence of diarrhoea. Rather, mothers should stop breastfeeding gradually over a one month period.

Replacement Feeding

Fresh cow's milk, soy milk, condensed milk or powdered milk should not be given to infants. HIV-infected mothers should only give commercial infant formula milk as a replacement feed to their HIV-uninfected infants or to infants who are of unknown status, when **specific conditions** are met as outlined in Box 1. See the *National Guidelines for the Prevention of Mother-to-Child Transmission of HIV* for further details.

[1] Breastfeeding should only stop once a nutritionally adequate and safe diet without breast milk can be provided

Box 1: Conditions required for safe replacement feeding

In order to safely feed an infant using commercial infant formula, the following conditions must be met:

- safe water and sanitations are assured at the household level and in the community, **and**
- the mother, or other caregiver can reliably provide sufficient infant formula milk to support normal growth and development of the infant, **and**,
- the mother or caregiver can prepare it cleanly and frequently enough so that it is safe and carries a low risk of diarrhoea and malnutrition, **and**,
- the mother or caregiver can, in the first six months, exclusively give infant formula milk, **and**,
- the family is supportive of this practice, **and**,
- the mother or caregiver can access health care that offers comprehensive child health services.

Source: Rapid Advice, HIV and Infant Feeding, WHO 2009

1.5 Cotrimoxazole and fluconazole prophylaxis

HIV-infected infants are at very high risk of rapid disease progression and death, with mortality peaking at 4-6 months. Prior to routine administration of cotrimoxazole prophylaxis, 30% of infants died by age 12 months and 50% by 24 months. Twenty percent will have severe immunosuppression by 6 weeks of age, and >90% have an indication for ART by 1 year of age if a %CD4+ of 25% is used to initiate ART. **All infants and children under 2 years of age are now eligible for ART in Cambodia**.

Because of the high risk of progression and death, it is vitally important that HIV-exposed infants are closely followed and that all receive cotrimoxazole prophylaxis and DNA PCR testing at 6 weeks of age in accordance with the *National Guidelines for the Prevention of Mother to Child Transmission.* **Cotrimoxazole prophylaxis must be continued until HIV is ruled-out by age-appropriate HIV-testing 6 weeks after the cessation of breastfeeding**.

Indications for cotrimoxazole prophylaxis are listed in Table 4. Cotrimoxazole dosing is shown in Box 2.

Table 4: Indications for cotrimoxazole prophylaxis

Age/Category	Start*	Stop
HIV-exposed infant	6 weeks of age	PCR or antibody negative 6 weeks after complete cessation of breastfeeding
HIV-infected infants and children <5 years of age	6 weeks of age OR as soon as possible after diagnosis if >6 weeks of age	Age >5 years *and* on ART with CD4 >350 cells/mm^3 on 2 separate measurements >6 months apart
HIV-infected children ≥5 years	WHO clinical stage 3 or 4, OR CD4 <350 cells/mm^3	On ART *and* CD4 >350 cells/mm^3 on 2 separate measurements >6 months apart
HIV-infected child of any age with recurrent bacterial infections OR living in malaria area	Start as soon as possible after diagnosis	Continue cotrimoxazole indefinitely, regardless of ART or CD4 recovery
HIV-infected child with history of PCP pneumonia	Start immediately after PCP treatment completed	Continue cotrimoxazole until age >5 years and on ART with CD4 >350 cells/mm^3 on 2 separate measurements >6 months apart
HIV-infected child with active TB	Start as soon at TB is diagnosed regardless of CD4 count or percentage	Continue for duration of TB therapy then discontinue IF the above requirements are met

*If at any time the CD4 falls below these thresholds, cotrimoxazole should be re-started

Box 2: Cotrimoxazole prophylaxis dosing

Cotrimoxazole prophylaxis dosing for exposed infants* **(6 mg/kg trimethoprim component once daily)**	
<5 kg:	¼ tablet or 2.5 ml syrup
5-9kg:	½ tablet or 5 ml syrup
10-14kg:	1 tablet or 10 ml syrup
15-24kg:	1½ tablet or 15 ml syrup
>25kg:	2 tablets or 20 ml syrup

*Syrup = 40mg TMP/200mg SMX/ml; Single-strength tablet = 80mg TMP/400mg SMX/tablet

Cotrimoxazole side effects

Prophylaxis with cotrimoxazole is usually tolerated well in infants. Rarely, rash, granulocytopenia, anemia, and/or hepatitis can occur.

Children with intolerance to cotrimoxazole should be changed to dapsone 2 mg/kg daily. Note that dapsone provides protection from PCP but not toxoplasmosis.

Management of cotrimoxazole-related rash is outlined in Table 5.

Table 5: Management of cotrimoxazole-related rash

Severity	Description	Management
Grade 1	Diffuse or patchy erythema May be pruritic	Continue cotrimoxazole Followup in 3-4 days Consider antihistamines for symptom relief
Grade 2	Dry maculopapular rash May appear morbilliform Minimal exfoliation	Continue cotrimoxazole Followup in 1-2 days Consider antihistamines for symptom relief
Grade 3	Early bullae or mucosal ulceration	Discontinue cotrimoxazole immediately Hospitalize for supportive care **Never restart cotrimoxazole**
Grade 4	Toxic epidermal necrolysis or Stevens Johnson Syndrome	Discontinue cotrimoxazole immediately Hospitalize for supportive care **Never restart cotrimoxazole**

Fluconazole prophylaxis

In Southeast Asia, fluconazole prophylaxis in severely immunosuppressed adults has been shown to decrease morbidity and mortality due to cryptococcal meningitis. Although rare, cryptococcal meningitis in children has been described in Cambodia and therefore prophylaxis of severely immunosuppressed HIV-infected children is recommended. A minority of HIV-infected children will qualify for fluconazole prophylaxis. Fluconazole prophylaxis *should not* be given to exposed infants without confirmed HIV-infection and severe immunosuppression.

Table 6: Indications for fluconazole prophylaxis

Age/category	Start	Stop
HIV-infected infants and children <5 years of age	%CD4+ <15%	On ART *and* %CD4+ >15% on 2 separate measurements >6 months apart
HIV-infected children ≥5 years of age	CD4 cell count <100 cells/mm^3	On ART *and* CD4 > 100 cells/mm^3 on 2 separate measurements >6 months apart
HIV-infected child with history of cryptococcal meningitis	Immediately after consolidation therapy is completed	Age ≥5 years, on ART *and* CD4 >100 cells/mm^3 on 2 separate measurements >6 months apart

Box 3: Fluconazole prophylaxis dosing

Fluconazole prophylaxis dosing for HIV-infected children (3 – 6 mg/kg fluconazole daily)*
<7 kg: ¼ tablet
7-14kg: ½ tablet
15-24kg: 1 tablet
25-35kg: 1 ½ tablets
>35kg: 2 tablets

*100 mg tablets. Maximum dose 1 tablet if no prior history of cryptococcal meningitis

1.6 Immunization, vitamin A, de-worming

Infants born to HIV-infected mothers are at higher risk of death even when they do not become infected with HIV. HIV-exposed children should receive all scheduled immunizations, vitamin A supplementations, and deworming treatments as routinely given to non-HIV-exposed children. BCG vaccine should be given at birth per-routine, unless a child is strongly suspected of symptomatic HIV (see Chapter 10 for more details). **For a full schedule of exposed infant follow-up and current National vaccination schedule, see Annex A.**

Table 7: Routine vaccination schedule for HIV-exposed infants

	Age				
	Birth	*6 weeks*	*10 weeks*	*14 weeks*	*9 months*
Schedule	BCG, HepB [0]	DPT-HepB-Hib [1], OPV [1]	DPT-HepB-Hib [2], OPV [2]	DPT-HepB-Hib [3], OPV [3]	Measles

Table 8: Routine vitamin A supplementation

Age	Dosage	Frequency
6 - 11 months	100,000 IU	Once
12 – 59 months	200,000 IU	Every 6 months

Table 9: Routine deworming

Age	Medication	Dose
12 – 23 months	Mebendazole	250mg single dose every 6 months
≥24 months	Mebendazole	500mg single dose every 6 months

1.7 Growth Monitoring of the HIV-exposed infant

Failure to gain adequate weight may be one of the earliest signs of HIV-infection in HIV-exposed infants. Severely malnourished infants should always be strongly suspected of HIV-infection. Close growth monitoring of HIV-exposed infants is essential; when inadequate weight gain is noted, thorough evaluation should be performed with particular attention to ruling out TB, GI infections, neonatal sepsis, and HIV. At each visit the child's weight, length, weight-for-height, and head circumference should be recorded. Any growth faltering should prompt evaluation of nutritional

adequacy, infection, or HIV. Breastfeeding advice and food supplementation should be offered to the breastfeeding mother as deemed necessary and as guided by the *National Interim Guidelines for the Treatment of Acute Malnutrition*.

1.8 When to perform HIV testing

All HIV exposed infants require DNA PCR testing at 6 weeks of age. If breastfeeding, they require an age-appropriate test 6 weeks after complete cessation of breastfeeding. Refer to the *National Guidelines for the Prevention of Mother to Child Transmission*.

HIV testing should also be performed when any signs or symptoms that could be due to HIV are noted. Identifying children who have underlying HIV early in their clinical course is challenging, because many of the signs and symptoms of early HIV disease are also common in HIV-uninfected children (Box 4). In addition to those with known exposure or with suspected clinical HIV, certain high-risk children should also receive testing as outlined below.

At a minimum, the following groups of children should receive HIV testing according to the appropriate testing algorithm as outlined in the *National Guidelines for the Use of Pediatric Antiretroviral Therapy*:

- HIV-exposed infants
- Siblings of an HIV-infected child
- Orphans and abandoned children
- Children with tuberculosis
- Children with severe malnutrition
- Children with severe pneumonia not responding to the usual therapy

Box 4: Signs and Symptoms in Children with HIV Infection

Common in HIV-infected children and uncommon in other children

- Recurrent severe pneumonia or severe bacterial infections
- Bronchiectasis
- Bilateral painless parotid swelling
- Recurrent or persistent oral candidiasis (thrush)
- Generalized lymphadenopathy or hepatosplenomegaly
- Recurrent or persistent unidentified fever
- Neurologic dysfunction of unexplained cause
- Herpes zoster
- Persistent generalized dermatitis

Common in HIV-infected children and in HIV-uninfected children

- Anemia
- Chronic ear infections
- Recurrent or persistent diarrhea
- Severe pneumonia
- Tuberculosis
- Marasmus or failure to thrive

Signs and symptoms strongly suggestive of HIV-infection

- *Pneumocystis jiroveci* pneumonia (PCP)
- Esophageal candidiasis
- Cryptococcal meningitis
- Invasive non-typhoidal salmonella infection
- Lymphoid interstitial pneumonitis (LIP)
- Herpes zoster of >1 dermatome
- Lymphoma

Adapted from:
Guidelines for the Management of HIV in Children, Department of Health, South Africa, 2010

1.9 Post-exposure prophylaxis

After penetrative sexual abuse, the risk of HIV-acquisition may be minimized by the administration of ARVs as soon as possible within 72 hours of exposure. Penetrative sexual abuse includes forced:

- Receptive oral intercourse
- Receptive vaginal intercourse
- Receptive anal intercourse

For guidelines on the prophylaxis of children after sexual abuse, see the *National Guidelines on Post-exposure prophylaxis.*

CHAPTER 2

CLINCAL STAGING IN HIV-INFECTED CHILDREN

Key points:

- WHO clinical staging should be determined in all children with confirmed HIV-infection at baseline as well as every follow-up visit
- WHO clinical staging can provide evidence of immunosuppression and criteria for initiation of ART while CD4 results are pending
- Clinicians must be aware of differences between the pediatric and adult staging systems
- New WHO stage 3 or 4 events while receiving ART may represent IRIS or clinical treatment failure and should be thoroughly investigated

2.1 Summary of WHO Staging

Specific signs and symptoms may be used to estimate an individual patient's degree of immunosuppression when CD4 cell count is not available or is pending. Clinical staging may allow initiation of ART in some children prior to the return of CD4 results, and also can prompt the initiation of cotrimoxazole prophylaxis in children over 5 years of age.

Cambodia has adopted the World Health Organization system of clinical staging.

2.2 Pediatric Staging Compared to Adult Staging

The clinical manifestations of progressive HIV in children are different compared to adults. See Annex B for WHO Clinical Staging in Children with confirmed HIV infection.

- Clinical stage 2 in children includes several conditions not included in adult staging, such as lineal gingival erythema, parotid enlargement, unexplained hepatosplenomegaly, extensive wart virus infection, and extensive molluscum contagiosum
- Pediatric stage 3 includes lymphoid interstitial pneumonitis, lymph node tuberculosis, and bronchiectasis, which are not included in the adult staging system
- Cervical cancer is not listed in the pediatric staging system
- Children may suffer from congenital forms of toxoplasmosis, HSV, or CMV infections unrelated to HIV, so care should be taken to evaluate children with these conditions to determine their relationship to HIV infection

2.3 How to Use WHO Staging for Children

Clinical staging should be used for patients with confirmed HIV infection based on antibody or DNA PCR testing. For infants <18 months of age who do not have access to DNA PCR testing, clinical staging may be applied to those with a positive HIV antibody test who meet the criteria for presumptive severe HIV disease.

Box 5: Presumptive diagnosis of severe HIV

Presumptive diagnosis of severe HIV in children <18 months of age where PCR is not available

- The infant is confirmed HIV positive by antibody testing

AND EITHER:

- Diagnosis of any AIDS-indicator condition(s) has been made;

OR

- The infant is symptomatic with 2 or more of the following:
  - Oral Thrush
  - Severe pneumonia
  - Severe sepsis

WHO clinical staging should be performed at every visit. The occurrence of new stage 3 or 4 events in children receiving ART for ≥6 months suggests clinical treatment failure, and the child must be promptly evaluated with immunologic and virologic testing. See the *Cambodian National Guidelines for use of Pediatric Antiretroviral Therapy* for further details.

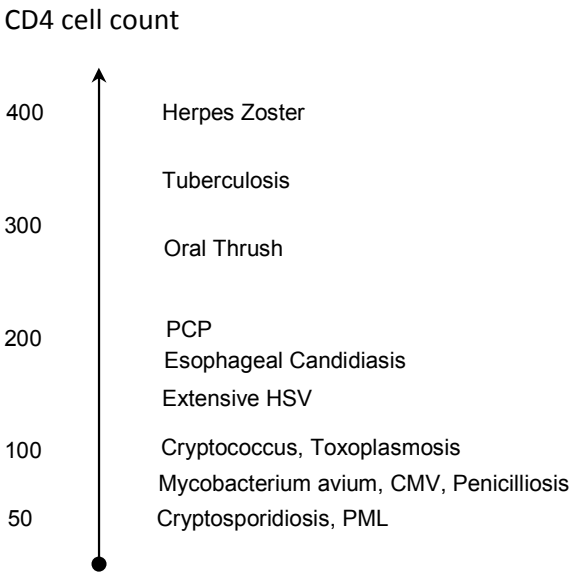
To determine clinical stage, a thorough history and physical examination is necessary, along with a complete blood count. Historical information is important to determine the past experience with complications, not simply those present at the time of evaluation. For example, a child who is currently asymptomatic but who has suffered from four episodes of pneumonia in the past year should be considered in clinical stage 3 even if he or she does not have pneumonia at the time of evaluation.

All children diagnosed with HIV also require baseline immunologic staging by determination of the CD4 count and percentage. For immunologic criteria that define ART eligibility and immunologic failure on treatment, see the *National Guidelines for the use of Pediatric Antiretroviral Therapy*.

<u>The importance of the CD4 cell count and percentage</u>

A child's likelihood of having various opportunistic and non-opportunistic diseases varies with the CD4 count. The CD4 level helps clinicians to stratify a child's risk of infection, which becomes critically important when an HIV-infected child presents with an acute complaint. Figure 1 shows a list of common OIs stratified by the the CD4 at which they are likely to first be seen. This can be used as a rough guide to help initiate work-up in the acutely ill child over the age of 5 years.

Figure 1: Risk of HIV-related illness by CD4 count



Do NOT rely on CD4 determination to help stratify illness in infants with HIV. CD4 can decline rapidly in infants, and even PCP often occurs with CD4% of 25% or higher.

Chapter 3 discusses common non-opportunistic illnesses in HIV-infected children.

CHAPTER 3

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 with a high CD4 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.

3.1 Fever

3.1.1 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^{o}C axillary
- >38^{o}C oral
- >38.5^{o}C rectal

3.1.2 Etiology

Fever may be caused by:

- Infection: bacterial, viral, fungal, or protozoal

- Malignancy: Non-Hodgkin's lymphoma, CNS lymphoma
- Medication: cotrimoxazole, 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 will be at risk for opportunistic infections and AIDS defining illnesses as discussed in following sections of this guideline. Knowledge of a child's treatment history and CD4 count is essential to constructing an appropriate differential diagnosis in patients with HIV.

3.1.3 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 degrees and no identifiable source should receive the following:
    - CBC
    - Blood and urine cultures
    - Chest radiograph
    - Lumbar puncture

3.1.4 Management

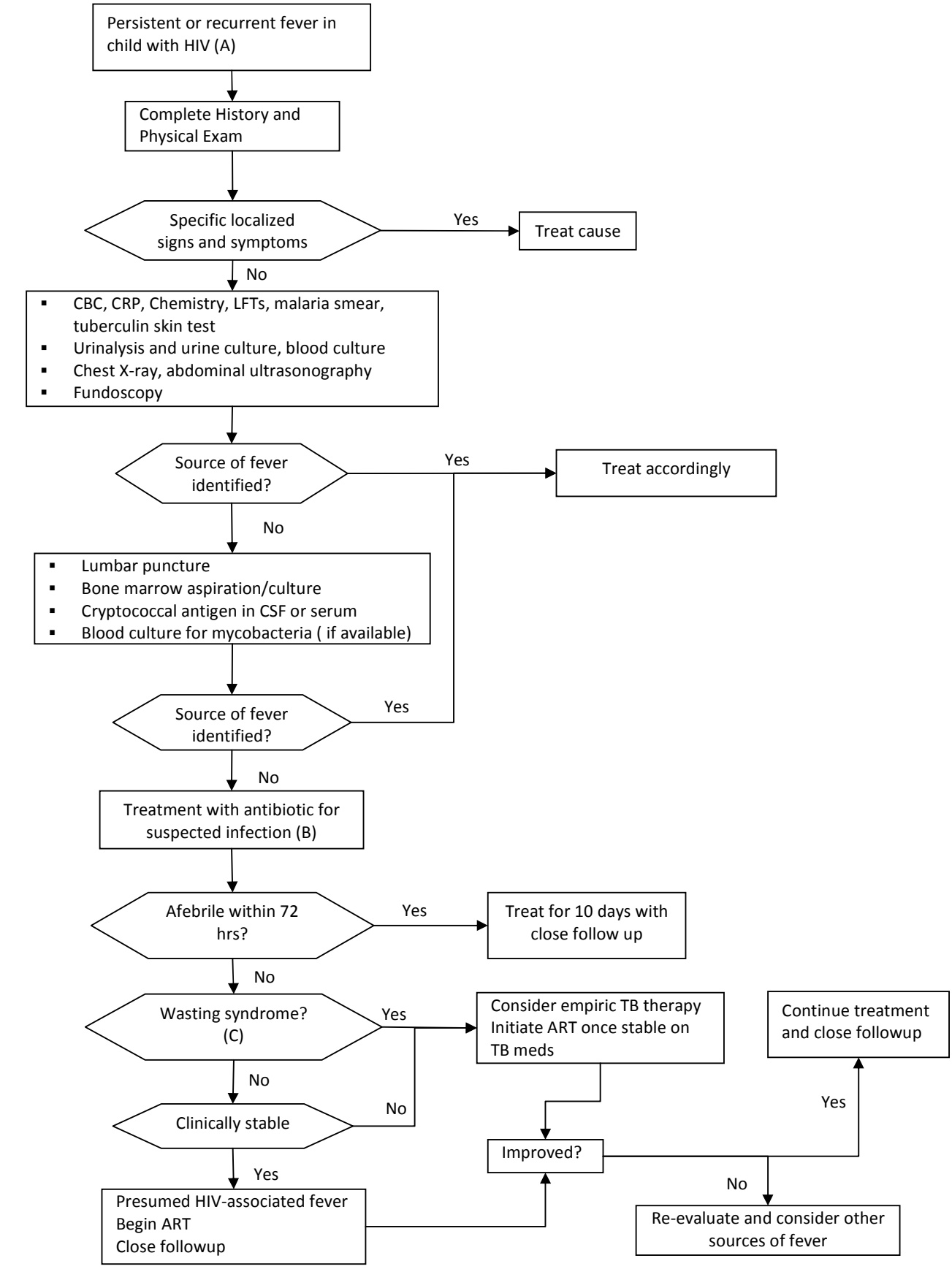
Treatment with antibiotics is indicated when:

- 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 (ANC <500) is present
- <3 months of age and febrile without a source

3.1.5 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 2: Workup of persistent fever in children with HIV



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.

3.2 Upper Respiratory Tract Infection

3.2.1 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.

3.2.2 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 AFB and fungal stain and/or culture where available.

3.2.3 Mastoiditis

- Mastoiditis is a complication of otitis media.
- A child with mastoidits will have a tender, swollen, erythematous, warm area behind the ear.
- Mastoiditis requires treatment with intravenous antibiotics and occaionally 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.

3.2.4 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.

3.3 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 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.
- Occasionally large staphylococcal parotid abscesses require drainage.
- Surgery is not required.

3.4 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 not be assumed to have PGL.
- In children with fever and lymphadenopathy, lymph node biopsy can often be useful in determining the correct diagnosis.

3.5 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.

CHAPTER 4

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 or 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.

4.1 Clinical manifestations

4.1.1 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 deficiences 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.

4.1.2 Oral hairy leukoplakia

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.

4.1.3 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.

4.1.4 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.

4.1.5 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 ulcer*s occur as a crop of numerous small lesions (1-2 mm) disseminated on the soft palate, tonsils, tongue, and/or buccal mucosa.

4.1.6 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.

4.1.7 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. 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.

4.2 Treatment

Table 10: Treatment of oral lesions

Oral lesions	Treatment	Comments
Oral candidiasis	**Topical** • Nystatin suspension 200,000-400,000 U/day divided in 4-6 doses for 14 days. • Gentian violet 1% aqueous solution painted in the affected area q8h **Systemic** • Fluconazole 6 mg/kg on day 1 then 3 mg/kg daily x 7-14 days (oral) or 21 days (esophageal) **Prophylaxis** • Consider prophylaxis for severe/recurrent disease until established on ART • Nystatin 100,000-400,000 U PO q12h for long period • Fluconazole 3 mg/kg PO daily	• 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	**Topical** • 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	• Lesions tend to heal slowly because of the repeated opening of the mouth.
Herpes Simplex Virus (HSV) Infection	**Systemic** • 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	• Patients taking acyclovir should be instructed to drink plenty of fluids.
Lineal Gingival Erythema (LGE)	**Local** • Scaling and root planing • 0.12% Chlorhexidine gluconate • (Periogard, Peridex) 0.5 oz q12h rinse, for 30 sec. and spit	• Prophylaxis with regular brushing, flossing, and use of mouth rinses. • Treat concomitant oral thrush if present
Parotid Enlargement	**Systemic** • Non-steroidal anti- inflammatories • Analgesics • Antibiotics (for superinfection only, usually due to staphylococcus)	• Surgical removal of the parotid gland should be avoided. • Symptoms may improve with provision of ART
Oral Hairy Leukoplakia (OHL)	**No treatment**	• OHL is rare in children. • Consider ART if severe symptoms

Necrotizing Ulcerative Gingivitis (NUG), Necrotizing Ulcerative Periodontitis (NUP), Necrotizing Stomatitis (NS)	• **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	• Prolonged use of chlorhexidine may cause staining of teeth, altered taste, and gum irritation. • Metronidazole may cause peripheral neuropathy when used for proloned periods or with ddI, d4T
Recurrent Aphthous Ulcers	• **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	• 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.
Oral Warts	• **Topical** • Podophyllin resin 25% applications q6h for long period • Cryotherapy with liquid nitrogen	• Recurrence rate is high. • ART decreases recurrence.

CHAPTER 5

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 11 lists common dermatologic manifestations in HIV-infected children.

Table 11: Causes of skin disease in HIV infection

Category	Causes

Infections	• Varicella zoster
	• Herpes simplex virus
	• Superficial fungal infection (eg Tinea)
	• Disseminated fungal infection
	  ○ Cryptococcosis
	  ○ Penicilliosis
	  ○ Histoplasmosis
	• Human papillomavirus
	• Impetigo
	• Mycobacterial infection
	• Secondary syphilis
	• Furunculosis
	• Folliculitis
	• Pyomyositis
	• Verucca planus

Neoplasia	• Kaposi's sarcoma • Lymphoma • Squamous and basal cell carcinoma • Sarcoma
Others	• Pruritic papular eruption • Seborrheic dermatitis • Drug eruptions • Vasculitis • Eczema • Psoriasis • Granuloma annulare • Thrombocytopenic purpura • Telangiectasia • Hyperpigmentation

Common cutaneous manifestations of HIV are summarized below.

5.1 Herpes simplex virus

- Stomatitis is the most common manifestation of HSV in children
- 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

5.2 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 PO with acyclovir 10 mg/kg/dose IV every eight hours for seven days.
  - Treat superinfection with cloxacillin as above.

5.3 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.
- 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.

5.4 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 12 summarizes the bacterial causes of skin disorders seen in HIV infected children, including a brief description and suggested initial treatment.

Table 12: Causes of bacterial skin infection and initial suggested treatment

Bacterial skin infection	Causative organism	Description	Treatment
Folliculitis	*Staphylococcus aureus*	Inflammation, infection of the hair follicles	• Warm compress • Cleansing • Cloxacillin in severe cases
Cellulitis	*Streptococcus, Staphylococcus aureus, Haemophilus influenzae*	Inflammation of skin and subcutaneous tissues, characterized by edema, erythema, and pain	• Cloxacillin 100-200 mg/kg daily divided q6 hourly
Skin abscess	*Staphylococcus aureus, Haemophilus influenzae*	Localized collection of pus in a cavity formed by disintegration of tissue; may complicate untreated cellulitis	• Surgical drainage • Systemic antibiotics if cellulitis
Impetigo	*Staphylococcus aureus, Streptococcus*	Vesicles or bullae with characteristic honey-colored crusting	• Topical mupirocin • Cloxacillin for disseminated lesions
Furunculosis (boil)	*Staphylococcus aureus, Streptococcus*	Infection of the skin and subcutaneous tissues surrounding a hair follicle; larger than folliculitis	• Warm compress • Cleansing • Occasionally need drainage • Rarely requires systemic antibiotics
Paronychia	*Staphylococcus aureus*	Infection involving the folds of tissue surrounding the fingernail or toenail	• Surgical drainage • Cloxacillin for 5-7 days
Bacillary angiomatosis	*Bartonella henslae*	Disseminated vascular lesions that may mimic Kaposi's sarcoma	• Azithromycin or erythromycin • Consult expert
Staphylococcal Scalded Skin Syndrome	*Staphylococcus aureus*	Diffuse bullous lesions starting on face, most common in infants; may mimic Stevens Johnson Syndrome but without precipitating exposure and NO mucosal involvement	• Cloxacillin 200 mg/kg/day IV divided q6 hours • Surgical consultation • Aggressive wound care and attention to hydration status

5.5 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.

5.5.1 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.

5.5.2 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

5.6 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 occuring in patients with advanced HIV is called Norweigen 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 availble. 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% gammabenzene hexachloride (lindane) applied from neck to toe may be used, but has been associated with neurotoxicity so is not preferred
  - Norweigen scabies is best treated systemically with ivermectin, 200 micrograms/kg in a single dose, where available. A repeat dose may be given on day 14 if lesions persist.
  - 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.

5.7 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.

5.8 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.

5.9 Pruritic Papular Eruption

- Chronic eruption of papular lesions on the skin
- May be related to disordered inflammatory response to common antigens such as those due to repeated mosquito bites.
- Very pruritic.
- 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.

CHAPTER 6

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:

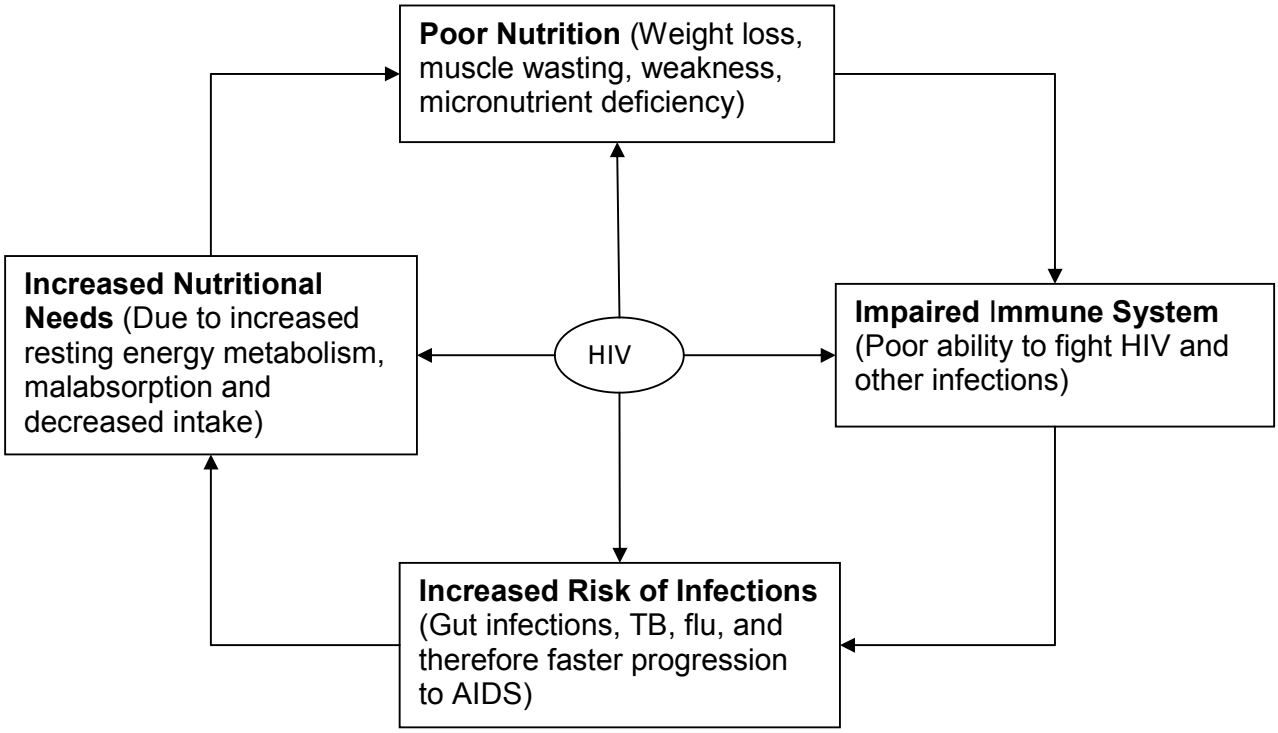
Malnutrition and inadequate growth are extremely common in HIV-infected infants and children, and is often the earliest sign of HIV-infection. This occurs due to a significant increase in metabolic needs in HIV-infected children, leading to loss of both lean (muscle) and fat body mass; once evidence 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.

6.1 Causes of malnutrition

HIV-infected children are at increased risk of malnutrition for many reasons (See Figure 3), 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: Because HIV often infects those with poorer socio-economic status, and because parents of HIV-infected children are often ill, limited food supply and loss of household income are common

Figure 3: Cycle of malnutrition and infection in HIV



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

6.2 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 6: Nutritional assessment in HIV-infected children

Nutritional assessment in HIV-infected children

- 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 D 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 and as guided by the MPA Module 10 on Nutrition.

6.3 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 7: 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

6.4 Diagnosis and evaluation of acute malnutrition

Table 13: Classification of malnutrition in children

	Mild malnutrition	Moderate malnutrition	Severe malnutrition
Symmetrical edema?	No	No	Yes
Weight-for-height	<5th 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)			• <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.

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

Table 14: Medical complications in severe malnutrition requiring inpatient care

MEDICAL COMPLICATIONS **According to severe classifications for 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. The following must be evaluated and excluded. This may be easier to accomplish in the inpatient setting at some sites.

- Workup for active tuberculosis
- Evaluation for oral or esophageal candidiasis, chronic intestinal infection, and disseminated fungal infection
- Early initiation of ART if not already receiving treatment
- Evaluation for treatment failure if receiving ART for ≥6 months
- Evaluation for 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 8: Energy goals for HIV-infected children with severe malnutrition

Energy goals for HIV-infected children with severe malnutrition

Stabilization phase (day 1 – 7)

- F75, goal 100 kcal/kg/day

Recovery phase

- F100 or Ready to Use Therapeutic Food (BP100)
  - 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)

CHAPTER 7

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

7.1 Anemia

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

Table 15: Causes and etiology of anemia in HIV infection

Causes of anemia	Etiology
Poor production of RBCs	HIV infection: o Anemia of chronic disease o HIV infection of bone marrow cells Infections: o CMV, parvovirus B19, tuberculosis Malignancy: o Lymphoma, Kaposi's sarcoma Drugs: o Cotrimoxazole, dapsone, AZT
Destruction of RBCs	Disseminated intravascular coagulation (DIC) Drug-associated hemolytic anemia o Primaquine, dapsone, cotrimoxazole
Ineffective production of RBCs	Folate and iron deficiency o Dietary o Intestinal malabsorption o Helminth-related GI bloodloss Vitamin B-12 deficiency o Intestinal malabsorption o 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.

7.2 Neutropenia

- Absolute neutrophil count (ANC) <1000/mm^3 in infants <1 year of age or <1500/mm^3 in children >1 year
- The risk of serious bacterial infection increases when the ANC falls below 500/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= WBC x (percentage of segmented neutrophils + bands)

Table 16: Causes and etiology of neutropenia in HIV infection

Cause of neutropenia	Etiology
Bone marrow infiltration or infection	• TB, penicilliosis, MAC, histoplasmosis • HIV-related bone marrow suppression • Lymphoma
Drugs	• 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/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

7.3 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

- 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 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 DIC, but the PT and PTT will be in the normal ranges. Treatment for TTP requires urgent plasma exchange until platelet count and 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.

CHAPTER 8

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 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

8.1 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.

8.1.1 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 17: Site-dependent symptoms of NHL

Mediastinal or Phayngeal tumor	**Abdominal tumor**
• Tachypnea • Nasal flaring • Stridor • Localized decrease in breath sounds • Dry cough	• Abdominal distension • Ascites • Palpable abdominal mass • Jaundice • Pain
Central nervous system disease	**Maxillofacial tumor**
• Headache • Vomiting • Visual disturbances • Gait instability • Cranial nerve palsies • Hemiparesies • Seizures	• Jaw mass • Numbness of the chin (peripheral facial nerve compression) • Asymmetric facial expression

8.1.2 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.

8.1.3 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.

8.2 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 CT scan or MRI of the brain.
- EBV virus is often detectable in the 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.

8.3 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.

CHAPTER 9

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 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.

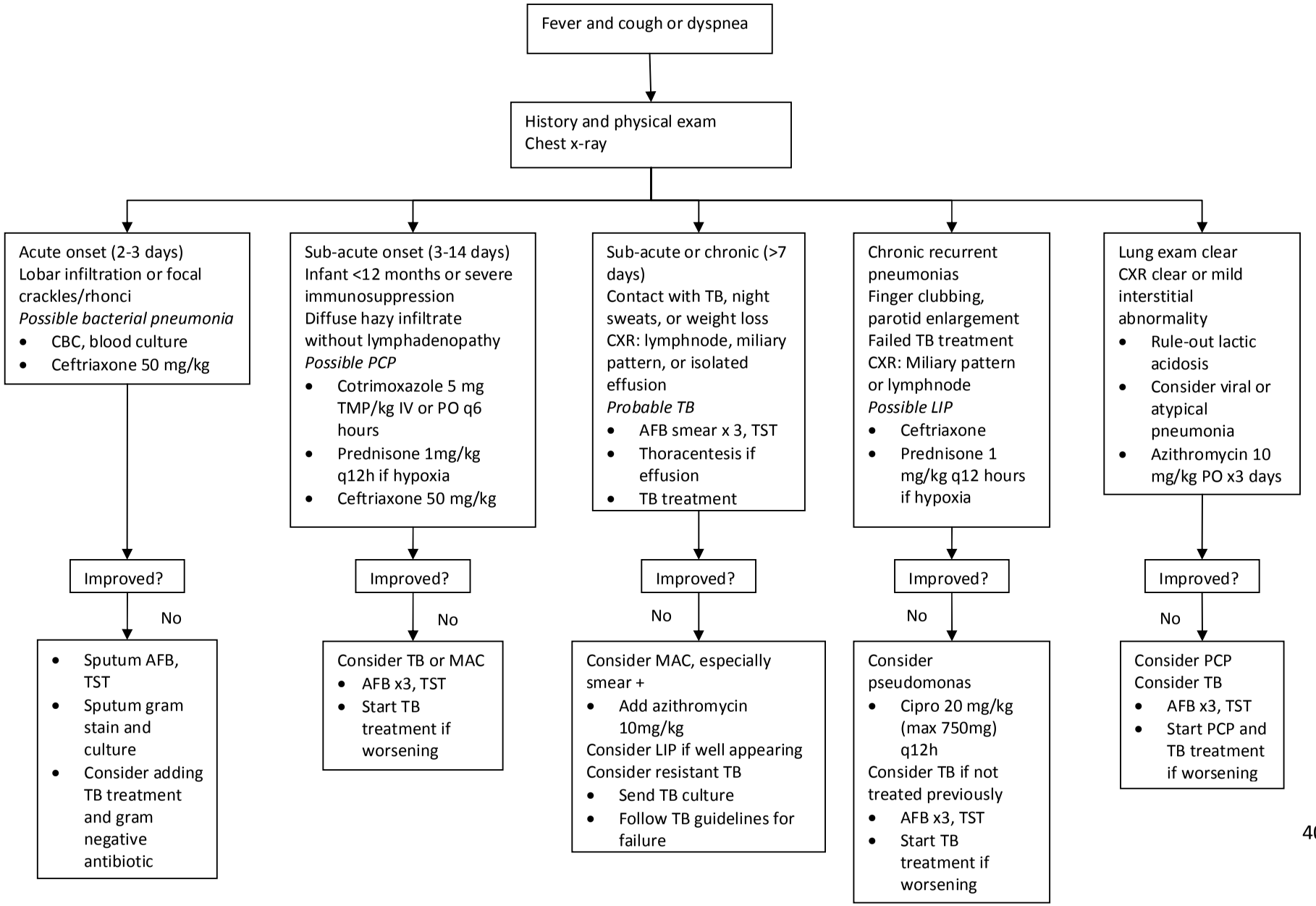
Introduction

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 4 for a suggested approach to respiratory complaints in children with HIV.

Figure 4: Evaluation of respiratory complaints in children with HIV



9.1 Bacterial Pneumonia

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

- *Streptococcus pneumoniae*
- *H. influenzae*
- *Klebsiella*
- *Staphlococcus 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 (O2 <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

- First-line antibiotics include intravenous ceftriaxone, 50 - 80 mg/kg once daily, if available
    - Chloramphenicol 75 mg/kd/day divided q8 hours is an alternative
- 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

9.2 *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 (**P**neumo**C**ystis **P**neumonia)
- 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 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.

<u>Corticosteroids</u>

- Indication:
  - Room-air PaO_2 value of <70 mmHg, or alveolar-arterial gradient of >35 mmHg
  - When blood gas not available: O_2 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

Cotrimoxazole prophylaxis significantly decreases the risk of PCP pneumonia in infants, children, and adults. In addition, the incidence of toxoplasmosis, invasive bacterial infections, and malaria all decrease substantially. Mortality benefit has been shown in HIV-infected patients receiving cotrimoxazole prophylaxis in nearly all instances, and is particularly dramatic when the CD4 cell count is low or they are diagnosed with active tuberculosis. Studies are conflicting about the CD4 level above which cotrimoxazole is no longer beneficial. **For cotrimoxazole indications, see Chapter 1.**

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.

9.3 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

9.4 Bronchiectasis

Introduction

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 bronchietasis 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; 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. Appropriate use of cotrimoxazole 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.

CHAPTER 10

TUBERCULOSIS IN HIV-INFECTED CHILDREN

Key Points

- 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

10.1 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. In Cambodia, 64% of population is infected with TB (8 million), with an estimated 40,000 active cases in 2009.

Table 18 shows the effect of HIV infection on lifetime risk of an *M. tuberculosis* infected individual developing TB.

Table 18: Lifetime risk of active TB with and without HIV

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

10.2 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 9: Clinical manifestations of tuberculosis

- 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:
    - 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

10.3 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 in the following two circumstances (treatment for TB should begin without delay):

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

OR

2) Symptoms suggestive of TB, *and either*
   - History of TB contact or positive TST, *or*
   - Abnormal chest x-ray suggestive of TB

Children who do not meet this 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.

10.4 Treatment

10.4.1 Antiretroviral Treatment (ART) in Patients with TB

Early initiation of ART decreases mortality in adults with active TB. While no randomized pediatric trials exist, the same is believed true in children. **ART is a vital component of TB treatment in all HIV-infected children and should begin within 2 weeks of TB diagnosis.** Drug-drug interactions occur between rifampicin and ARV medications. For details regarding ART regimen selection in patients with active TB, refer to the *National Guidelines on the Use of Pediatric Antiretroviral Therapy.*

10.4.2 Treatment Regimens

All HIV-infected patients with new pulmonary TB infection should be treated as category 1 patients.

Category 1**:** 2 RHZE / 4 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
- Category 1 for severe TB disease (miliary TB and TB meningitis): 2 RHZS/4RH

Category 2: 2 months RHZES / 1 month RHZE / 5 months RHE for:

1. Smear positive relapse, failure and treatment after default.

Category 3 is intended for patients without HIV

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

Table 19: 2009 WHO-recommended target doses of TB medications in children

Drug	Daily dosage in mg/kg (range)	Maximum dose/day
Rifampicin (**R**)	15 (10-20)	600 mg
Isoniazid (**H**)	10 (10-15)	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 FDC formulations and dosing recommendations for Cambodia, please refer to the *National Guidelines for Diagnosis and Treatment of TB in Children*.

10.4.3 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.

10.4.4 Common side-effects of TB medications

Table 20: Management of anti-tuberculosis drug side-effects

Side-effects	Drug(s) probably Responsible	Management
Minor side effects		*Continue anti-TB drugs*
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
Severe side effects		*Stop drug(s) responsible*
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	Most anti-TB drugs	Stop all anti-TB drugs, urgent liver function tests

liver failure if jaundice present)		
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.*

10.5 Severe forms of tuberculosis requiring special treatment

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 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/mm^3 with predominance of lymphocytes
  - Protein usually very elevated and glucose very low
  - Rarely, bacilli in CSF smear
- Treatment is as follows:
  - 2 RHZS/ 4RH
  - 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
  - Many experts would extend the continuation phase to 10 months

10.5 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

10.7 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 1/3 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

10.8 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:

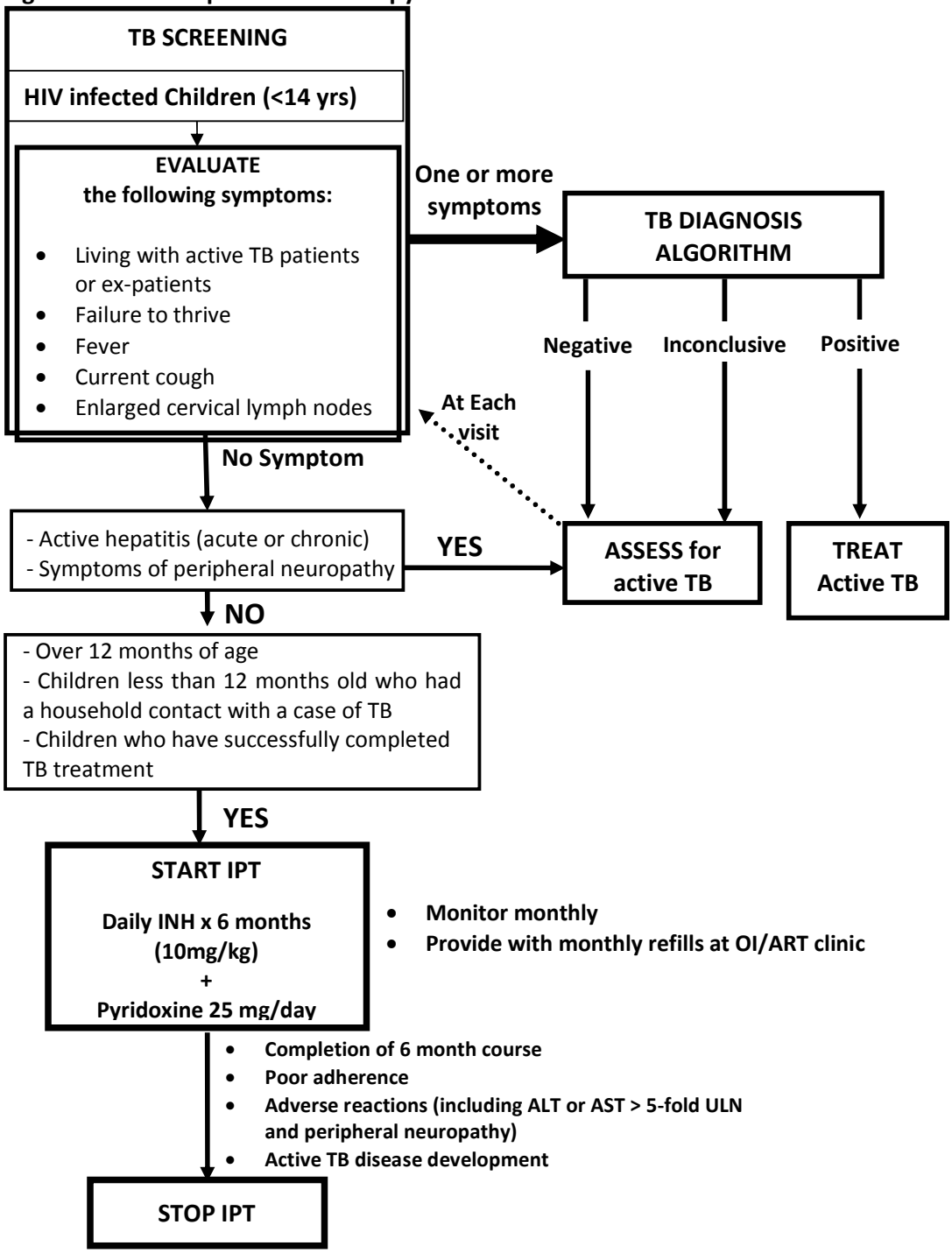
- Active hepatitis (acute or chronic) with ALT ≥2 N
- Symptoms of peripheral neuropathy

IPT Regimen

Isoniazid 10 mg/ kg once daily for 6 months total duration

Pyridoxine (vitamin B6) 25 mg once daily for 6 months total duration

Figure 5: Isoniazid preventive therapy in children



10.9 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

<u>BCG complications</u>

- 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.

CHAPTER 11

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

11.1 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.

11.1.1 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.

11.1.2 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.

11.1.3 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.

11.1.4 Prevention

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

11.2 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:

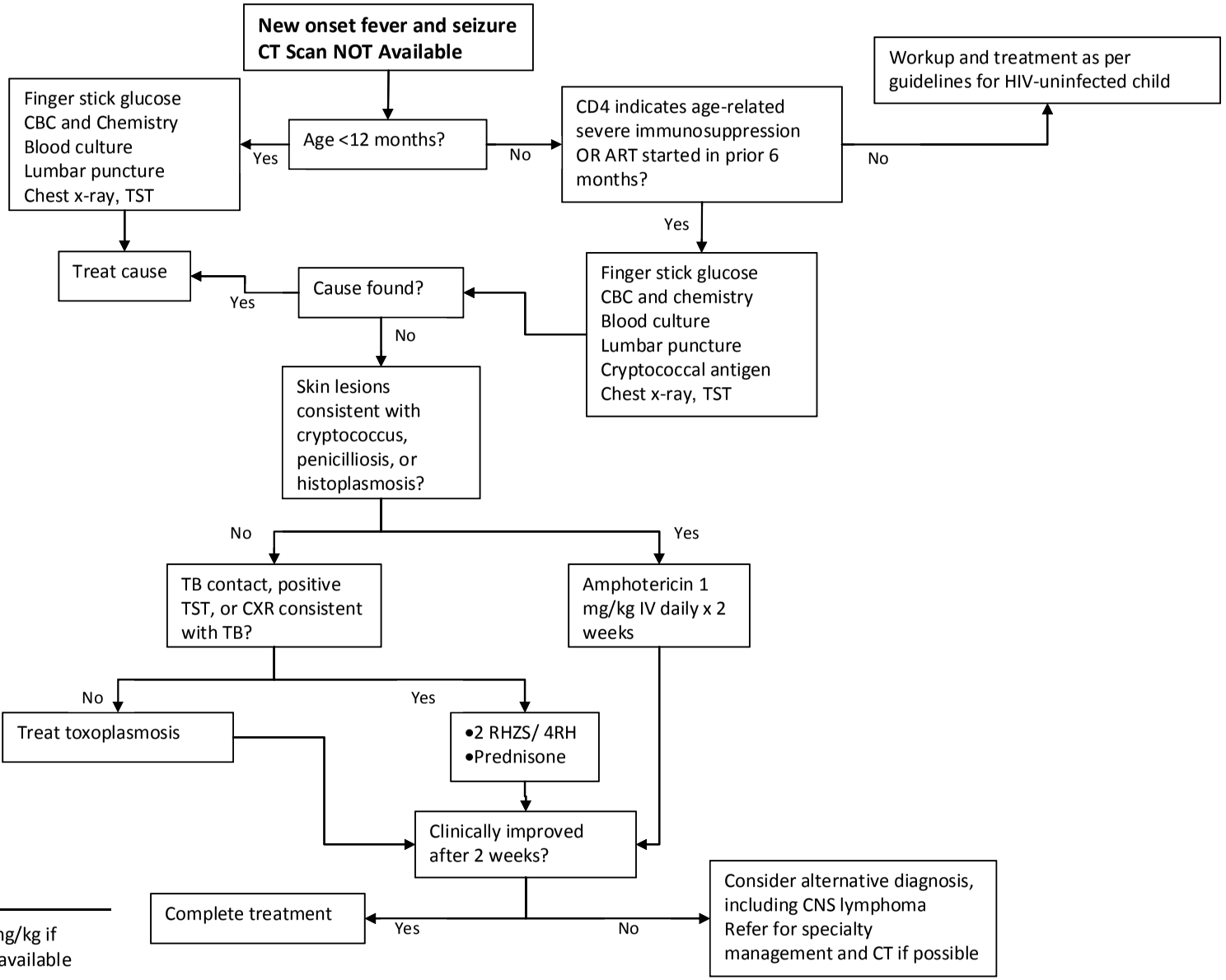
- Space-occupying lesions, including toxoplasmosis, tuberculoma, fungal infection, and lymphoma
- Meningitis or meningoencephalitis (cryptococcal, TB, bacterial, viral)
- Cerebral malaria
- Febrile convulsions (age 6 months – 5 years)
- Metabolic disturbances (e.g. hypoglycemia)
- Epilepsy

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.

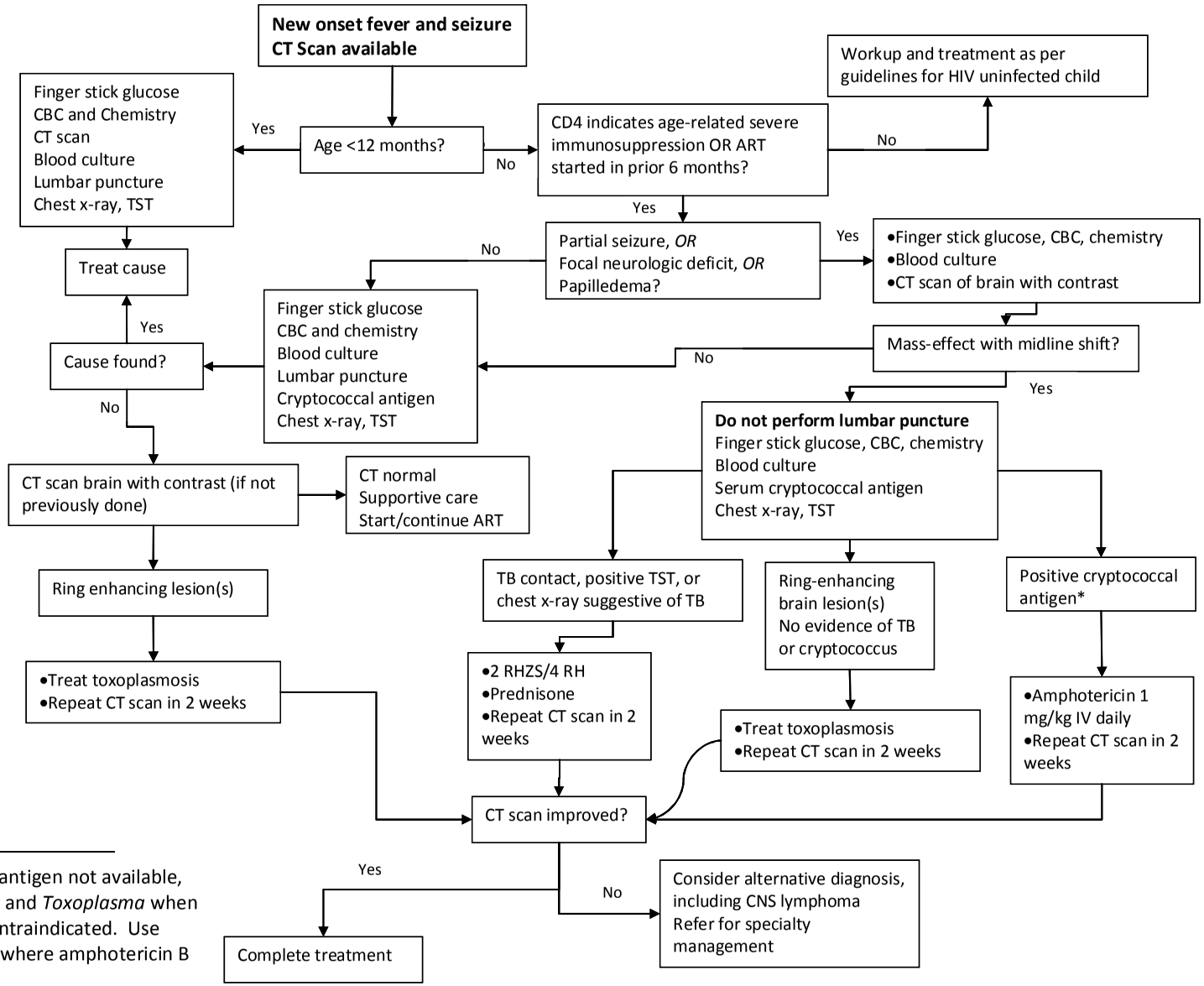
Many anti-epileptic agents interact with ARVs, which may result in either abnormally low or high serum concentrations of the anti-seizure drug. Valproate is the preferred agent in children with seizures who are receiving ART.

Figure 6: Workup of seizure and fever when CT scan NOT available*



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

Figure 7: Workup of seizure and fever when CT scan available*



* Where cryptococcal antigen not available, treat for *Cryptococcus* and *Toxoplasma* when lumbar puncture is contraindicated. Use fluconazole 12 mg/kg where amphotericin B is not available

11.3 Infections of the Central Nervous System

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.

11.3.1 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

11.3.2 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
    - Prehydration with 10 ml/kg normal saline may minimize renal toxicity
    - 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/mm^3 for >6 months on adherent ART

Primary Prophylaxis:

- See Chapter 1 for guidelines on fluconazole primary propylaxis.

11.3.3 Tuberculous meningitis

Symptoms:

- Gradual onset of headache and vomiting, decreased consciousness, drowsiness, convulsion, low grade fever
- Neck stiffness and positive Kernig's sign
- Cranial nerves palsies may result from exudates around the base of the brain

Diagnosis:

- CSF typically shows clear fluid with lymphocytic pleocytosis and very high protein with very low glucose
- CT scan of the brain may show basilar cistern enhancement with hydrocephalus and/or basal ganglia infarction. In early disease the CT will be normal.

Treatment: 2RHZS/4RH, dexamethasone 0.6 mg/kg/daily x 28 days, pyridoxine 25mg daily, and cotrimoxazole prophylaxis daily for duration of therapy. Many experts extend the continuation phase to 10 months. See Chapter 10.

Table 21: 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

11.3.4 *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 hemmorhage
- 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/mm^3 for >6 months on adherent ART

11.3.5 Viral encephalitis

Viral encephalitis may be caused by a wide-variety of agents, including CMV, HSV, enteroviruses, and Japenese 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 encephalitits 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

11.4 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

11.5 Peripheral neuropathy

- Causes of peripheral neuropathy in children with HIV infection include:
    - HIV-related autoimmune effects
    - Vitamin deficiencies
    - Side effects of d4T and ddI (rarely AZT)
    - 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.

CHAPTER 12

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 caries a high mortality
- ART should be initiated in all HIV-infected children with chronic diarrhea

12.1 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 22: 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 23: Rehydration plans and fluids

Indication	Route	Fluid choice	Dose*
Plan A: Prevention of dehydration in the setting of diarrhea. No current dehydration	Oral	ORS solution+	Children <2 years: 50-100 ml after each loose stool 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.
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

12.2 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 persitent 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 zing 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 zing 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

12.3 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 8: Approach to the child with chronic diarrhea

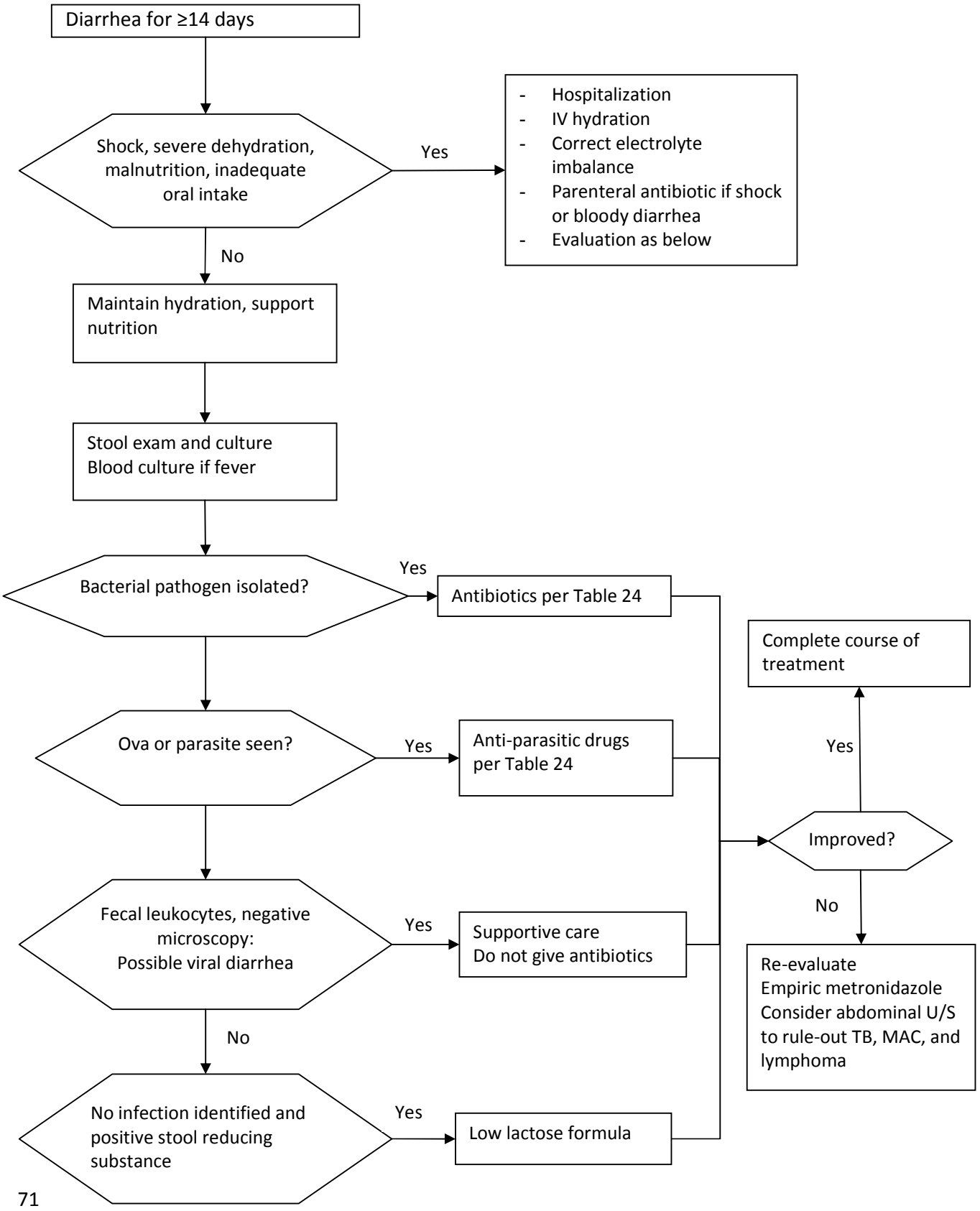


Table 24: Treatment of diarrhea when specific cause is known

Etiology	Treatment
Bacteria:	
Salmonella (non-typhoidal)	Ciprofloxacin 15mg/kg PO twice daily for 3-7 days
Salmonella typhi	Ceftriaxone 50-75mg/kg OD, IV for 7 days *Or* Ciprofloxacin for 15mg/kg PI BID for 7 days
Shigella	Ciprofloxacin 15mg/kg PO BID for 3 days
Escherichia coli	No antibiotic
Campylobacter jejuni	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
Mycobacterium avium Complex	Clarithromycin 15mg/kg/day Bid *Or* Azithromycin 10mg/kg OD *PLUS* Ethambutol 15-25 mig/kg OD *PLUS* Rifabutin 10-20mg/kg OD *Or* Ciprofloxacin 20-30mg/kg OD
Tuberculosis	2RHZE/4RH
Yersina enterocolitica	TMP-SMZ (TMP 8mg/kg/day) divided BID for 5 days.
Protozoa:	
Cryptosporidium	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
Isospora belli	TMP-SMZ (TMP 5mg/kg/dose) qid for 10 days then bid for 3 weeks.
Giardia lamblia	Metronidazole 20mg/kg/day PO divided tid for 10 days
Entamoeba histolytica	Metronidazole 35-50mg/kg/day PO divided tid for 10 days
Microsporidia	Albendazole 20mg/kg/day bid x 4 weeks
Cyclospora	TMP-SMZ (TMP 5mg/kg/dose) qid for 10 days then bid for 3 weeks

12.4 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 contamined 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
- Adolescents ≥12 years of age with HBV-HIV coinfection should receive ART containing a tenofovir and 3TC or FTC 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
- Treatment for hepatitis C is with interferon and ribavirin, but is not widely available
- Children with chronic HCV should be monitored carefully for toxicity when hepatotoxic drugs are administered

CHAPTER 13

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 marneffei* 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

13.1 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/mm^3
- Children 12-24 months: <500 cells/mm^3
- Children 2 – 5 years: <75 cells/mm^3
- Children ≥6 years: <50 cells/mm^3

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

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

13.2 Penicilliosis

Epidemiology

- Penicilliosis is an invasive fungal disease cause by the organism *Penicillium marneffei* which is endemic in Southeast Asia
  - Highest prevalence in Northern Thailand
- CD4 counts in adults below 100 cells/mm^3 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*
- 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/mm^3 after 6 months of adherent ART

13.3 Histoplasmosis

Epidemiology

- Histoplasmosis is caused by infection with the dimorphic fungus *Histoplasma capsulatum*
- CD4 counts in adults below 150 cells/mm^3 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/mm^3 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

13.4 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/mm^3 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/mm^3
- 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/mm^3 should be attempted whenever possible

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ANNEXES

Annex A: Schedule of Routine Follow-Up Visits for HIV-Exposed Infants

Age of Infant	Birth	1.5 months (6 weeks)	2.5 months (10 weeks)	3.5 months (14 weeks)	6 months	9 months	12 months	15 months	18 months
Visit Number	Maternity	Visit #1 to pediatric service	Visit #2 to pediatric service	Visit #3 to pediatric service	Visit #4 to pediatric service	Visit #5 to pediatric service	Visit #6 to pediatric service	Visit #7 to pediatric service	Visit #8 to pediatric service
Immunizations	BCG, HBV[0]	OPV [1], DTP, Hib, HBV [1]	OPV [2], DTP, Hib HBV [2]	OPV [3], DTP, Hib, HBV [3]		Measles			
Assess Patient By*	H, P, G, D	H, P, G, D	H, P, G, D	H, P, G, D	H, P, G, D	H, P, G, D	H, P, G, D	H, P, G, D	H, P, G, D
Provide for all Families	Education on feeding; Counseling Services	Education on feeding; Counseling Services	Education on feeding; Counseling Services	Education on feeding; Counseling Services	Education on feeding; Counseling Services	Education on feeding; Counseling Services	Education on feeding; Counseling Services	Education on feeding; Counseling Services	Education on feeding; Counseling Services
HIV Testing and Care for Breastfeeding Infants	PMTCT regimen	Begin cotrimoxazole prophylaxis Perform HIV PCR 1 Test -- Refer to Child Testing Algorithm 1			If 6 weeks after complete cessation of breastfeeding, perform PCR 2 test Refer to Child Testing Algorithm 1 (a)	If 6 weeks after complete cessation of breastfeeding, perform PCR 2 test Refer to Child Testing Algorithm 1 (a)			Confirmatory HIV Antibody Test (b,c)
HIV Testing and Care for Non-Breastfed Infants	PMTCT regimen	Begin cotrimoxazole prophylaxis HIV PCR Test -- Refer to Child Testing Algorithm 2					HIV Antibody Test (b,c)	HIV Antibody Test (b,c)	Confirmatory HIV Antibody Test (b,c)

***H, P, G, D =** access by **H**istory, **P**hysical examination, **G**rowth, and **D**evelopment

(a) If 6 weeks after complete cessation of breastfeeding, any one negative PCR result defines the infant as HIV uninfected.

(b) For HIV antibody test, follow national guidelines algorithm for HIV antibody testing. If 6 weeks after complete cessation of breastfeeding, a negative HIV Antibody test at 12-18 months defines the infant as HIV uninfected.

(c) If infant is asymptomatic and has had at least one negative PCT test 6 weeks after the complete cessation of breastfeeding, cotrimoxazole prophylaxis may be stopped at 12 months. If PCR test is unavailable, cotrimoxazole prophylaxis may be stopped if infant has had one negative HIV antibody test at 12-18 months.

Annex B: 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 brochiectasis
- Unexplained* anaemia (<8.g/dl), neutropaenia (<0.5 x 10^9 per liter) and/or chronic thrombocytopaenia (<50 x 10^9 per liter)

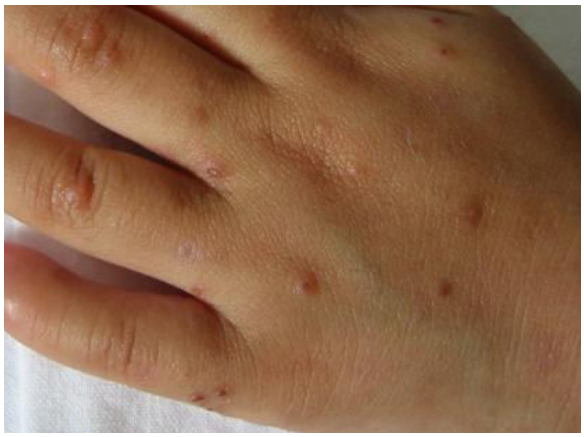
Stage 4

- 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)

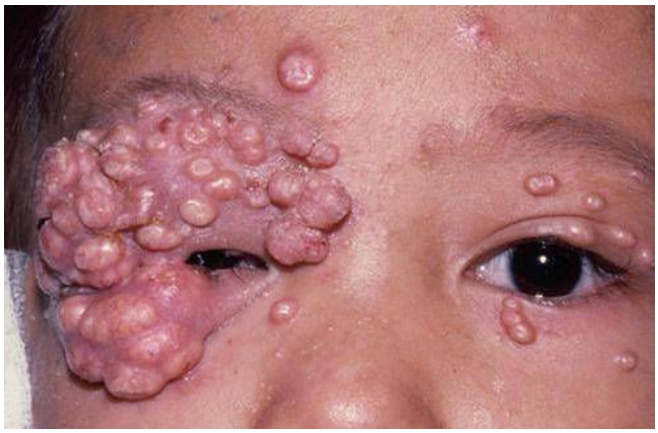
- Central nervous system toxoplasmosis (after one month of life)
- HIV encephalopathy
- Cytomegalovirus infection: retinitis or cytomegalovirus infection affecting another organ, with onset at age older than one month
- Extrapulmonary cryptococcosis (including meningitis)
- Disseminated endemic mycosis (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

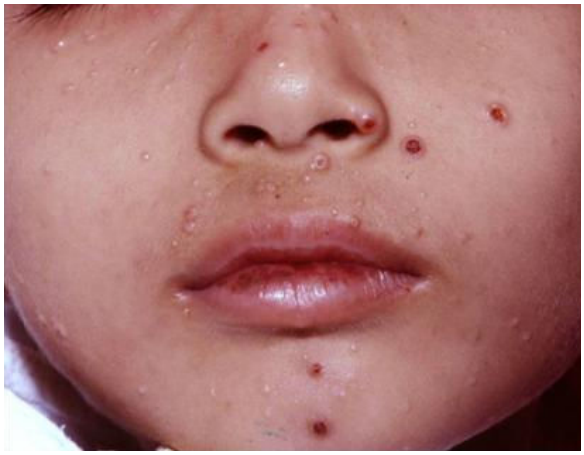
Annex C: Photos of Oral and Skin lesions in HIV-infected Children



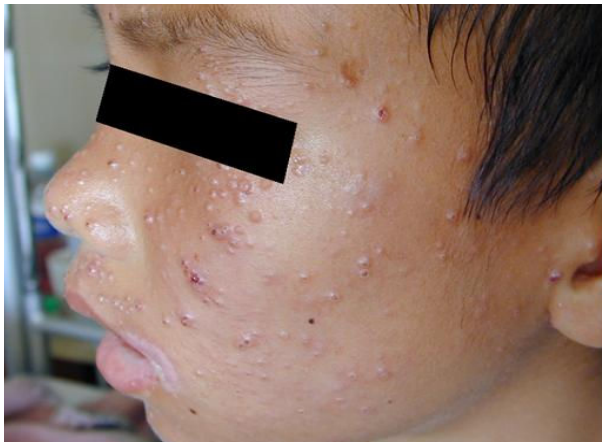
Pruritic Papular Eruption



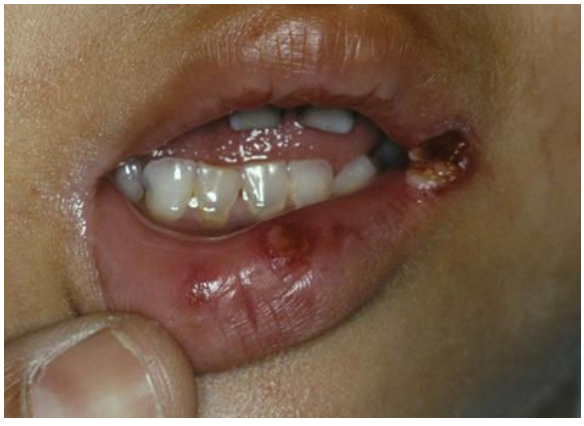
Molluscum Contagiosum with Giant Molluscum



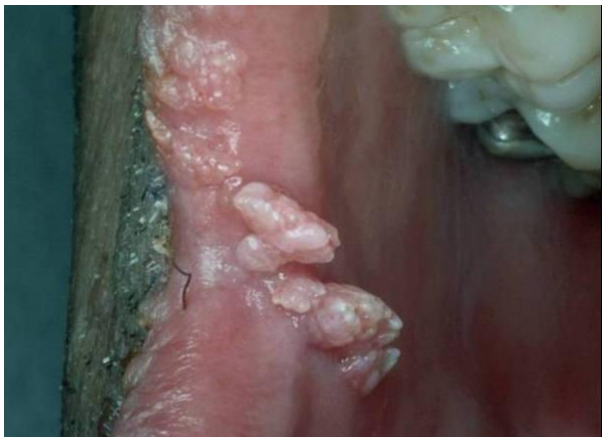
Cryptococcosis



Penicilliosis



Herpes Simplex Virus



Oral Human Papilloma Virus

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

Annex D: WHO growth monitoring tables and charts

WHO Child Growth Standards 2006. **Weight for Length (up to 87 cm)**

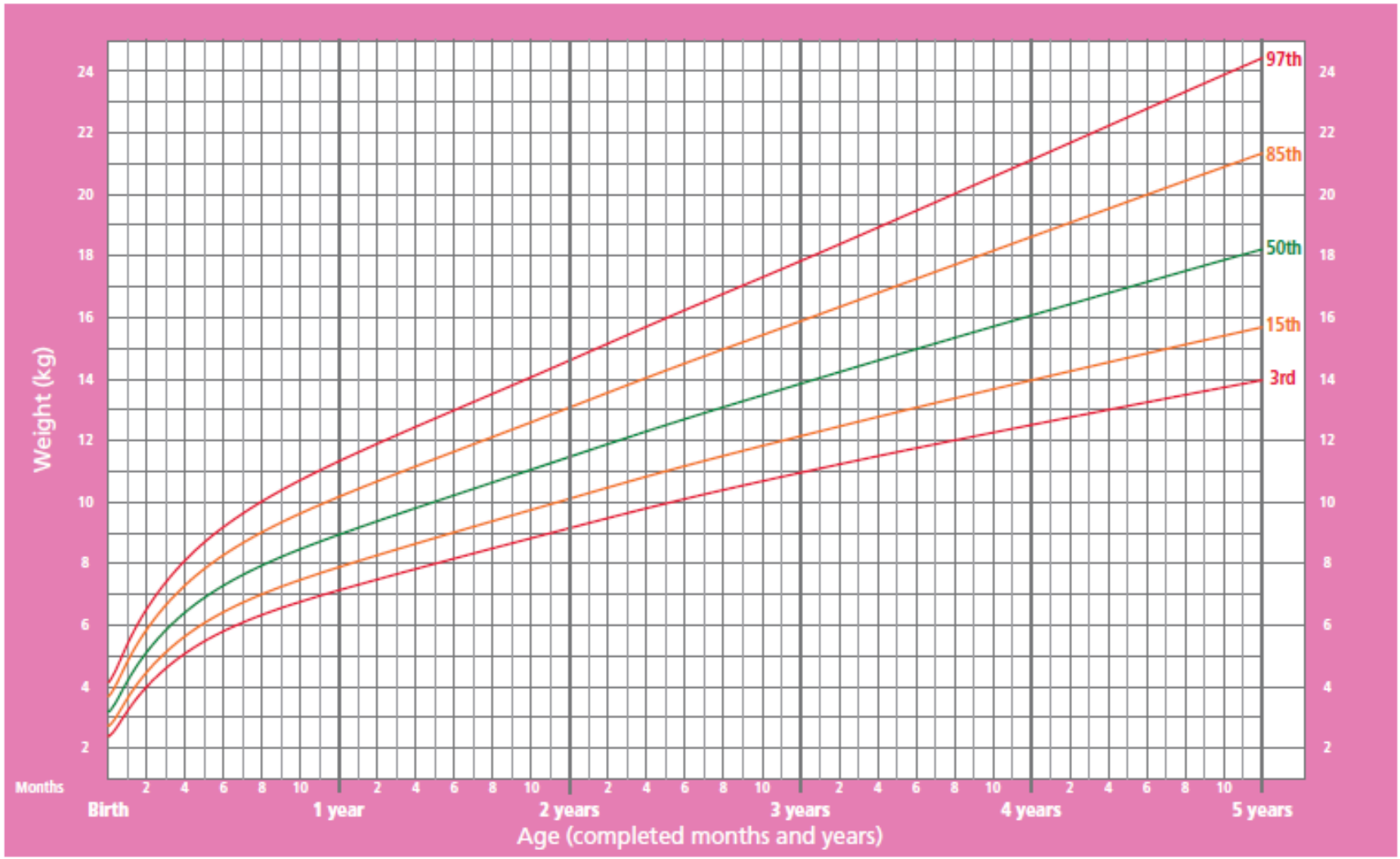
GIRLS					BOYS			
weight (kg)	weight (kg)	weight (kg)	weight (kg)	length (cm)	weight (kg)	weight (kg)	weight (kg)	weight (kg)
-3SD	-2SD	-1 SD	median		median	-1 SD	-2SD	-3 SD
3.1	3.4	3.7	4.0	53.0	4.0	3.7	3.4	3.1
3.3	3.6	3.9	4.3	54.0	4.3	3.9	3.6	3.3
3.5	3.8	4.2	4.5	55.0	4.5	4.2	3.8	3.6
3.7	4.0	4.4	4.8	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					**BOYS**			
weight (kg)	**weight (kg)**	**weight (kg)**	**weight (kg)**	**Height (cm)**	**weight (kg)**	**weight (kg)**	**weight (kg)**	**weight (kg)**
-3 SD	**-2 SD**	**-1 SD**	**median**		**median**	**-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)

World Health Organization

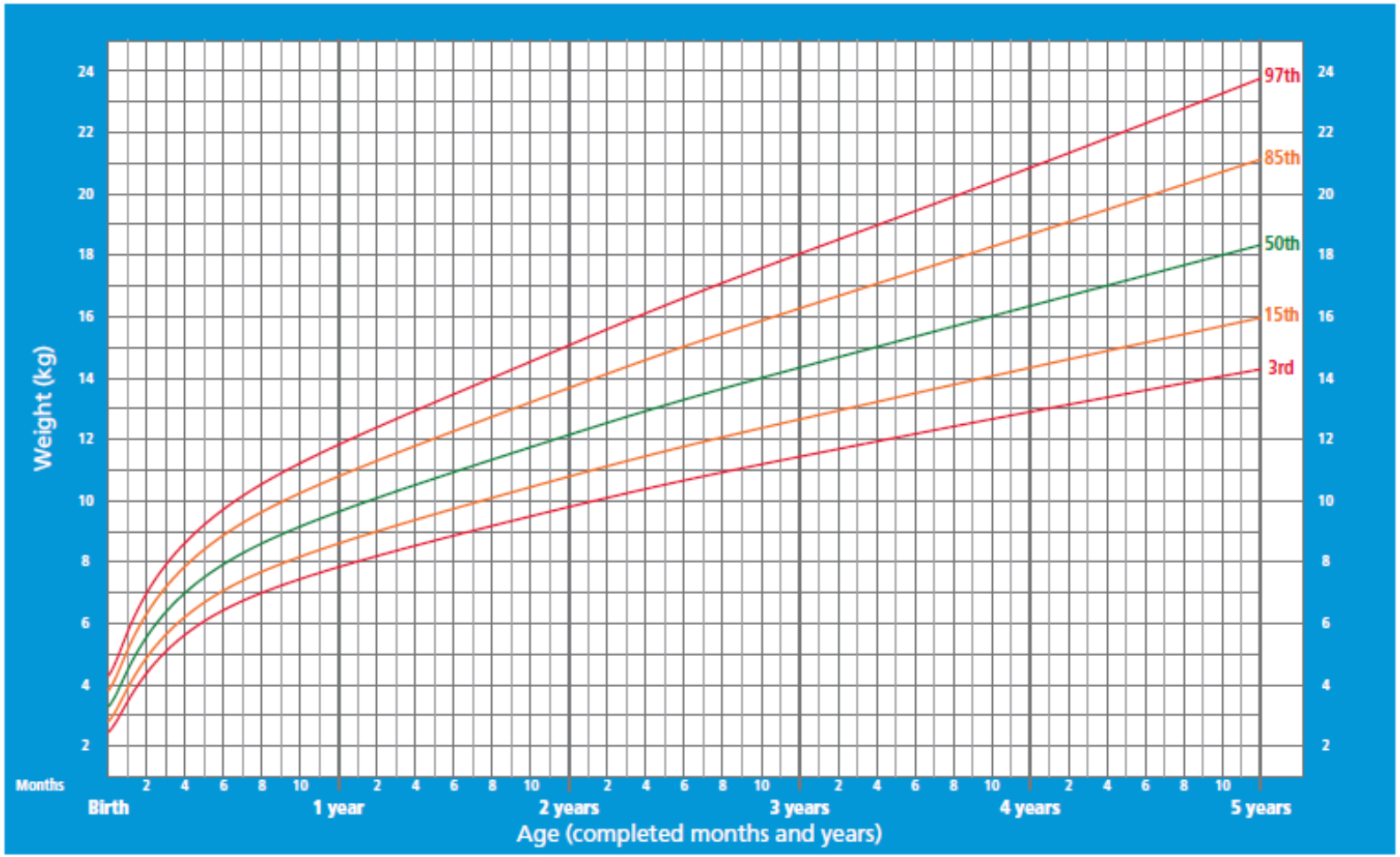


WHO Child Growth Standards

Weight-for-age BOYS

Birth to 5 years (percentiles)

World Health Organization

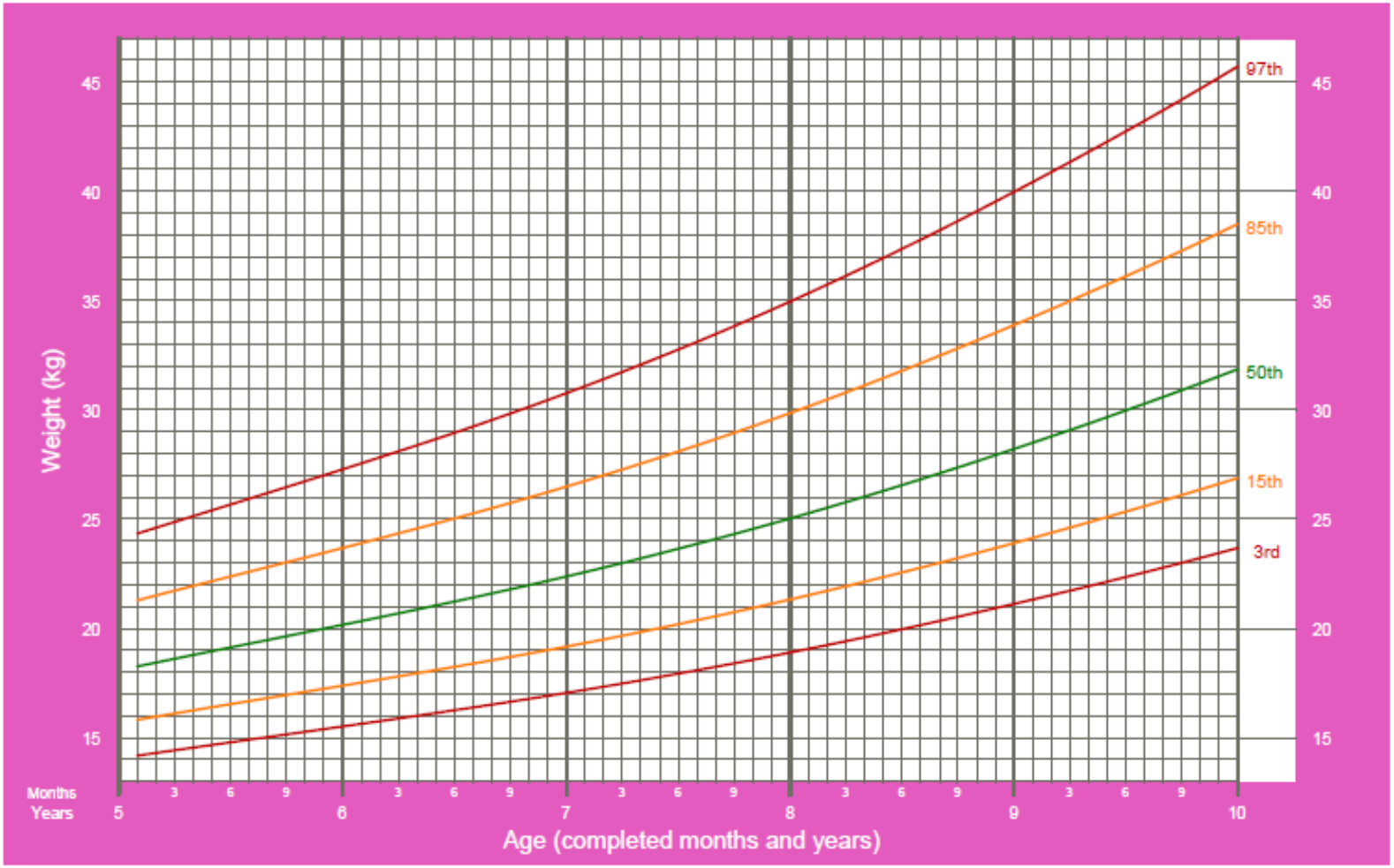


WHO Child Growth Standards

Weight-for-age GIRLS

5 to 10 years (percentiles)

World Health Organization

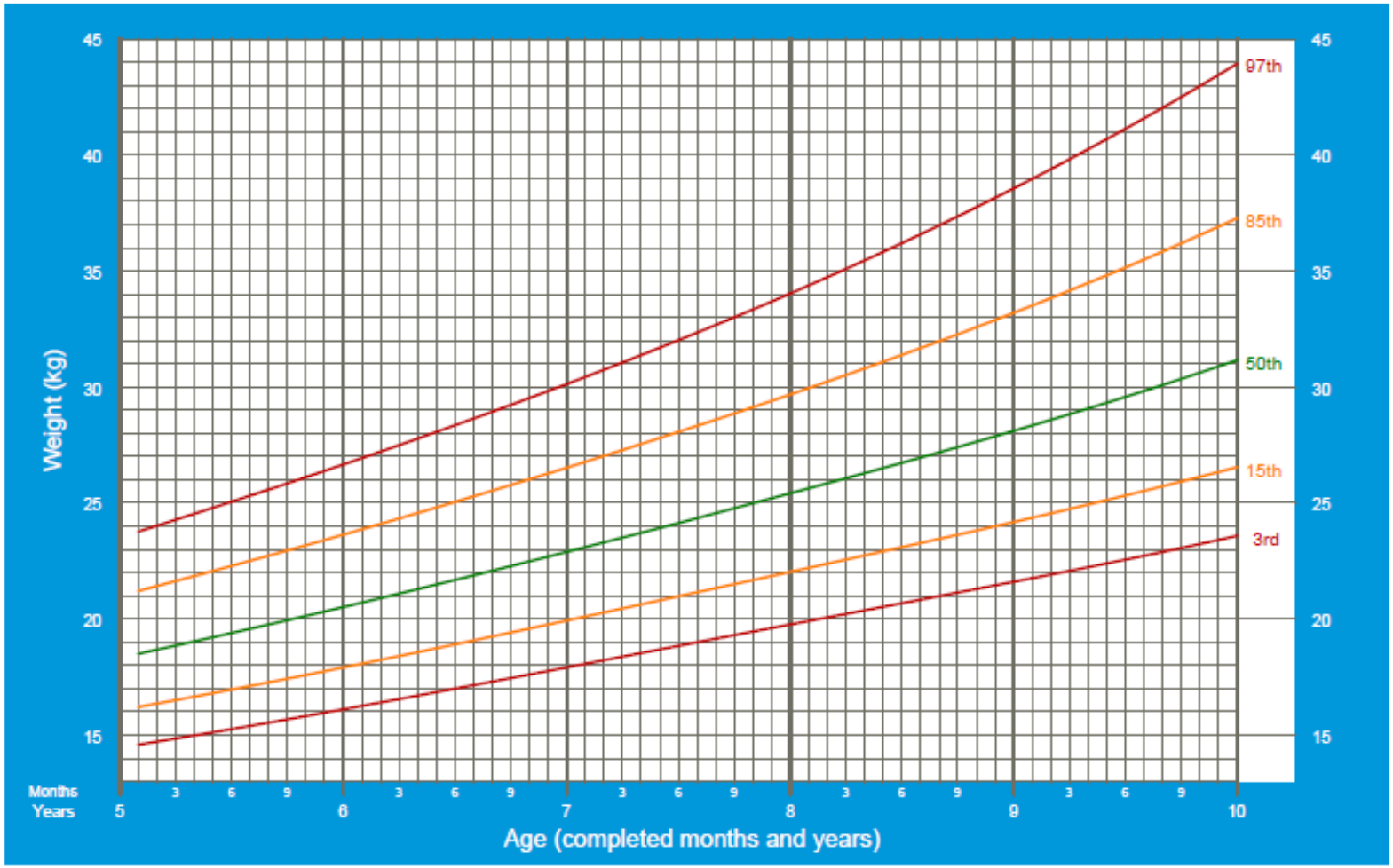


2007 WHO Reference

Weight-for-age BOYS

World Health Organization

5 to 10 years (percentiles)



2007 WHO Reference

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

<table>
<tr><th>Diagnosis</th><th>Symptoms</th><th>Workup</th><th>Treatment</th></tr>
<tr><td colspan="4">Mycobacterial Diseases</td></tr>
<tr><td>Tuberculosis</td><td>• 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</td><td>• History of TB contact?
• Chest x-ray, TST
• Symptom directed:
○ Abdominal U/S
○ Lumbar puncture
○ Retina exam
○ Tissue aspirate:
▪ Lymph node
▪ Bone/joint
▪ Bone marrow</td><td>• Category 1:
○ 2 RHZE/ 4 RH
• Miliary TB/TB meningitis:
○ 2 RHZS/ 4 – 10 RH
○ Predisone 2 mg/kg x28d. if TB meningitis
• Consider adding azithromycin 10 mg/kg daily if CD4 below age-related MAC threshold
<table><tr><th>Drug</th><th>Daily dosage in mg/kg (range)</th><th>Maximum dose/day</th></tr><tr><td>Rifampicin (R)</td><td>15 (10-20)</td><td>600 mg</td></tr><tr><td>Isoniazid (H)</td><td>10 (10-15)</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></table></td></tr>
<tr><td>BCG infection</td><td>• Abscess or ulceration at the vaccination site
• Lymphadenitis in the axilla, supraclavicular area, or neck on same side as BCG vaccination
• Disseminated BCG
○ Fever, weight loss
• Bone infection
• Erythema nodosum, iritis, lupus vulgaris</td><td>• Chest x-ray
• Lymph node aspirate
• Retina exam
• Culture is important to distinguish from TB</td><td>• 6 RHE
○ Ensure dosed at weight-based upper limit (higher than usual for TB)
○ Consider 2 RHZE/ 4 RHE to treat BCG and TB if diagnosis uncertain and culture not available</td></tr>
<tr><td>Mycobacterium avium complex</td><td>• Persistent or recurrent fever
• Weight loss/Failure to thrive</td><td>• CBC and LFTs
○ Pancytopenia, high</td><td>• Azithromycin 10mg/kg PO daily, and
• Ethambutol 15 mg/kg PO daily, +/-</td></tr>
</table>

	• Sweats, fatigue • Persistent diarrhea or recurrent abdominal pain • Lymphadenopathy, hepatomegaly, and splenomegaly	alkaline phosphatase • Lymph node aspirate for smear and culture • Bone marrow aspirate	• 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: ○ <12 months: <750 cells/mm^3 ○ 12-24 months: <500 cells/mm^3 ○ 2 – 5 years: <75 cells/mm^3 ○ ≥6 years: <50 cells/mm^3
Fungal Diseases			
Cryptococcal meningitis	• Fever and headache • Vision change • Neck stiffness, cranial nerve palsy (late stages) • Usually age >6 years and CD4 <100 cells/ mm^3	• CBC, chemistry, LFT • Blood culture • CSF evaluation for: ○ Opening pressure ○ CSF Gram stain and culture ○ India (Chinese) ink stain ○ Cryptococcal antigen • Ophthalmologic exam • Chest xray	• 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 >100 cells/mm^3 for >6 months on adherent ART • If opening pressure >20 cm CSF: ○ 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
Histoplasmosis	• Acute pulmonary histoplasmosis: ○ Cough, fever, malaise, chills,	• Pancytopenia, elevated transaminases, and very	• Amphotericin B 1 mg/kg/day IV for at least 2 weeks, *followed by*

	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	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	• 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: ○ >5 years of age ○ >12 months of antifungal treatment ○ CD4 >15% and >150 cells/mm^3 after 6 months of adherent ART • Restart itraconazole or fluconazole in if the CD4 count falls below the thresholds above
Penicilliosis	• 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* • CNS disease with brain abscess has been reported	• 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	• 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 intraconazole is not available • Itraconazole 5 mg/kg PO daily should be given until immune restoration occurs. • Secondary prophylaxis may be discontinued if: ○ >5 years of age ○ >12 weeks of antifungal treatment ○ Immunological restoration

			with CD4 >150 cells/mm^3 after 6 months of ART

Pneumocystis jiroveci pneumonia (PCP)	• Fever, tachypnea, dyspnea, and cough, usually infant 2 – 6 months
	  ○ CD4 does not determine risk in infants
	• Abrupt or slow onset
	• Poor feeding or weight loss
	• Hypoxia often severe, room-air O2 below 85% common
		• CXR: bilateral hazy, 'ground-grass', granular, **or normal**.
		• Lung sounds often only mildly abnormal
		• LDH usually elevated
		• Sputum silver stain or DFA where available
			• Cotrimoxazole 15-20/75-100 mg/kg/day, 3-4 divided doses IV for 21 days.
			  ○ May add clindamycin 30 – 40 mg/kg/day divided q8 hours for severe disease
			<u>Corticosteroids</u>
			• Indication:
			  ○ PaO2 <70 mmHg, alveolar-arterial gradient >35 mmHg, or O2 saturation <90%
			• Initial doses:
			  ○ Prednisone 1mg/kg/12h (max 40mg/12h)
			  ○ Methylprednisolone iv 1 mg/kg/6h

Parasitic Diseases			

Toxoplasmosis	• Acute onset over <1 week
	• Focal neurologic dysfunction, *and/or*
	• New seizures, *plus*
	• Fever and headache or altered level of alertness
		• 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
			• Preferred:
			  ○ 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 • Dexamethasone 0.6mg/kg/day for clinical evidence of mass effect or edema on CT • Cotrimoxazole prophylaxis after treatment
Viral Diseases			
CMV	• Acute painless vision loss • CD4 usually very low • Often shortly after starting ART • Disseminated disease: ○ Cough and wheezing ○ Clinical hepatitis ○ Diarrhea, often bloody ○ Pancytopenia ○ Encephalitis	• Retina exam with perivascular exudates • Pancytopenia on CBC • Elevated ALT, LDH, and alkaline phosphatase • Definitive diagnosis of disseminated disease requires biopsy or PCR	• Intra-ocular ganciclovir injections for retinitis • Ganciclovir IV (where available) for disseminated or CNS disease • ART