

KINGDOM OF CAMBODIA  
NATION RELIGION KING



MINISTRY OF HEALTH

# NATIONAL HIV CLINICAL MANAGEMENT GUIDELINES FOR INFANTS, CHILDREN AND ADOLESCENTS IN CAMBODIA

Fifth edition 202



NATIONAL CENTER FOR HIV/AIDS, DERMATOLOGY AND STD (NCHADS)

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## PREFACE

Cambodia is one of the successful countries in the Western Pacific Region in the national responses to HIV epidemic in reducing the HIV prevalence among people aged 15 – 49 years old from 1.7% in 1998 to 0.5% in 2018 with an estimation of 73,000 People Living with HIV (PLHIV). Cambodia has launched the comprehensive continuum of care (COC) framework for PLHIV in 2003, achieved the 90-90-90 targets in 2017 and announced its intent to further control the HIV epidemic by achieving the UNAIDS 95-95-95 targets moving towards the elimination of new HIV infection by 2025.

One of key successful elements of HIV response, Cambodia has developed and published the first HIV clinical guidelines during the launch of COC in 2003 to ensure high coverage and improve quality HIV/AIDS care and treatment services for Cambodian people. These guidelines are an important part of the national AIDS strategy to eliminate mother to child transmission (MTCT) of HIV and reduce HIV-related mortality.

The first version of the National Guidelines for the Use of Pediatric Antiretroviral Therapy was published in October 2004 to improve high quality HIV/AIDS care and treatment for Cambodian children. The guidelines were periodically revised in November 2007, 2012, 2015 and at this time in 2019. These guidelines were updated to align with 2019 WHO recommendations on the use of Antiretroviral Drugs for Treating and Preventing HIV Infection.

During a series of technical working group meetings and at a consultative workshop, staff from NCHADS, National Pediatric Hospital, University of Health Sciences, Angkor Hospital for Children, clinical mentors, UN agencies, and other non-governmental organization (NGO) partners reviewed and revised the 2015 guidelines. Their comments, as well as clinical experience from pediatric AIDS care sites in Cambodia, were incorporated in the revised edition of the guidelines.

The Ministry of Health Cambodia has officially approved the National HIV Clinical Management Guidelines for Infants, Children and Adolescents in Cambodia and encourages pediatricians to references the guidelines when providing antiretroviral therapy to HIV-infected infants, children and adolescents in Cambodia.

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**Prof. ENG HUOT**  
SECRETARY OF STATE

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

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



Dr. Ly Penh Sun

# ABBREVIATIONS

ART	Antiretroviral Therapy	NCHADS	National Center for HIV/AIDS, Dermatology
ARV	Antiretroviral drug(s)	NMCHC	National Maternal and Child Health Centre
AZT	Zdovudine	NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
CBC	Complete Blood Count	NRTI	Nucleoside Reverse Transcriptase Inhibitor
CD4	T-CD4+ Lymphocyte	NPH	National Pediatric Hospital
CDC	Center for Disease Control	NVP	Nevirapine
CENAT	National Centre for Tuberculosis and Leprosy Control	OI	HIV related Opportunistic Infection
CK	Creatine Kinase	PCP	Pneumocystis jiroveci pneumonia
CMV	Cytomegalovirus	PCR	Polymerase chain reaction
CNS	Central Nervous System	PLHIV	Person/people living with HIV
CrCl	Creatinine Clearance	PI	Protease Inhibitor
CTX	Cotrimoxazole	PID	Pelvic Inflammatory Disease
DBS	Dried Blood Spot	PMTCT	Prevention of Mother to Child Transmission
DNA	Deoxyribonucleic acid	PPD	Purified Protein Derivative (skin test for tuberculosis)
DOT	Directly Observed Therapy	PPE	Papular Pruritic Eruption
EC	Enteric Coated	PTB	Pulmonary Tuberculosis
EFV	Efavirenz	R	Ritonavir (when given in association with other PIs for boosting effect)
EIA	Enzyme immune assay	R	Ritonavir
ELISA	Enzyme linked immunosorbent assay	RNA	Ribonucleic acid
EPTB	Extra-pulmonary Tuberculosis	SGC	Soft Gelatin Capsules
ESRF	End Stage Renal Failure (Dialysis dependent)	STI	Sexually Transmitted Infection
FDC	Fixed Dose Combination	TAMs	Thymidine analog mutations
FTC	Emtricitabine	TB	Tuberculosis
GI	Gastrointestinal	TDF	Tenofovir disoproxil fumarate
HAART	Highly Active Antiretroviral Therapy	TST	Tuberculin Skin Test
HBsAg	Hepatitis B Surface Antigen	VCCT	HIV voluntary confidential counseling and testing
HBV	Hepatitis B Virus	UNICEF	The United Nations Children's Fund
HCV	Hepatitis C Virus	VDRL	Venereal Diseases Reference Laboratory (refers to a test for syphilis)
HGC	Hard Gelatin Capsules	VL	Plasma HIV Viral Load
HIV	Human Immunodeficiency Virus	WHO	World Health Organization
HLA	Human Leukocyte Antigen		
HSS	HIV Sentinel Survey		
HSV	Herpes Simplex Virus		
IPT	Isoniazid Preventive Therapy		
KBH	Kantha Bopha Hospital		
KSFH	Khmer Soviet Friendship Hospital		
LDH	Lactate Dehydrogenase		
LDL	Low-Density Lipoprotein		
LIP	Lymphoid interstitial pneumonitis		
LPV	Lopinavir		
LPV/r	Lopinavir/ritonavir coformulated in 4:1 dosing ratio		
PLV/R	Lopinavir/ritonavir with extra ritonavir boosting in 1:1 ratio		
MAC	Mycobacterium avium complex		
MTCT	Mother to Child Transmission		

# CHAPTER 1: BACKGROUND AND INTRODUCTION

Through concerted efforts of all stakeholders including the Royal Government of Cambodia, UN agencies, development partners, civil society, and the community, the prevalence of HIV infection among the general population aged 15-49 years has decreased from 1.7% in 1998 to 0.5 % in 2018. In 2018, it was estimated that over 73,000 people are living with HIV/AIDS. Among those, 60,000 PLHIV received ART. Of those, 30,301 women over 14 years-old were receiving antiretroviral therapy (ART). In addition, there are an estimated 3,242 children living with HIV of whom 2,983 were receiving antiretroviral therapy (ART) at the end of 2018.<sup>1</sup> Despite diminishing prevalence rates, the HIV/AIDS treatment and care is still a critical demand over the next decade, especially considering the expanded treatment thresholds children and the number of HIV-infected adolescents transitioning into adult care.

Since 2003, the National Center for HIV/AIDS, Dermatology and STD (NCHADS) has implemented a Continuum of Care (CoC) framework, which is a comprehensive care, treatment, and support system for people living with HIV. The Guidelines for Diagnosis and Antiretroviral Treatment of HIV Infection in Infants, Children and Adolescents in Cambodia is 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. This revision represents the 5<sup>th</sup> edition of the National Guidelines for the Use of Pediatric Antiretroviral Therapy, which were previously approved by the Ministry of Health in October 2004 and revised in 2007, 2010, 2012, and 2015.

The 2019 revision of the Guidelines for Diagnosis and Antiretroviral Treatment of HIV Infection in Infants, Children and Adolescents in Cambodia is a collaborative effort led by NCHADS and other partners include National Pediatric Hospital, Angkor Hospital for Children, University of Health Sciences, Center of HOPE, CHAI, FHI 360 and other partners who have contributed to the treatment, care, and support of children living with HIV/AIDS in Cambodia.

These guidelines have been updated to align with recommendations from the WHO Guidelines for the diagnosis, prevention and management of Cryptococcal disease in HIV-infected adults, adolescents and children, March 2018, WHO Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV Interim guidance, 27 December 2018 and Update of recommendations on first- and second-line antiretroviral regimens, July 2019<sup>2,3,4</sup> WHO continues to review their guidelines and updated their recommendations after the printing of this guidelines and NCHADS will communicate to clinicians to provide up to date medical sciences particularly on HIV/AIDS management.

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<sup>1</sup> UNAIDS Country factsheet 2018 <https://www.unaids.org/en/regionscountries/countries/cambodia>

<sup>2</sup> WHO Guidelines for the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children, Mar 2018 <https://www.who.int/hiv/pub/guidelines/cryptococcal-disease/en/>

<sup>3</sup> WHO Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV Interim guidance, 27 December 2018

<sup>4</sup> Update of recommendations on first- and second-line antiretroviral regimens <https://www.who.int/hiv/pub/arv/arv-update-2019-policy/en/>

## What is new in the guidelines?

- These guidelines have combined into one, the guidelines for diagnosis, antiretroviral therapy, and the guidelines for the management of common opportunistic infections in infants, children and adolescents.
- LPV/r-based regimen is the preferred initial ART regimen for children weighing < 20kg regardless of exposure to NNRTI for PMTCT.
- In addition to the existing formulation of heat stable LPV/r tablets (100/25mg), LPV/r granules (40/10mg) are a new formulation which has been available in Cambodia since February 2020. The mode of administration is simpler and can be mixed with water. LPV/r oral granules are recommended for infants and children 14 days of age and older in combination with other ARVs.
- For neonates who cannot start with LPV/r-based regimen, the ARVs regimen should consider using NVP-based or RAL-based regimen, according to stock availability.
- DTG-based regimen is the preferred first line for children weighing  $\geq$  20kg.
- ABC is preferred as part of the NRTI backbone in first line therapy for children weighing < 30 kg, with AZT as an alternative.
- TDF is recommended as part of the NRTI backbone for children  $\geq$  30kg.
- The regimens of children with HIV/HBV co-infection are also updated based on the preferred LPV/r-based or DTG-based regimen with recommended ARVs backbone available for each weight group.
- The testing algorithm followed the previous 2016 Guidelines. However, it is emphasized that for HIV-exposed infants who missed receiving HIV PCR testing at birth, the first PCR test should be performed as soon as possible and follow-up testing should be done according to the testing algorithm.
- The management of prophylaxis for HIV exposed infants was emphasized for those HIV exposed infants who did not receive prophylaxis since at birth and come late to the PAC sites.
- A committee is established to help guide decisions on the use of third line therapies. Please consult a mentor or the Paediatric AIDS Care Technical Working Group (PAC TWG) if a case is considered eligible for third line therapy.
- The TB section is aligned with the National HIV/TB guidelines, and in addition outlines issues regarding drug resistant TB, introduces the use of the now widely available GeneXpert MTB/RIF test, and includes the expanded recommendation for all PLHIV to have a course of tuberculosis prevention therapy (TPT). The TPT eligible criteria and regimen options were also updated.
- The section on Post Exposure Prophylaxis (PEP) has been updated to include new ARV regimens option.
- Prevention of opportunistic infections has been updated, with cryptococcal antigen screening to take the place of routine fluconazole prophylaxis.

## **Who should use the guidelines?**

These guidelines should be used as a reference document for all healthcare workers providing care and treatment for children living with HIV/AIDS in Cambodia. The guidelines are designed to assist clinical judgment for pediatricians and other health care workers in order to provide high quality and standardized treatment to HIV-infected children. The updated curriculum and ready accessible Job aids to assist with patient management have been developed to complement the guidelines. Training on the updated guidelines will also occur.

## CHAPTER 2: HIV OVERVIEW

### 2.1 Pathophysiology of HIV infection

Human immunodeficiency virus (HIV) is lentivirus (subtype of retrovirus) 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, ribonucleic acid (RNA) enters the nucleus and is converted to deoxyribonucleic acid (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. 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 becomes weaker resulting in increased susceptibility to infections.

### 2.2 HIV transmission to children

HIV can be transmitted to children from HIV-infected pregnant women:

- During pregnancy
- At the time of delivery
- During breastfeeding.

HIV can also be transmitted later in childhood and adolescence through:

- Sexual abuse
- Consensual sex
- Unsafe injections or infusions, including piercing, tattooing and the use of inadequately sterilized medical equipment
- Transfusion of inadequately screened blood products
- Accidental needle stick injury contaminated with HIV-infected blood (see below section on post-exposure prophylaxis).

Mother to child transmission can be greatly reduced by the provision of antiretroviral therapy (ART) to the HIV-infected mother during pregnancy and delivery, with continued ART through the duration of breastfeeding. Without intervention, approximately one-third of infants will become HIV-infected; however, ART given to HIV-infected pregnant women may reduce HIV transmission to below 2%.

**Table 1: Risk Factors for Maternal HIV Transmission**

Maternal factors	Infant factors
High Viral load	Prematurity
Low CD4 count	Use of fetal scalp electrode monitoring
Advanced AIDS	Prolonged rupture of membranes and traumatic delivery
Chorioamnionitis	Receipt of mixed feedings

Prolonged rupture of membranes	Breastfeeding
Cracked or bleeding nipples while breastfeeding	Mouth lesions
New maternal infection during pregnancy or breast feeding	Receipt of pre-chewed foods

## CHAPTER 3: ELIMINATION OF MOTHER TO CHILD TRANSMISSION (EMTCT)

Cambodia committed to the dual elimination of mother-to-child transmission (eMTCT) of HIV and syphilis by 2025. In order to achieve the dual EMTCT goals in Cambodia, all women presenting for antenatal care (ANC) should be offered HIV and syphilis tests. Women presenting at delivery or post-partum with unknown status should also be offered HIV and syphilis testing. In this way, the exposure status of virtually all infants should be known, which will help guide the further management of the mothers and infants in order to prevent mortality and morbidity from these conditions.<sup>5</sup>

Cambodia's prevention of mother-to-child transmission (PMTCT) program has made substantial progress over the last 10 years. As HIV prevalence among pregnant women (PW) has fallen, mother-to-child transmission of HIV (MTCT) has similarly declined. The modeled rate of transmission has declined to 6.2% at 6 weeks in 2015 from an estimated 37% in 2007. However, MTCT rate at the end of breastfeeding period, projected via latest SPECTRUM for 2017, is 13%, which is concerning and is indicative of programmatic challenges to identifying HIV+ PW, initiating them on ART, and providing care and testing to HIV-exposed infants (HEI).

Based on the Health Information System (HMIS) 2017 – 2018, 100% of PW received ANC1 from a trained provider at least once. In 2018, 90.06% of ANC clients and 88.5% of delivery clients in government facilities knew their HIV status.<sup>6</sup> According to NMCHC report in 2018, 89.7% of HIV-positive pregnant women received antiretroviral therapy during pregnancy to reduce the risk of MTCT<sup>6</sup>. The number of HIV infected PW is expected to decline from 954 in 2015 to 766 by 2020 and below 500 by 2025.<sup>7</sup>

### 3.1 Immediate Care of the HIV-exposed Newborn Baby

- HIV DNA-PCR at birth
- Infants should be vaccinated as per the Expanded Program on Immunizations (EPI) schedule below (Table 2).
- BCG must be given to all infants, unless the baby has signs of HIV at the time of vaccination (e.g., failure to thrive, lymphadenopathy, hepatosplenomegaly).
- Nevirapine (NVP) prophylaxis is given at birth for 6 weeks to all HIV-exposed children not in high-risk situations of HIV transmission
- Dual Nevirapine (NVP) and Zidovudine (AZT) prophylaxis is given at birth to HIV-exposed infants **in high-risk situations** to reduce MTCT regardless of maternal ART. This is also highly effective in reducing MTCT through breast milk. NVP and AZT should be administered for 6 weeks for both breastfed and non-breastfed infants. Breastfed infants

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<sup>5</sup> Standard Operating Procedure for Implementation of the Boosted Linked Response between HIV and SRH for Elimination of New Pediatric HIV Infections and Congenital Syphilis in Cambodia, 2013

<sup>6</sup> Source: NMCHC 2018, NIS 2013-2023

<sup>7</sup> National Road Map for eMTCT in Cambodia, July 2018

should continue infant prophylaxis with NVP alone for an additional 6 weeks (total of 12 weeks of prophylaxis)<sup>8</sup>.

- **High-risk infants are defined as those**
  - born to women with established HIV infection who have received less than four weeks of ART at the time of delivery, OR
  - born to women with established HIV infection with VL >1000 copies/mL in the four weeks before delivery, if VL available, OR
  - born to women diagnosed HIV positive at the delivery or during the postpartum period.
- Mothers living with HIV should breastfeed for at least 12 months and can continue breastfeeding for up to 24 months or longer (as for the general population) while being fully supported for ART adherence.<sup>9</sup>
- Mothers living with HIV and healthcare workers can be reassured that ARV treatment is effective at reducing the risk of postnatal HIV transmission in the context of mixed feeding and that mixed feeding in itself is not a reason to stop breastfeeding.
- Mothers living with HIV and healthcare workers can be reassured that shorter durations of breastfeeding less than 12 months are better than never initiating breastfeeding.
- For HIV exposed infant who did not receive prophylaxis since birth and come late to the PAC sites
  - If the child is not breastfed, then ARV prophylaxis isn't needed as it is too late to initiate the ARVs prophylaxis after 48-72 hours.
  - If the child is breastfed, then the infant should be started prophylaxis;
    - a) If mother is newly diagnosed or otherwise fits into “high risk” category then the infant should be initiated with dual ARV as high-risk scenario.
    - b) If mother is on ART and in “low risk” category, and infant is just presenting late, then HEI should be started prophylaxis as low risk scenario.

**Table 2: Expanded Program on Immunization (EPI) Vaccination Schedule**

Vaccine	Age						
	At birth	6 weeks	10 weeks	14 weeks	6 months	9 months	18 months
BCG	x						
Hepatitis B	x						
bOPV		x	x	x			
IPV				x			
DTP-HepB-Hib		x	x	x			
PCV		x	x	x			
Measles-Rubella					x	x	x
JE:SA14-14 2 vaccines						x	

<sup>8</sup> Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, WHO, 2016 and WHO Updated recommendations on first-line and second-line antiretroviral regimens and post exposure prophylaxis and recommendations on early infant diagnosis of HIV Interim guidance, 27 December 2018.

<sup>9</sup> Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, WHO, 2016

**Table 3: Nevirapine and Zidovidine Dosing (10mg/ml)**

Infant age	Weight at birth	Dosing of NVP	Dosing of AZT
From birth to 6 weeks (Breastfeeding or non-breastfeeding infants)	2000 – < 2500g *	10 mg once daily (1ml of syrup once daily)	10 mg twice daily (1ml of syrup twice daily)
	≥ 2500g	15 mg once daily (1.5ml of syrup once daily)	15 mg twice daily (1.5ml of syrup twice daily)
From 6 weeks to 12 weeks (for breast feeding infants)		20 mg once daily (2ml of syrup once daily OR ½ of a 50mg tablet once daily)	

\* For Infants weighing <2000g and above 35 weeks gestational age the suggested doses are: NVP 2mg/kg per dose once daily and ZDV 4mg/kg per dose twice daily. Premature infants below 35 weeks gestation should be dosed using expert guidance.

**Table 4: Summary of Mother on ART and Infant ARV Prophylaxis**

Mother	Risk Status of HIV Exposed Infant HIV	Infant feeding status	Infant prophylaxis *
<b>Urgently initiate</b> TDF +3TC + DTG** <i>(Fixed-Dose Combination)</i>  regardless of WHO stage and CD4 count and continue lifelong	<b>High Risk situations:</b> 1. Mother on ART who have received less than 4 weeks of ART at the time of delivery <b>or</b> 2. Mother diagnosed HIV positive at delivery or during postpartum period or 3. Mother with established HIV infection with VL >1000 copies/mL in the 4 weeks before delivery, if VL available	Formula feeding	Dual NVP and AZT for 6 weeks
		Breast feeding	Dual NVP and AZT for 6 weeks then continue NVP alone for another 6 weeks
	<b>Low Risk situations:</b> Not fall in the high-risk situations.	Breast feeding or formula feeding	NVP for 6 weeks

\* In case of NVP reaction, discuss with ART clinic.

\*\* Same day ART should be done with pregnant women if no contra-indication.

# CHAPTER 4: DIAGNOSIS OF HIV INFECTION IN CHILDREN

## Tests available for diagnosing children and how to use them.

Two types of HIV tests are available for diagnosing children in Cambodia:

- HIV antibody detection tests (e.g. rapid tests)
- HIV viral detection tests e.g. HIV DNA PCR (polymerase chain reaction).

### 4.1 Antibody tests

- Maternal HIV antibodies are transferred via the placenta to the baby during pregnancy, so that all vertically exposed babies will be born with HIV antibodies, and will test positive on antibody detection tests, whether they are infected with HIV or not. Thus, HIV antibody detection tests cannot determine HIV status in an infant under 18 months of age, or until six weeks after breastfeeding cessation.
- Almost all infants will have lost maternal HIV antibodies by 18 months of age if they are not HIV-infected.
- If antibodies to HIV are found in children <18 months of age, this indicates HIV exposure has occurred, and an HIV PCR test is **required** to establish the infection status of the child (see figure 1 below).
- A negative antibody detection test at any age excludes HIV infection, if the child was last breastfed  $\geq 6$  weeks before the test and has no clinical signs of HIV infection.
- Children who are breastfed by HIV positive mothers are at ongoing risk of acquiring HIV.
- Children diagnosed with HIV infection using repeat HIV PCR tests who are then treated with ART should **not** receive repeat antibody testing. Some children with confirmed HIV infection using PCR who receive ART early enough may have a negative antibody test later and this will lead to confusion in caregivers.
- Antibody testing is recommended for all children over 18 months of age with known HIV exposure who have not previously been diagnosed with HIV infection to confirm their infection status.
- A positive antibody test in a child  $\geq 18$  months of age indicates that the child is HIV-infected, and ART should be started according to these guidelines.
- The same HIV antibody tests used for diagnosing adults can be used in children and may be done wherever healthcare providers suspect that a child may have HIV (see figure 1 below), and where antibody testing is available. If test kits are unavailable, refer to the nearest VCCT, Health Centre, Referral Hospital, or Provincial Hospital where HIV testing can be performed.

### 4.2 HIV PCR test

- HIV PCR tests (DNA or RNA) detect proviral DNA or viral RNA, indicating HIV infection of the child. Only a drop of blood is necessary for these tests and can be taken from a baby by pricking the heel. The blood is dropped onto special paper and dried and sent to the National Laboratory. For the process of dried blood spot (DBS) testing please see DBS Job Aid. The DNA PCR test is a qualitative test. The result will be either POSITIVE or NEGATIVE. HIV RNA PCR test (viral load test) is quantitative (i.e. provides the number of

copies of HIV virus in 1mm<sup>3</sup> of blood and is used for monitoring the amount of HIV in the blood in response to ART). Either HIV PCR can be used for the initial detection of the HIV virus in the infant but DNA PCR is recommended for infant diagnosis in Cambodia.

- HIV PCR testing is used to determine the HIV infection status of an infant less than 18 months of age. All infants who test PCR positive must have a confirmatory second HIV PCR test prior to initiation of ART.
- Obtaining the second HIV PCR to confirm every positive PCR test is mandatory.
- While a second test for confirmation is mandatory, initiation of ART should **not be delayed** while awaiting the result of the confirmatory HIV DNA PCR test.
- If the positive HIV status of a child already initiated on ART is disputed, the patient should receive additional HIV testing at the closest PAC site.

### 4.3 When should HIV testing be conducted in children

HIV-infected infants progress to clinical disease very rapidly, with 20% having severe immunosuppression at 6 weeks of age. Effective ART dramatically reduces the risk of death in HIV-infected infants and children. Always remember to assess, on an ongoing basis, the health of the mother, father and other family members and recommend HIV testing and referral for ART in an attempt to safeguard the family.

The following scenarios describe the different approaches to diagnosing HIV in infants and children, depending on their age and HIV-exposure status.

#### 4.3.1 Child <18 months and the mother is known to be HIV positive

Figure 1 explains as follows:

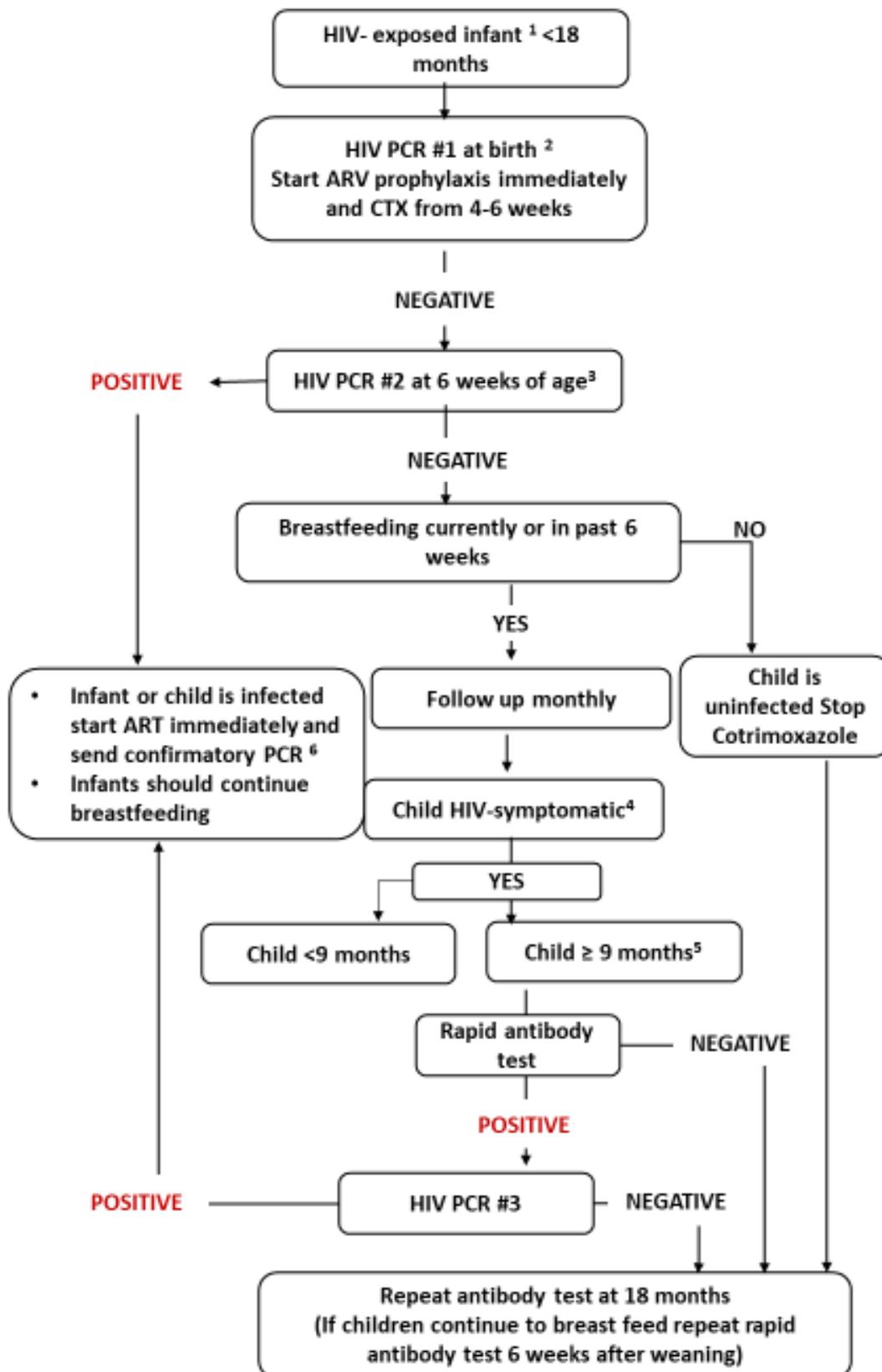
- All HIV-exposed infants require **HIV PCR testing at birth**<sup>10</sup> and ARV prophylaxis should be started. If the initial HIV PCR test is negative at birth, a **further HIV PCR test should be performed at 6 weeks of age**, or at any time of their first contact with the healthcare system after the age of 6 weeks.
- If HIV-exposed infant missed to receive HIV PCR testing at birth, the first PCR test should be performed as soon as possible and follow-up testing should be done according to the testing algorithm.
- If the HIV PCR test is positive, **ART should be started as quickly as possible** and ARV prophylaxis should be stopped. A repeat HIV PCR test confirmatory is required, however do not delay ART initiation while waiting for the confirmatory test result.
- The confirmatory of HIV PCR test could perform at the same time when ART is initiated.
- **A negative birth PCR test does not mean the infant is uninfected and continued follow-up is essential.**
- Cotrimoxazole (CTX) prophylaxis should be started when the child is 6 weeks old.
- In children with a negative HIV PCR at 6 weeks, repeat HIV testing should be conducted ≥6 weeks after the complete cessation of breastfeeding in order to reasonably exclude HIV infection in the breastfed infant. This testing should be conducted as follows:
  - Infants <9 months require HIV PCR testing.

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<sup>10</sup> WHO March 2014 Supplement to the 2013 Consolidated Guidelines on the Use of Antiretroviral drugs For Treating and Preventing HIV Infection, Recommendations for a public health approach.

- Infants  $\geq 9$  months can first have an antibody test. If this antibody test is positive, a HIV PCR test is indicated. If the antibody test is negative, the child is considered uninfected as long as weaning occurred  $\geq 6$  weeks prior to the test.
- Any infants  $< 18$  months who have signs and symptoms of HIV (figure 1) or are found to be exposed after birth, require HIV PCR testing at the earliest possible opportunity (if  $\geq 9$  months and not breastfeeding for  $\geq 6$  weeks, HIV antibody testing can be done and a negative test indicates no HIV infection, positive antibody indicates the need for an HIV PCR test).
- Infants who have completely stopped breastfeeding for at least 6 weeks and have a negative HIV antibody or PCR test are presumed to be HIV uninfected.
- HIV antibody testing is recommended at 18 months of age for all exposed infants, to confirm that the child is uninfected if negative antibody status has not been previously documented.
- Any infant or child with ongoing HIV exposure (e.g. through breastfeeding) must remain on CTX until HIV infection is ruled-out with a negative HIV DNA PCR or antibody test  $\geq 6$  weeks after stopping breastfeeding.

Figure 1: Diagnosis of a known HIV-exposed Infant < 18 months of age



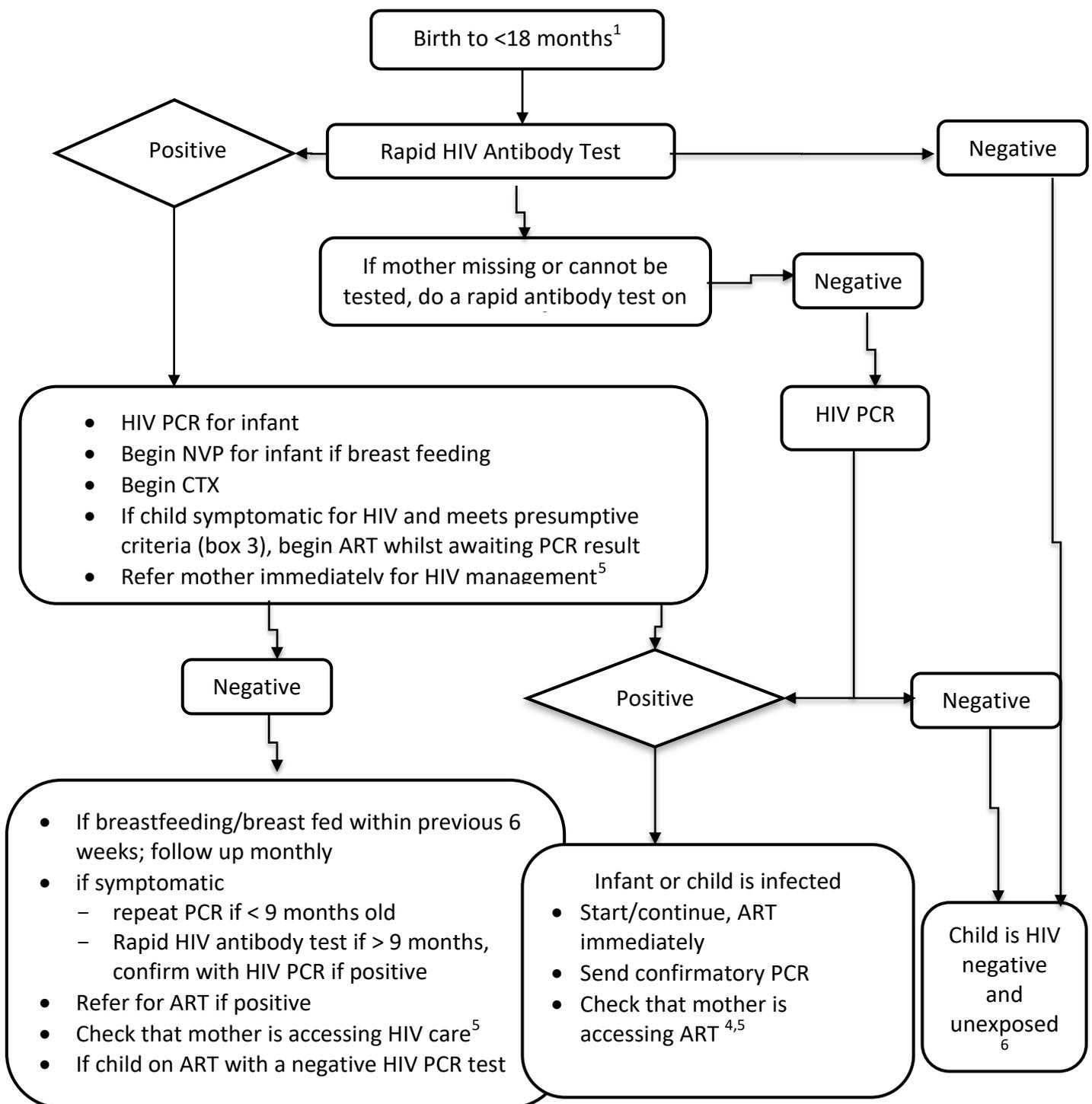
1. *All women should be offered HIV testing during pregnancy or delivery. Infants of HIV seropositive mothers are considered HIV-exposed. Some women may not be identified before the baby is born. Healthcare workers should ask mothers whether they have been tested when they bring their babies for EPI visits, and what the test results showed. Active case management should be conducted to trace known HIV-exposed infants who fail to show up for scheduled visits.*
2. *Birth testing is recommended and may identify high-risk intrauterine infections.*
3. *If birth HIV PCR is negative, the child may still be infected and a second test must be performed at around 6 weeks, to increase detection of HIV-infected infants. Caregivers should not be told that the birth PCR test indicates the child is not infected, as this test has low sensitivity.*
4. *At any time during follow-up, if an HIV-exposed infant develops signs and symptoms of HIV infection (e.g. recurrent infections, thrush >6 weeks of age, hepatomegaly, failure to gain weight, neurological development problem), HIV testing should be conducted at that time.*
5. *A DNA PCR test should be conducted if < 9 months of age. From 9 months of age infants can be screened for infection with a rapid HIV antibody test. If the antibody test is positive, a DNA PCR test should be performed.*
6. *Once a child is confirmed to have HIV-infection, there is no need for subsequent repeat testing.*

#### **4.3.2 Child <18 months and the mother's HIV status is unknown**

When the child < 18 months and the mother's HIV status is unknown, it is recommended to undertake the testing procedure as indicates in figure 2 below.

- **HIV antibody testing** is the initial recommended test where a child has unknown HIV exposure status and presents with signs or symptoms that could indicate HIV infection or who are at risk of being HIV infected (see figure 1 and 2).
- Start with HIV antibody testing **of the mother** if the mother is present.
- **The infant should have an antibody test if mother is absent or has died.**
- If the antibody test of mother or child is positive this will indicate that the baby is exposed, and the infant should then have an HIV PCR test.
- Begin CTX and either ARV prophylaxis or presumptive ART if child been given a presumptive diagnosis of HIV infection whilst waiting for HIV PCR result (See box 3: Presumptive diagnosis of HIV in children, page 33).
- If the HIV PCR test is positive then the child is infected, and ART should be initiated immediately (within two weeks). Stop ARV prophylaxis and continue CTX. Infants already receiving ART because of presumed severe HIV disease should continue ART.
- If the child's or mother's antibody test is negative this indicates that there is no HIV exposure and the child is considered to be HIV negative. An antibody-negative child may still have HIV exposure if mother becomes infected after birth and is currently breastfeeding.
- If the HIV PCR is negative, the child can be considered HIV negative provided this was performed  $\geq 6$  weeks after the complete cessation of breastfeeding. Stop ARV prophylaxis and CTX.
- Be sure to refer mothers for evaluation and treatment if they have a positive antibody test. If a mother with HIV wishes to breast feed, she should first initiate life-long ART.

**Figure 2: Diagnosis of a child <18 months of age whose HIV exposure status is unknown**



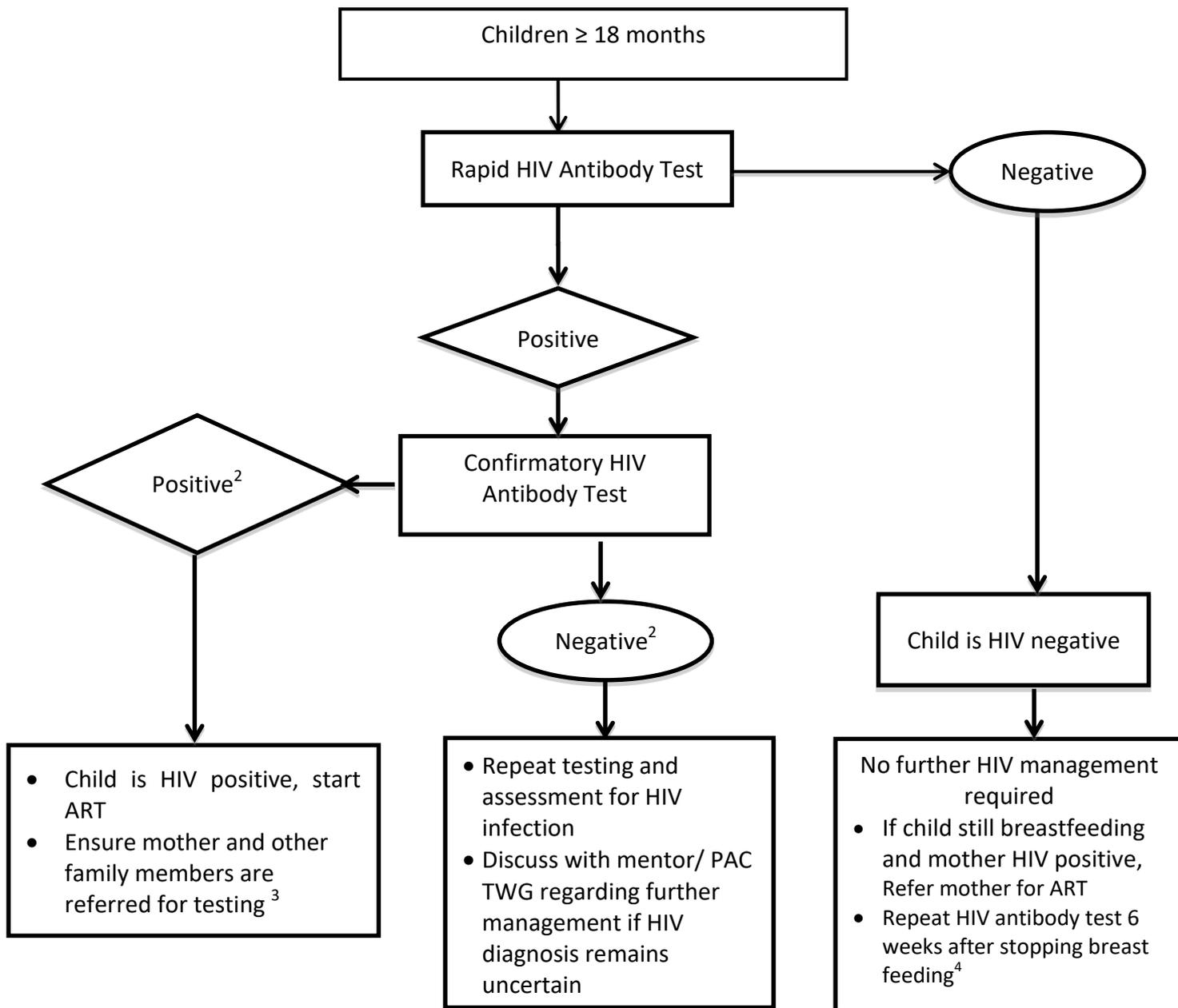
1. *Some children may present at health services with signs and symptoms of HIV or condition such as TB and malnutrition, indicating a need for an HIV test. If the mother has not been previously identified as HIV+, she should also be offered testing.*
2. *Mother (and father if available) should be tested first, if positive this indicates that the child is exposed and should indicate a need for HIV PCR testing in the child.*
3. *If the mother has died, or is absent then antibody testing can be conducted on the infant. A positive antibody test indicates that the baby is HIV exposed and the infant should have an HIV PCR test.*
4. *A negative antibody test for the baby may be misleading as passively transferred antibodies from the mother may decrease from 4 months of age. Encourage absent mothers to come in for testing if possible. If the mother cannot be traced or has died perform HIV PCR testing of the baby as the diagnostic test of choice*
5. *Always consider the mother's health ensuring that she and the rest of the family have access to testing, care and treatment.*
6. *An HIV antibody negative child who is breastfeeding, may still be exposed if the mother becomes infected after delivery.*

#### **4.3.3 Children ≥ 18 months**

- **HIV antibody testing of the child** is the initial recommended test in those ≥ 18 months presenting for the first time with signs or symptoms that could indicate HIV infection or who are at risk of being HIV infected (See figure 1 and 2).
- If the antibody test is positive, a confirmatory antibody test should be performed. If the antibody test is confirmed, a positive result indicates HIV infection, and the child should be started on CTX and ART within two weeks of diagnosis.
- A negative result indicates no HIV infection.
- Discordant results may occur (when the result of the second test differs from that of the first), repeat testing according to national guidelines three test algorithm.

ALL CHILDREN DIAGNOSED WITH HIV SHOULD BE ENROLLED IN PEDIATRIC AIDS CARE AND STARTED ON ART AS QUICKLY AS POSSIBLE

**Figure 3: Diagnosis of a child 18 months or older**



1. Children who present at health services with signs and symptoms of HIV or conditions such as TB or malnutrition should receive an HIV test. If the mother has not been previously identified with HIV, she should be offered testing.
2. Discordant results indicate the need for repeated testing, patients with confusing results should be discussed with the HIV mentor or PAC TWG for decision on further management.
3. Always consider the mother's health status and ensure that she and the rest of the family have access to testing, care and treatment.
4. An HIV antibody negative breastfeeding child may be exposed if the mother becomes infected after delivery.

#### **4.4 HIV-Exposed Uninfected Children (HEU)**

HIV-exposed infants who have negative PCR testing more than 6 weeks after stopping breastfeeding or who have never breast fed, should remain in follow-up care and have a confirmatory rapid test at 18 months of age.

In the first year of life, monthly visits that incorporate vaccinations should be scheduled for all infants during which routine health checks should be performed. Every contact with the healthcare service should be used to ensure that the child's HIV-exposure status is known and documented. At every visit, monitor growth and discuss infant feeding, and check in with the mother about her own health and adherence to ART.

Discuss management of all HIV-infected babies born to women on 2<sup>nd</sup> or 3<sup>rd</sup> line therapy with NCHADS AIDS Care Unit, a clinical mentor or the PAC Technical Working Group (TWG) as they will likely need genotyping and may need individualized regimens.

# CHAPTER 5: POST EXPOSURE PROPHYLAXIS FOR CHILDREN AND ADOLESCENTS EXPOSED TO HIV BY MEANS OTHER THAN MOTHER-TO-CHILD TRANSMISSION<sup>11</sup>

Children or adolescents may be exposed to HIV through:

- Sexual abuse
- Consensual sex
- Unsafe therapeutic injections or infusions, including piercing, tattooing and the use of inadequately sterilized medical equipment
- Transfusion of inadequately screened blood products
- Accidental needle stick injury contaminated with HIV-infected blood
- Human bites (if the biter’s saliva is bloody and a piercing wound is inflicted)
- Exposure to blood or blood-contaminated bodily fluids from an HIV-infected source where there is a breach in skin (e.g., open cuts or wounds) or direct contact with mucous membranes.

In these situations, the risk of HIV-acquisition may be minimized by the administration of ARVs as soon as possible after exposure. This is called Post Exposure Prophylaxis or PEP. PEP must be initiated within 72 hours post exposure but preferably as soon as possible after the event (within 4-6 hours). PEP is of little benefit if given more than 72 hours after the exposure.

A triple combination of drugs is recommended for 28 days. Table 5 provides regimen recommendations for post-exposure prophylaxis; dosing should be given according to the dosing chart or wheel. Intensive adherence counseling to promote adherence to 28 days of treatment should be conducted (See chapter 19: Adherence support for ART in Children, page 92).

**Table 5: Treatment Recommendations for Post-Exposure Prophylaxis**

Age	Preferred Treatment Regimen	Duration
Children < 20Kg	ABC (or AZT) + 3TC + LPV/r*	28 days
Children 20 - 30Kg	ABC (or AZT) + 3TC + DTG	28 days
Adolescents > 30kg	TDF (or ABC) + 3TC + DTG or AZT + 3TC + ATV/r ** (LPV/r)	28 days

\* LPV/r is used for infant > 2 weeks

\*\* ATV/r is used for children’s weight ≥ 35kg

<sup>11</sup> WHO Guidelines on post-exposure prophylaxis for HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children: recommendations for a public health approach: December 2014 supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection

## 5.1 Laboratory assessment and follow up

After potential exposure to HIV, individuals should have baseline and follow-up testing (Table 6 below) for HIV and other infections (depending on mode of exposure).

Table 6 sets out the recommended schedule of testing for individuals who are prescribed PEP. Follow-up HIV testing is no longer recommended at six months. The management of an exposed patient who seroconverts is not included in this laboratory follow up. The symptoms of seroconversion include fever, maculopapular rash, lymphadenopathy and pharyngitis, oral thrush, malaise, arthralgia should be explained to all patients or guardians, with advice to present if these or any other symptoms occur.

Individual need to be referred to family health clinic (STI clinic) for appropriate care and treatment of STI in case sexual exposure, including Hep B vaccination, STI prevention, and post-exposure prophylaxis for HIV infection (Refer to national guidelines for management violence against women and children in health system in 2014 and the National Guidelines for Post-Exposure Prophylaxis after Occupational and Non-occupational Exposure to HIV in 2019. And if a victim is a woman in a reproductive age, she should be referred to family planning service for emergency contraception.

**Table 6: Timing of laboratory tests of Pre and Post PEP includes sexual exposures**

Test	Baseline	Week 6	Month 3
HIV serology	x	x	x
Syphilis serology	x	x	x
Hepatitis B serology	x		x
Hepatitis C serology	x		x
Pregnancy test	x	x	

## 5.2 Pregnancy prophylaxis

Adolescent girls of child-bearing potential who are victims of sexual assault should be offered pregnancy testing at baseline and follow-up. Emergency contraception should be offered as soon as possible and within 5 days following sexual exposure.

## 5.3 Principles in caring for children who have experienced sexual violence

The UNHCR Guidelines on Sexual Violence Response and Prevention and the United Nations Convention for the Rights of the Child (UNHCR 1995) provide some guidance on how to manage children exposed to sexual violence. Health care providers should attempt to adhere to these principles on behalf of the child and promote standards of care that will benefit the child's health and well-being. It is critical that care and support are provided in a child-friendly manner and that the child is not re-victimized in the process for guidance on how to manage children exposed to sexual violence <sup>12</sup> (See Annex 2: Principal for managing child

<sup>12</sup> Day, Kim and Jennifer Pierce-Weeks. 2013. The Clinical Management of Children and Adolescents Who Have Experienced Sexual Violence: Technical Considerations for PEPFAR Programs. Arlington, VA: USAID's AIDS Support and Technical Assistance Resources, AIDSTAR-One, Task Order 1. [www.forensicnurses.org/resource/resmgr/Education/PEPFAR\\_Clinical\\_Mngt\\_of\\_Chil.pdf](http://www.forensicnurses.org/resource/resmgr/Education/PEPFAR_Clinical_Mngt_of_Chil.pdf)

victims of sexual assault, page 169).

Further information, please see the post-exposure prophylaxis after non-occupational and occupational exposure to HIV, NCHADS, Feb, 2019.

**Box 1: Signs and symptoms of HIV disease in children with HIV infection<sup>13</sup>**

**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

**Conditions 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.

Source: Guidelines for the Management of HIV in Children, Department of Health, South Africa

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<sup>13</sup> Guidelines for the Management of HIV in Children, Department of Health, South Africa, 2010

**Box 2: Children who must be tested for HIV**

- HIV-exposed infants and children, including those over 5 years-old
- 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 3: Presumptive diagnosis of HIV in children**

If HIV PCR testing is not immediately available for HIV-exposed infants under 18 months, a presumptive diagnosis of severe HIV disease may be made in certain cases to facilitate appropriate management, including starting ART, according to the following criteria:

- The infant is confirmed to be HIV exposed by antibody testing

AND

- 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

Starting ART in children < 18 months without a confirmed Diagnosis of HIV Infection.

## CHAPTER 6: CORE COMPONENTS OF CARE FOR HIV INFECTED AND EXPOSED INFANTS

- Counseling on appropriate feeding practices, with emphasis on encouragement of exclusive breastfeeding for 6 months and avoidance of mixed-feeding for first 6 months.
- Routine immunization, vitamin A supplementation, and deworming according to the standard schedule for children without HIV.
- Support from Active Case Management and Community-Action Approach [(Facility Based Workers (FBW), Community Action Workers (CAW) and Community Action Counselors (CAC)] to ensure access to maternal ART and follow-up of HIV-exposed infants to ensure appropriate testing and treatment.
- Infant testing as directed above, initiation of ARV prophylaxis from birth and initiation of CTX prophylaxis at 4-6 weeks of age, as well as ongoing reassessment for HIV exposure and testing as necessary.
- Symptom screening for TB at every visit and screening for TB exposure.
- Malnutrition assessment and support.

### 6.1 Recommendations for infant feeding

#### 6.1.1 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.<sup>14</sup> 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. Oral medication should be given as prescribed.

- All HIV-infected mothers taking maternal combination ART for lifelong, HIV-infected women on ART should continue and adhere to their lifelong drugs for their own health and to prevent HIV transmission through breast milk.
- Mothers returning to work before 6 months:
  - Should be encouraged to express milk and can store the milk in an icebox if available for up to 24 hours.
  - May need to switch to formula feeding. Abrupt weaning is not recommended. See requirements for safe formula feeding in Box 4 below.
  - In all cases, hygienic practices of bottle cleaning and sterilization should be taught to the mothers and caregivers of the baby.

#### 6.1.2 After six months of age

The complementary foods should be introduced and breastfeeding continued up to 24 months or longer for all children (HIV-exposed or HIV-infected), and mothers should be supported to ensure lifelong adherence to ART treatment.

Every effort should be made to determine the HIV status of women who have not yet been

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<sup>14</sup> Cambodian National Interim Guidelines for the Management of Acute Malnutrition. Cambodia December 2011

tested so that they can be referred for appropriate care for their infection and ART for their own health if necessary and to prevent transmission of HIV to the child if they are breastfeeding.

### **IMPORTANT NOTE**

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.

Infants of HIV-positive mothers who are on second or third-line ART for > 3 months and have a viral load >1000 copies/ml should be advised not to breastfeed if this is feasible. The baby might be at risk of acquiring a highly resistant strain of HIV. Please refer to clinical mentors or PAC TWG for support with replacement feeding and for a decision about genotyping and ART options. The VL testing and further Management should be performed according to the current National HIV Clinical Management Guidelines for Adolescents and Adults.

### **6.1.3 Replacement Feeding**

In selected cases, some mothers may choose replacement feeding, or there may be an indication where breastfeeding is not possible (e.g. maternal death/illness/mastitis). HIV infected mothers, who choose not to breast feed their babies, should **only give international standard commercial infant formula milks as** a replacement feed to their HIV-infected infants or to infants who are unknown status, **when specific conditions** are met.

Fresh cow's milk, soymilk, condensed milk or powdered milk should **NEVER** be given to infants.

The specific conditions for replacement feeding are described in the box 4.

#### **Box 4: Measure for safe formula feeding<sup>15</sup>**

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

- Safe water (boiled 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 feeding materials cleanly and frequently enough so that it is safe and carries a low risk of diarrhea 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.

- It should be noted that in case of mixed feeding with non-exclusive breastfeeding for whatever reason, health workers and mothers living with HIV can be reassured that ARV treatment is effective at reducing the risk of postnatal HIV transmission. Thus, mixed

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<sup>15</sup> Source: Rapid Advice, HIV and Infant Feeding, WHO 2009.

feeding in itself is not a reason to stop breastfeeding as long as the mother is adherent on ART.

- When considering replacement feeding, health-care providers must take care to ensure that an uninterrupted supply of formula is available for the infant for at least 12 months and that women are clear about how to prepare formula feeds correctly.
- Replacement feeding practices should not be encouraged amongst the general population.
- Orphaned HIV-exposed infants should be supported with replacement feeding for at least 12 months, through referral to appropriate organizations.
- Mother should be encouraged to give complementary feeding to children from 6 months.

## 6.2 Prevention of opportunistic infection

### 6.2.1 Prevention of severe bacterial infection and malaria

#### 6.2.1.1 Cotrimoxazole

Cotrimoxazole (CTX) prophylaxis has demonstrated benefit in preventing morbidity and mortality from HIV. In areas where severe bacterial infections are prevalent and where malaria is endemic, CTX given on an indefinite basis has proven more beneficial than stopping the drug.

**All HIV-exposed infants should receive CTX prophylaxis starting at 4-6 weeks.** CTX prophylaxis must be continued until HIV infection is excluded by age-appropriate HIV-testing 6 weeks after the cessation of breastfeeding (See Table 7 below).

All children diagnosed with HIV should continue or be started on CTX until children are transitioned into adult care at age 15 (See Box 5: Dosage recommendations for Cotrimoxazole prophylaxis for HIV exposed infants, page 37).

**Table 7: When to Initiate and Stop Cotrimoxazole Prophylaxis**

	Start Cotrimoxazole	Stop Cotrimoxazole
HIV-exposed infant	4-6 weeks of age	PCR or antibody negative 6 weeks after complete cessation of breastfeeding
<b>All HIV-infected infants and children regardless of age or clinical stage of disease</b>	4-6 weeks of age as for exposed infants, and continue after diagnosis of HIV has been confirmed Immediately after HIV diagnosis made in a child presenting for the first time at any age > 6 weeks In children with PCP, subsequent to PCP treatment being completed.	Stop CTX if the child is anemic as CTX may cause bone marrow suppression or if Grade 3/4 toxicity rash occurs (see Table 8). <b>Otherwise continue CTX until children transition to adult care, regardless of ART or CD4 recovery.</b>

**Box 5: Dosage Recommendations for Cotrimoxazole Prophylaxis for HIV-exposed infants<sup>16</sup>**

Drug	Strength of tablet or oral liquid (mg or mg/5 ml)	Number of tablets or ml by weight band once daily					
		3.0–5.9 kg	6.0–9.9 kg	10.0–13.9 kg	14.0–19.9 kg	20.0–24.9 kg	25.0–34.9 kg
Co-trimoxazole	Suspension 200/40 mg per 5 ml	2.5 ml	5 ml	5 ml	10 ml	10 ml	–
	Tablets (dispersible) 100/20 mg	1	2	2	4	4	–
	Tablets (scored) 400/80 mg	–	0.5	0.5	1	1	2
	Tablets (scored) 800/160 mg	–	–	–	0.5	0.5	1

***Cotrimoxazole side effects***

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

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

Management of CTX -related rash is outlined in Table 8 below.

**Table 8: Management of Cotrimoxazole-related Rash**

Severity	Description	Management
Grade 1	<ul style="list-style-type: none"> <li>Diffuse or patchy erythema</li> <li>May be pruritic</li> </ul>	<ul style="list-style-type: none"> <li>Continue CTX</li> <li>Follow up in 3-4 days</li> <li>Consider antihistamines for symptom relief.</li> </ul>
Grade 2	<ul style="list-style-type: none"> <li>Dry maculopapular rash</li> <li>May appear morbilliform</li> <li>Minimal exfoliation</li> </ul>	<ul style="list-style-type: none"> <li>Continue CTX</li> <li>Follow up in 1-2 days</li> <li>Consider antihistamines for symptom relief.</li> </ul>
Grade 3	<ul style="list-style-type: none"> <li>Early bullae or mucosal ulceration</li> </ul>	<ul style="list-style-type: none"> <li>Discontinue CTX immediately</li> <li>Hospitalize for supportive care</li> <li>Never restart CTX.</li> </ul>
Grade 4	<ul style="list-style-type: none"> <li>Toxic epidermal necrolysis or Stevens Johnson Syndrome</li> </ul>	<ul style="list-style-type: none"> <li>Discontinue CTX immediately</li> <li>Hospitalize for supportive care</li> <li>Never restart CTX.</li> </ul>

<sup>16</sup> Guidelines on post-exposure prophylaxis for HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children: recommendations for a public health approach, Dec 2014, Supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection

## 6.2.2 Cryptococcus infection

### 6.2.2.1 Fluconazole prophylaxis

Fluconazole prophylaxis is no longer recommended for adults or children with HIV as primary prophylaxis.<sup>17</sup> Cryptococcal disease is very rare in children, and earlier access to ART should ensure that even fewer children develop cryptococcal disease. Children presenting with symptoms of meningitis and CD4 <15% (<5 years of age) or CD4 <100 cells/mm<sup>2</sup> (≥ 5 years of age) should be investigated for cryptococcal disease as outlined in Chapter 33: Infections of the central nervous system, page 146.

For children less than 10 years old, the screening and primary prophylaxis are not recommended, given the low incidence of cryptococcal meningitis in this age group.

### 6.2.3 Cryptococcal antigen (CRAG) screening

It is recommended that for adolescents aged 10-19 years old, the screening for cryptococcal antigen algorithm should be followed.<sup>18</sup>

**The CRAG testing is for screening purposes only. If a patient has symptoms of meningitis, they should proceed directly to LP rather than wait for CRAG test result.** (See chapter 33, infections of the central nervous system, *page 146*).

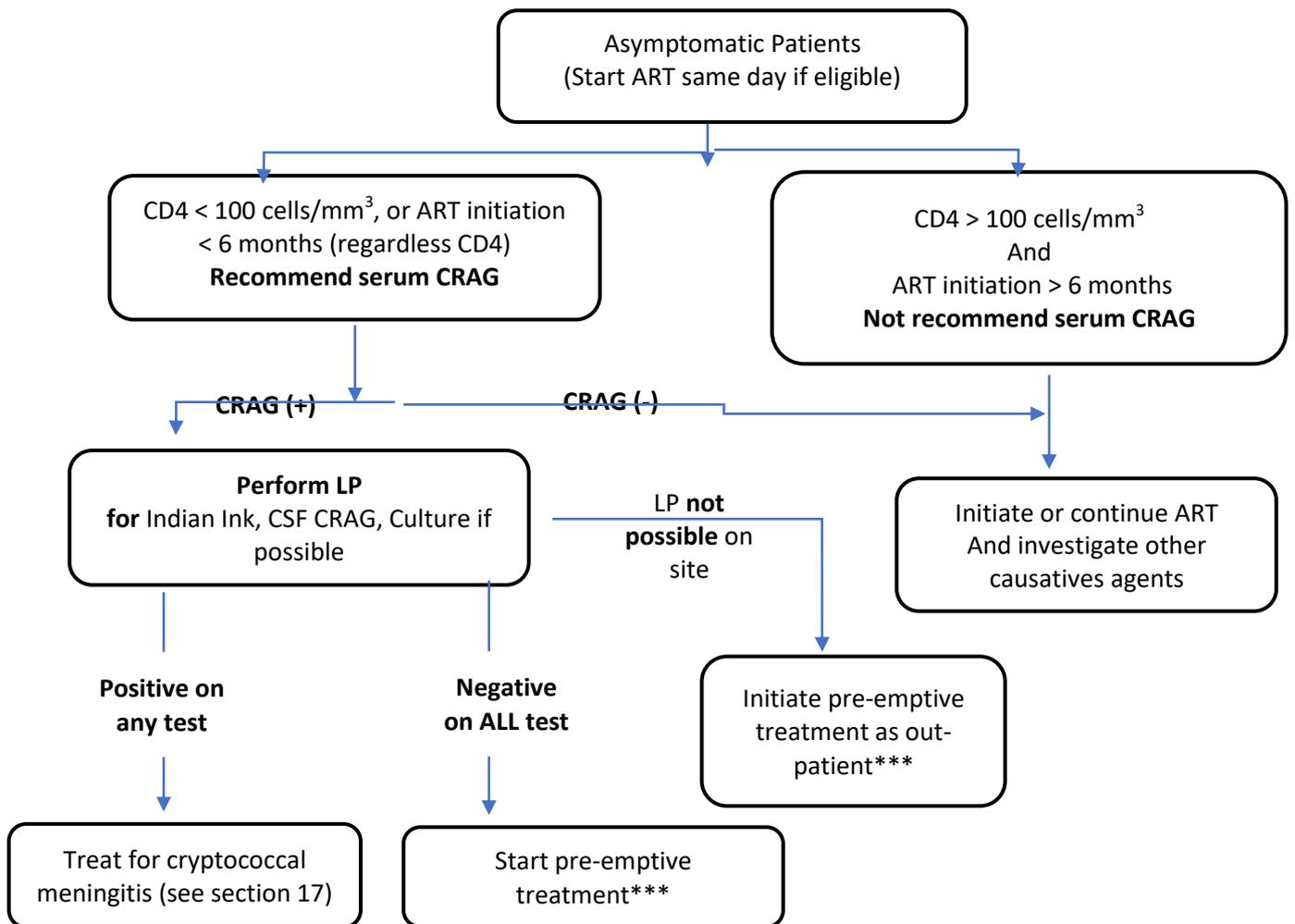
- For all newly enrolled children and adolescent PLHIV, if the CD4 < 100 cells / mm<sup>3</sup> the laboratory will automatically go on to perform a CRAG test on the same day.
- Serum CRAG + → call patient to return to be evaluated for symptoms / signs of meningitis.
- Serum CRAG +, and symptoms / signs of meningitis → immediately start fluconazole 1200mg one dose and refer for urgent lumbar puncture. (See Chapter 33: Infections of the central nervous system, *page 146*).
- If serum CRAG positive, and NO SYMPTOMS or SIGNS of meningitis, it is recommended for lumbar puncture where possible for CSF testing (CRAG, India Ink and culture).
  - If the result of any test is positive, treat Cryptococcus meningitis or
  - If all results of tests are negative, start pre-emptive treatment as outpatients.
  - In case of LP is unable to perform, start pre-emptive treatment
  - Pre-emptive treatment regimen: fluconazole 12mg/kg/day for 2 weeks followed by 6-12mg/kg/day for 8weeks and followed by Fluconazole 6mg/kg with maximum of 200mg/day until VL undetectable *and* CD4 > 100 cells/mm<sup>3</sup> on two occasions > 6 months apart.
- If CRAG negative → No fluconazole.

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<sup>17</sup> WHO Rapid advice: diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. December 2011

<sup>18</sup> WHO Guidelines for the Diagnosis, Prevention and Treatment of Cryptococcal Disease in HIV-infected Adults, Adolescents and Children; March 2018

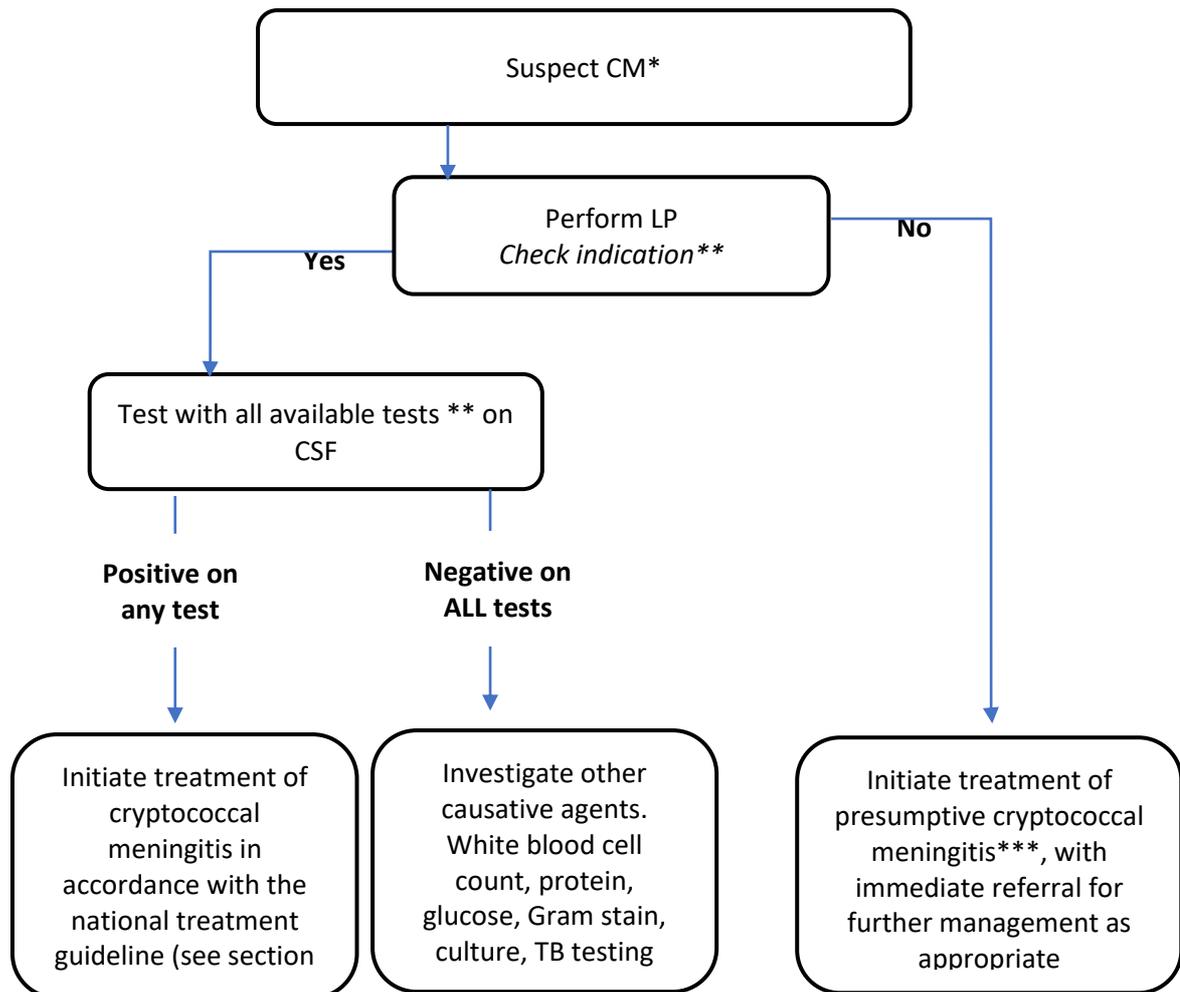
**Figure 4: Cryptococcal antigen screening for asymptomatic patients**



\*\*\*Start pre-emptive treatment:

Fluconazole 12mg/kg oral daily for 2 weeks; then 6-12mg/kg for 8 weeks and followed by maintenance of fluconazole 6mg/kg with maximum dose of 200mg daily until VL undetectable and CD4 > 100 cells/mm<sup>3</sup> in 2 consecutive measurements of 6 month apart.

**Figure 5: Cryptococcal antigen screening for symptomatic patients**



\*Headache, neck stiffness, sensitivity to light, seizures, fever, convulsion, blurred vision

\*\* Contraindications consist of focal nervous system signs (excluding cranial nerve VI palsy) or recurrent seizures and, where possible, confirmed by computed tomography. Raised intracranial pressure does not contraindicate lumbar puncture in (suspected) cryptococcal meningitis. Other contraindications include major spinal deformity and patient refusal after fully informed consent was sought.

\*\*all available tests include CRAG, Indian Ink and culture and result provided within 24h

\*\*\* provide Fluconazole 12mg/kg one dose and promptly refer the patient to RH where LP and management are able to provide.

### 6.3 Immunization, vitamin A and de-worming

Infants born to HIV-infected mothers are at higher risk of death even when they do not themselves become infected with HIV, which is why they should be followed up regularly. HIV-exposed and infected children should receive all scheduled immunizations (see Table 2: Expanded program on immunization (EPI) Vaccination Schedule, page 19), vitamin A supplementation (see Table 9 below), and deworming treatments (see Table 10 below) as routinely given to HIV-unexposed children. BCG vaccine should be given at birth per-routine, unless a child is strongly suspected of symptomatic HIV at the time of birth. Pneumococcal vaccine is introduced and health care workers are advised to refer to updated EPI schedules on a regular basis. **For a full schedule of exposed infant follow-up and the current national vaccination (see Table 2, page 19).**

**Table 9: Routine Vitamin A Supplementation**

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

**Table 10: Routine Deworming**

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

# CHAPTER 7: NUTRITION IN HIV INFECTED CHILDREN

## 7.1 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*.

## 7.2 Introduction

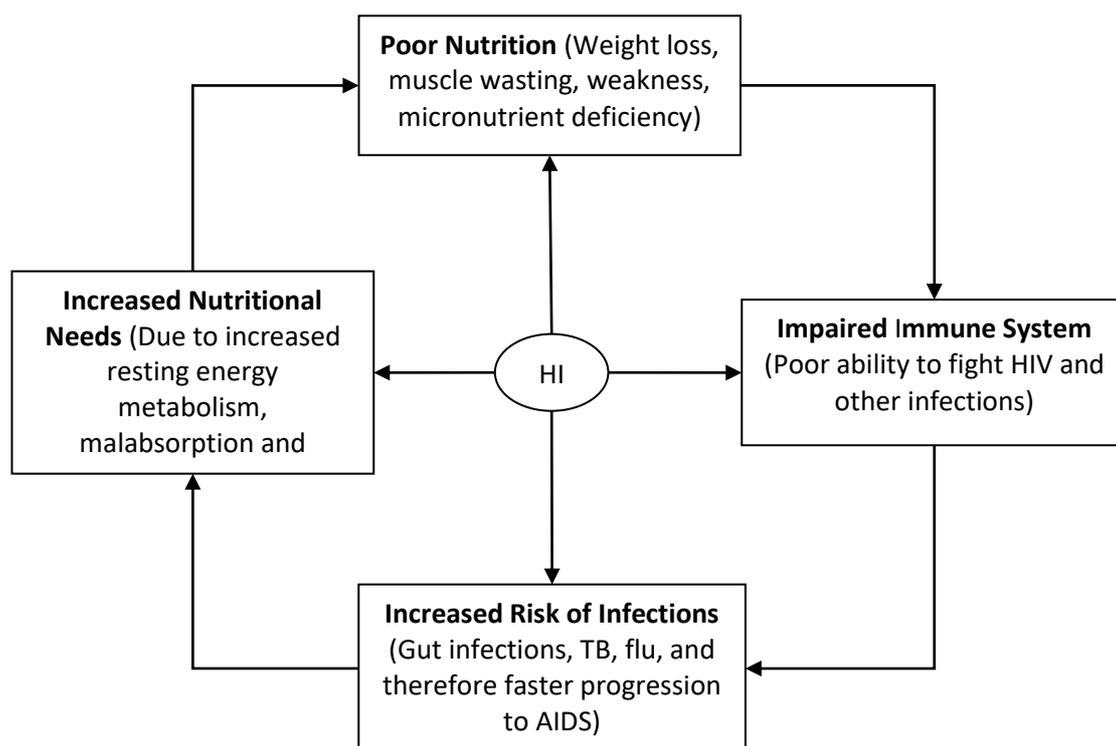
Malnutrition and inadequate growth are extremely common in HIV-infected infants and children, and is often the earliest sign of HIV-infection. This occurs due to a significant increase in metabolic needs in HIV-infected children, leading to loss of both lean (muscle) and fat body mass; once evidence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

## 7.3 Causes of malnutrition

HIV-infected children are at increased risk of malnutrition for many reasons (See Figure 4 below), including:

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

**Figure 6: Cycle of malnutrition and infection in HIV-infected children**



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

## 7.4 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 below:

### Box 6: 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 Annex 16: WHO growth monitoring tables and charts, page 198.

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.

Failure to gain adequate weight may be one of the earliest signs of HIV-infection in infants, children and adolescents and should indicate the need for an HIV test, regardless of whether the HIV exposure status of the child is known (Annex 16: WHO growth monitoring tables and charts, page 198). Consider and test for HIV infection in all infants or children with malnutrition (see Table 11 below).

For infants, breastfeeding advice to support exclusive breastfeeding or counseling on optimal replacement feeding if this is the chosen option should be offered to the mother (see above **Recommendations for infant feeding**). Advice on when and how to provide complementary feeding should be provided for the child according to recommendations in the *Cambodian National Interim Guidelines for the Treatment of Acute Malnutrition*.<sup>5</sup>

In children and adolescents diagnosed with HIV infection, nutritional needs may vary. Appropriate and adequate nutrition is needed to achieve the full benefits of ART. Children often gain weight and their height increases when ART is initiated, although height gain is generally slower than weight gain. Monitoring of weight while on ART is important, as growth failure is often an indicator of treatment failure.

HIV-exposed and infected children should be monitored using the **ABCDE** of nutritional care:

#### A. Anthropometry

Measure height and weight at all ages, with head circumference as well for children <2 years of age, and plot these on the relevant growth chart.

**Table 11: Classification of Malnutrition in Children**

	Mild malnutrition	Moderate malnutrition	Severe acute malnutrition (SAM)
Symmetrical edema?	No	No	Yes
Weight-for-height	< 5 <sup>th</sup> 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)
Visible wasting?	No	No	Yes
Mid-upper arm circumference (age)			<ul style="list-style-type: none"> <li>• &lt; 115 mm (≤60 months)</li> <li>• &lt; 129 mm (5 – 9 years)</li> <li>• &lt; 160mm (10 – 14 years)</li> </ul>

When inadequate weight gain is noted, thorough evaluation should be performed with particular attention to ruling out tuberculosis (TB), gastrointestinal (GI) infections, neonatal sepsis, and HIV (in HIV-exposed infants) or treatment failure in children who are on ART.

## **B. Biochemistry**

Such as total cholesterol, serum triglycerides, serum glucose and haemoglobin (Hb) where available

## **C. Clinical signs**

WHO recommends that children that have symptomatic HIV need an additional 30% energy supplement over and above the requirements of well children of the same age. HIV-symptomatic children with severe malnutrition require up to 100% more energy. It may be difficult to reach an additional 100% of energy requirements, thus the use of nutritional supplementation may be required (Box 7 below).

## **D. Dietary**

Assess dietary history at every visit, and, in children who are wasted, underweight or stunted, determine whether there is food insecurity. Assess and educate about hygiene practices with food preparation. Refer to NGO programs (e.g. UNICEF and Foundation for International Development/Relief (FIDR), Cambodia Children's Fund (CCF), or World Vision for support if there is food insecurity).

## **E. Evaluation**

Regular evaluation is required for children at risk. Monitor the response at least weekly or biweekly initially in those with moderate malnutrition and admit for hospitalization if deteriorating.

## **7.5 Severe Acute Malnutrition (SAM)**

Children should be hospitalized if they have severe acute malnutrition (SAM), and any medical complications (see Table 12 below), are below 6 months of age, are over 6 months with weight <4kg, have bilateral pitting edema, experience weight loss on 3 consecutive occasions, or are not recovering with outpatient management. HIV-positive children with SAM should be managed like all other children with SAM and receive urgent treatment including daily assessment by a doctor. They should be nursed in a high care area until they are feeding well, infections are under control, and diarrhea has stopped. Treatment is aimed at managing the following serious complications: hypoglycemia, hypothermia, dehydration, electrolyte imbalances, micronutrient deficiencies and infections.

### **Box 7: 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).

**Table 12: Medical Complications in Severe Acute Malnutrition Requiring In-patient Care**

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

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

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

For treatment of severe acute malnutrition described in Box 7: Energy goals for HIV infected children with severe malnutrition, page 45.<sup>19</sup>

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 CTX prophylaxis and 6 monthly vitamin A supplementation and de-worming medication as outlined in the routine care and follow-up of HIV-exposed infants (see *Guidelines for*

<sup>19</sup> National Interim Guidelines on the Management of Acute Malnutrition.

*Diagnosis and Antiretroviral Treatment of HIV Infection in Infants, Children and Adolescents in Cambodia).*

The presence of any medical complications (Table 12 above), which are significantly correlated with increased mortality, is an indication for admission. Weight-for-age is NOT a good indicator of severe malnutrition.

## 7.6. 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 8 below should receive 25-30% additional calories through additional household foods or nutritional supplementation.
- All children with symptoms listed in Table 13 below require ART and should be prepared for treatment without delay.

### Box 8: 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*

### Table 13: Indication for in-patient management

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 weighing Static weight for 5 consecutive weighing
Not recovered after 3 months in outpatient management of severe acute malnutrition and repeated home visits.

## CHAPTER 8: TUBERCULOSIS PREVENTIVE THERAPY

*Mycobacterium tuberculosis* (TB) is the most common cause of death in HIV-infected individuals worldwide. HIV infected people with TB have an increased risk of rapid progression to TB disease.

TB disease in children is most severe in those <5 years, and especially those <2 years of age are at greatest risk of developing severe, disseminated disease associated with a high morbidity and mortality. While pulmonary TB is the most common type of TB in children, extra-pulmonary disease is more common in children than adults and can occur in about 30-40% of cases with a wide variety of anatomical sites affected (see below clinical manifestations of TB disease in children).

Childhood TB is paucibacilliary and is therefore not highly infectious. Young children are usually unable to generate a forceful enough cough to transmit TB. Adolescents have an increased risk of the development of TB, which usually presents as adult-type pulmonary disease and is often sputum smear-positive. TB in adolescence is frequently infectious and a source of transmission for other household members and close contacts (school classmates).

WHO strongly recommends integration of services for HIV and TB. In Cambodia, all HIV infected patients, including children should be screened for TB at each clinic visit and all people diagnosed with TB should be tested for HIV. Early provision of ART for TB patients living with HIV and the Three I's for HIV/TB are recommended as part of the approach to reduce the burden of TB disease among HIV positive patients.

Three I's for HIV/TB:

- Intensified TB case-finding followed by high-quality anti-tuberculosis treatment.
- Isoniazid preventive therapy (IPT).
- Infection control for TB.

### 8.1 Routine Screening for TB

Health care workers need to know how to screen, diagnose, trace contacts, and prevent TB infection in children. Children living with HIV should be screened for TB at the pre-ART/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.

### 8.2 Tuberculosis Preventive Therapy (TPT)

If children living with HIV have none of the above symptoms, they are considered unlikely to have active TB and those over 12 months of age are recommended for TPT (See Figure 7 below). 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 TPT. INH-based TPT is only contraindicated in patients with:

- Active hepatitis (acute or chronic) with ALT  $\geq$  2 N
- Symptoms of peripheral neuropathy.

### 8.2.1 LTBI Treatment Regimen for PLHIV

**Table 14: Tuberculosis Preventive Therapy regimens**

Drug regimen	Doses	Considerations
Weekly isoniazid and rifapentine for 3 months (3HP) for all PLHIV > 2 years	<p><b>Isoniazid:</b> When INH is used in the 3 HP regimen it is advisable to use the following:</p> <ul style="list-style-type: none"> <li>• Individuals aged 2–11 years: isoniazid: 25 mg/kg</li> <li>• Individuals aged <math>\geq</math> 12 years: Isoniazid: 15 mg/kg</li> </ul> <p><b>Max dose: 900mg daily</b></p> <p><b>Rifapentine:</b> 10.0–14.0 kg = 300 mg 14.1–25.0 kg = 450 mg 25.1–32.0 kg = 600 mg 32.1–50.0 kg = 750 mg &gt; 50 kg = 900 mg Plus vit B6 25mg daily.</p>	12 doses. The drugs should be issued to align with ART schedule.
Daily INH for 6 months (6 H) for children 12-24 months, and for infants aged < 12 months only if in contact of a TB case	<p><b>Isoniazid:</b></p> <ul style="list-style-type: none"> <li>• Children: 10 mg/kg (range: 7–15 mg)</li> </ul> <p><b>Max dose: 300mg daily</b> Plus vit B6 25mg daily.</p>	180 doses
Daily Isoniazid and Rifampicine for 3 months (3RH) for PLHIV $\geq$ 2 years <15 years	<p><b>Isoniazid: 10 mg/kg</b> (Max dose per day: 300mg)</p> <p><b>Refampicine: 15 mg/kg</b> (Max dose per day: 600mg) Plus Vit B6 25mg daily.</p>	90 doses.

- **3 months of Isoniazid and Rifapentine (3HP):** This is a weekly 2-drug combination regimen consisting of 12 doses. The drugs should be issued and align with ART schedule. Missed doses can be taken subsequently. This regimen is ideally best given under a programme of strict supervision. Rifapentine has potential drug-drug interactions with multiple ARVs. Until further information becomes available, 3HP should not be prescribed for children on ART which includes protease inhibitors (lopinavir, atazanavir, darunavir),

nevirapine, or dolutegravir; efavirenz-based ART is safe to use with 3HP. Daily Vitamin B6 is given.

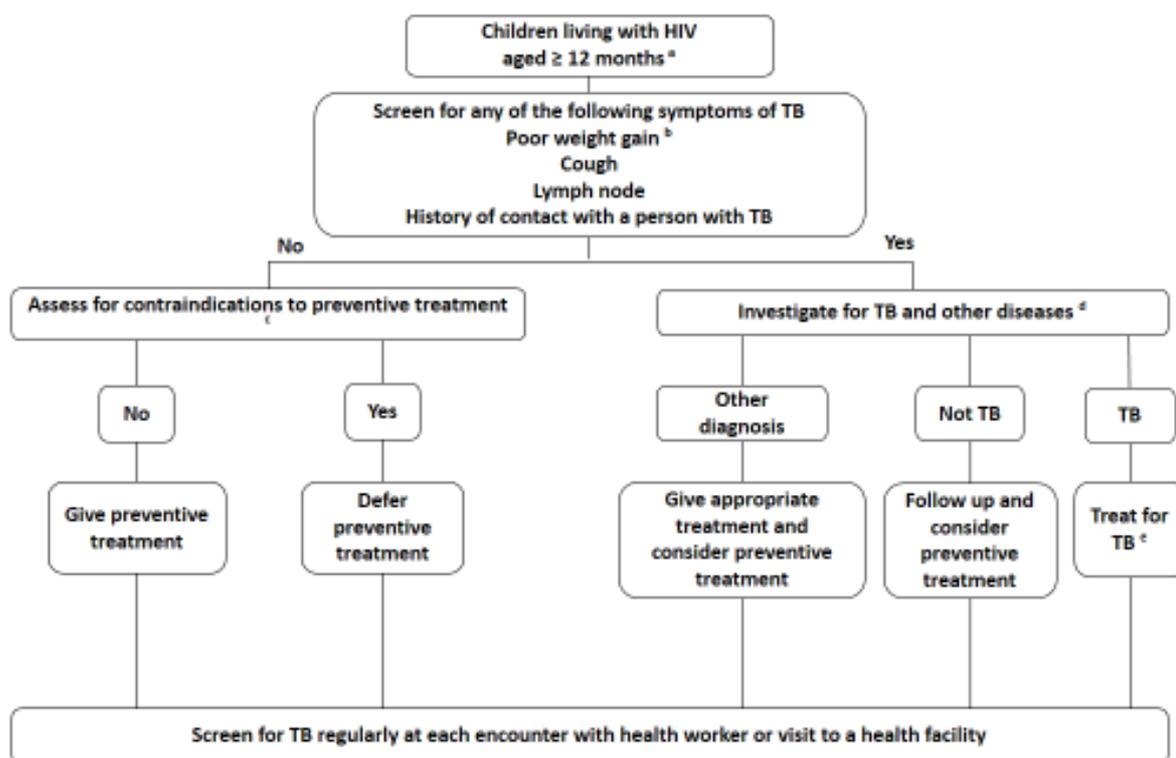
- **6 months of daily isoniazid (INH):** Infants aged < 12 months living with HIV who are in contact with a case of TB and are investigated for TB should receive 6 months of isoniazid preventive treatment (IPT) if the investigation shows no TB disease. Daily Vitamin B6 is given.
- **3 months of Isoniazid and Rifampicine (3RH):** This is a daily 2-drug combination regimen consisting of 90 doses **for children  $\geq 2$  and < 15 years**. Rifapicine has potential drug-drug interactions with multiple ARVs. Please see the important ARV drug interaction on p188. In addition, a supplement of 25 mg of Vit B6 may be given. Treatment completion is considered when patients completed at least 90 doses over 90 days.

**Note: There will be new regimens available but the national program does not endorse to be used in Cambodia.**

### **8.2.2 LTBI treatment for house hold contacts of MDR TB patients**

- Confirmation of infection by LTBI testing is required before individualized treatment is initiated.
- The choice of regimen needs to be made in consultation with the TB specialist at the provincial level.
- The preventive treatment should be individualized after a careful assessment of the intensity of exposure, the certainty of the source case, reliable information on the drug resistance pattern of the source case and potential adverse events.
- The preventive treatment should be given only to household contacts at high risk (e.g. children, people receiving immunosuppressive therapy and people living with HIV).
- Selection of drug regimen: The regimen of preventive treatment of MDR-TB contacts should be based on reliable information on the drug resistance profile of the source case. Later-generation fluoroquinolones (e.g. levofloxacin and moxifloxacin) are considered to be important components of a preventive treatment regimen unless the strain of the source case is resistant to them.
- Strict clinical observation and close monitoring for the development of active TB disease for at least 2 years are required, regardless of the provision of preventive treatment.

Figure 7: Algorithm for TB screening in children living with HIV aged ≥ 12 months



<sup>a</sup> All infants < 1 year of age should be given preventive treatment if they have a history of household contact with a TB case.

<sup>b</sup> Poor weight gain is defined as reported weight loss, very low weight-for-age (< -3 z-score), underweight (weight-for-age < -2 z-score), confirmed weight loss (> 5%) since the last visit or growth curve flattening.

<sup>c</sup> Contraindications include active hepatitis (acute or chronic) and symptoms of peripheral neuropathy. A history of TB should not be a contraindication for starting preventive treatment. Although LTBI testing is not a requirement for initiating preventive treatment, it may be done as a part of eligibility screening where feasible.

<sup>d</sup> Xpert MTB/RIF should be used as the initial diagnostic test for TB. Detailed algorithms for people living with HIV who have suspected TB are available in the WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection.

([http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf))

<sup>e</sup> Resume regular screening for TB after completion of treatment for active disease.

NOTE: Further reading on diagnosis and treatment of TB in children with HIV is in Chapter 30: Tuberculosis in HIV Infected Children, page 135.

# CHAPTER 9: WHEN TO START ANTIRETROVIRAL TREATMENT IN INFANTS, CHILDREN AND ADOLESCENTS

Since 2015, Cambodia recommends to initiate early treatment in HIV-infected people of all ages. The early treatment is associated with better morbidity and mortality outcomes. In infants in particular, dramatic reductions in mortality are demonstrated when ART is started before 3 months of age. Once the patient is diagnosed, ART should be initiated rapidly, preferably **within 1-2 weeks of diagnosis**.

In case of infants suspected of HIV infection with clinical sign or symptom, it is suggested to initiate treatment and then re-evaluate the treatment after the result is available. This avoids a delay of treatment initiation which may lead to mortality.

One randomized controlled trial, the PREDICT study which assessed the clinical benefits of early ART initiation among children, showed significantly better growth response among those who started ART immediately. Some other evidence also suggest earlier ART initiation could promote immune recovery, and mitigate the negative effect on mortality, morbidity, and nervous system development.<sup>20</sup>

The goals of ART for children living with HIV include:

- Preventing and reducing HIV-related morbidity and mortality;
- Restoring and/or preserving immune function
- Maximally and durably suppressing viral replication;
- Preventing emergence of viral drug-resistance mutations;
- Minimizing drug-related toxicity;
- Optimizing growth, sexual maturation, and neurocognitive development;
- Improving quality of life; and
- Preventing transmission of HIV to others.

**ALL CHILDREN REGARDLESS OF CD4 AND/OR CLINICAL STAGE SHOULD START ART AS SOON AS POSSIBLE, PREFERREDLY WITHIN 1-2 WEEKS OF DIAGNOSIS.**

## 9.1 Starting guidance for treatment in infants, children and adolescents

**All infants, children and adolescents living with HIV regardless of age and CD4 should be initiated on ART**

- Children <18 months who have been diagnosed HIV positive with an initial PCR test (treatment should be initiated without waiting for the confirmed result).

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<sup>20</sup> Consolidated Guideline on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection, 2<sup>nd</sup> Edition 2016.

- Children  $\geq 18$  months with positive HIV antibody testing.
- Infants who are confirmed to be HIV-exposed by antibody testing, and are at high risk of MTCT with a presumptive diagnosis of HIV (Box 3: Presumptive diagnosis of HIV in children, page 33) if PCR testing is not yet available (confirm PCR test should be done as soon as possible, ART treatment should be initiated immediately without waiting for the confirmed result, if the confirmed PCR is negative the ART would be discontinued).

## 9.2 Good practices in preparing ART initiation in children

At the first visit, HIV infected children should receive a comprehensive package of care, including assessing nutritional status, screening for opportunistic infections, thorough history note taking, physical examination to determine clinical staging, and providing required treatment and prophylaxis.

In order to begin ART, children should have a clearly defined caregiver who understands the child's needs for HIV medical care, understands the importance of medication adherence, and demonstrates commitment to ensuring clinic attendance according to the appointment date and will supervise medication.

The health-care providers should provide detailed discussion directly with parents or caregivers regarding the readiness of starting their children on ART (life-long treatment), regimen, dosage, scheduling visits, benefits of the treatment, possible side effects, and required follow-up and monitoring visits. Parents and caregivers should also be encouraged to disclose the HIV status to find a "treatment buddy" who may help with the child's treatment in their absence (however this should not serve as a barrier to starting ART if they do not wish to disclose). A plan to support treatment for each child must be made. Even the most vulnerable children such as orphans should also have early access to treatment.

A prolonged "adherence education" program is unnecessary prior to initiation of ART, especially for children whose mothers are already receiving treatment for their own infection. Treatment education for caregivers and children should vary according to the needs of the family. There is no specified number of visits that must be completed prior to initiation. If parents are on treatment themselves ART may be started immediately, provided all preliminary investigations have been conducted. The aim should be to start newly HIV diagnosed children on ART rapidly within 1 - 2 weeks from the time of HIV diagnosis.

## 9.3 Recommended first-line regimens

- The use of three ARV medications is currently the standard treatment for HIV infection in order to achieve the best possible suppression of viral replication and to arrest the progression of HIV disease.
- It is crucial to maximize the durability and efficacy of any first-line regimen by selecting the most potent and best tolerated available regimen and incorporating approaches to support adherence.

### 9.3.1 First line regimen for children < 20 kg

- The preferred initial ART regimen for this age group is **ABC + 3TC + LPV/r** regardless of exposure to NNRTI for PMTCT. **LPV/r should not be administered to premature**

**neonates (born one month or more before expected date of delivery) until 14 days after their due date.**

- Every effort should be made to support families to give LPV/r-based treatment:
  - **LPV/r syrup (80mg/20mg/ml)** is NOT heat stable and requires storage in a refrigerator between 2-8°C prior to dispensing. Once dispensed, the drug may be stored at room temperatures, preferably at <25°C for up to 42 days (6 weeks). Where conditions are too hot, families should be encouraged to store the LPV/r in an icebox or in a cool place in the house. This formulation contains 42% of ethanol and 15% of propylene glycol and has an unpleasant taste (See checklist in Annex 4: Anti-retroviral therapy dosing table, page 173).
  - Nevertheless, there are ways to disguise the unpalatable flavor by co-administering with other strong flavor such as:
    - Jam
    - Sugar
    - Peanut butter placed on the roof of the mouth just before giving medicine.
  - **LPV/r pellet (40mg/10mg):** solid, heat-stable formulation (not require cold storage), easier to use in younger children than the liquid preparation. It does not contain additives, and has taste-masking to reduce the unpalatable taste. The pellet formulation could be used for infant from 3 months and older. Once the child is developmentally able to swallow them.
    - For infant 3 to 6 months: the pellet could be placed on a child’s tongue, or mixed with a spoonful for breast milk.
    - For infant 6 months and older: the pellet could be mixed with a spoonful of soft food.
    - Pellet **MUST NOT** be stirred, crushed, or dissolved in food, or stored for later. This will cause the medicine to be bitter. Thus, the child must be developmentally able to swallow them.
  - **LPV/r granule (40mg/10mg):** expected to be as effective and acceptable as the pellet formulation, however its mode of administration is simple and could be mixed with water. Additional guidance on use of this formulation will be provided in separate job-aid as it is now available in Cambodia in February 2020. Note that LPV/r oral granule is recommended in infants and children 14 days of age and older, in combination with other ARVs.
  - **LPV/r tablet (100mg/25mg):** solid, heat-stable, formulated in a “melt extrusion” matrix, meaning that they **MUST** be swallowed whole and **MUST NOT be broken, or crushed, or chewed, or dissolved** before administration. This has been shown to reduce the absorption of LPV/r by as much as 40%. The tablets could be taken with or without food, and are suitable for children > 10kg who are **able to swallow tablet whole**.
- If after every effort has been made, LPV/r is not available, cannot be stored appropriately or tolerated, and in other special circumstances, NNRTIs based regimen may be used. (This is an inferior regimen and more children are likely to fail treatment if they are started on NVP or EFV containing treatment than if they start LPV/r-based

therapy).

WEIGHT BAND (KG)	NUMBER OF LPV/R ORAL PELLETS 40MG/10MG CAPSULES		LPV/R 80MG/20MG/ML ORAL LIQUID		NUMBER OF LPV/R 100MG/25MG TABLETS	
	AM	PM	AM	PM	AM	PM
3-4.9 kg <sup>11</sup>	2	2	1 ml	1 ml	NR	NR
5-5.9 kg	2	2	1 ml	1 ml	NR	NR
6 - 9.9kg	3	3	1.5 ml	1.5 ml	NR	NR
10- 13.9kg	4	4	2 ml	2 ml	2	1
14 - 19.9kg	5	5	2.5 ml	2.5 ml	2	2
20 - 24.9kg	6	6	3 ml	3 ml	2	2
25 - 29.9kg	7	7	NR	NR	3	3
30 - 34.9 kg	8	8	NR	NR	3	3

NR=NOT RECOMMENDED

Adapted from Cipla package insert approved by USFDA and WHO 2013 dosages of recommended antiretroviral drugs

- ABC + 3TC is the recommended NRTI backbone for all children < 20 kg. ABC + 3TC are co-formulated (120 mg /60 mg) and can be given once or twice daily with LPV/r as preferred regimen. Consult the paediatric dosing table for approved doses.
- AZT may be substituted if ABC hypersensitivity occurs.
- Children receiving rifampicin-based therapy for active tuberculosis may require alterations to their ART regimens. For selection of ART regimens in children with active tuberculosis, see below section on ART and TB Treatment.

**Note:**

- LPV/r (40mg/10mg) oral granule is recommended in infants and children 14 days of age and older, in combination with other ARVs and they should not be administered to premature neonates (born one month or more before expected date of delivery) until 14 days after their due date.
- For neonate who cannot start with LPV/r-based regimen, should consider using NVP-based or RAL-based regimen upon stock availability.

**9.3.2 First line regimen for children from weighing 20 kg – < 30 kg**

- Since July 2018, WHO recommended Dolutegravir (DTG) based regimen as preferred first line for adult and children aged from 4 weeks of ages. Currently, the only DTG formulations available in Cambodia are the DTG 50mg single tablet and the Fixed Dose Combination (FDC) of TDF/3TC/DTG. Children weighing  $\geq$  20 kg are eligible to take DTG 50 mg with the NRTI backbone ABC/3TC. A pediatric formulation of DTG for children < 20 kg is expected to be available in 2021.
- If the children start on LPV/r-based regimen, it is encouraged to continue the same regimen until they are 20 kg and switch to DTG regimen if virologically suppressed on at least two consecutive occasions.
- All children weighing at least 20 kg should be on a DTG-based regimen. Children weighing 20 kg – < 30 kg should take ABC + 3TC as co-formulated (120mg/60mg) with DTG 50 mg single tablet. This regimen can be dosed once daily.
- In special circumstances, when an NNRTI-based regimen is required for children < 20 kg due to an intolerance to LPV/r, EFV-based regimen is preferred over NVP as it can

be dosed once daily and EFV is more potent than NVP. Please see table 16: First line ART recommendation regimen.

- AZT may be substituted if ABC hypersensitivity occurs.
- A failing regimen containing AZT may predispose the child to the development of thymidine analogue mutations (TAMS), a resistance mutation that reduces the effectiveness of other NRTIs including ABC, d4T, DDI, TDF and 3TC. In this reason, AZT is preferred to use in second line therapy rather than first line.
- DTG dose adjustment to 50mg BID is recommended in adults/adolescents >30kg when administered with rifampicin-based TB therapy. Some data supports BID dosing of DTG in children 20 to < 30kg on rifampicin as well, but consultation with NCHADS or clinical mentors is recommended for such patients. Use of Efavirenz in place of DTG during TB treatment should be considered for those already on DTG-based ART.
- Children weight 20kg - < 30kg with chronic hepatitis B infection should begin a regimen that includes both TDF and 3TC along with DTG. Currently, TDF formulations for children < 30kg are not yet available in Cambodia but may be procured for these children in the future. However, the preferred regimen for children weight 20 - < 30kg is ABC + 3TC + DTG.

### **9.3.3 First line regimen for children weight $\geq$ 30kg**

- The preferred regimen is a combination of **TDF + 3TC + DTG** one daily.
- Creatinine clearance should be tested prior to starting TDF and should be monitored regularly (See toxicity monitoring table)
- For patients being treated with rifampicin for TB, DTG needs to be dosed at 50 mg twice daily. (This means one TDF + 3TC + DTG triple FDC once daily, followed by one DTG 50 mg single tablet 12 hours later).

**Table 15: Recommended First-line ART Regimens\***

Age/Weight	Preferred regimen	Alternative	Special Circumstances
Neonate (< 4 weeks)	AZT + 3TC + LPV/r <sup>1</sup>	AZT + 3TC + NVP	AZT + 3TC + RAL <sup>2</sup>
Children weight < 20kg	ABC + 3TC + LPV/r	ABC (or AZT) + 3TC + EFV <sup>3</sup> (or NVP)	ABC (or AZT) + 3TC + DTG <sup>4</sup> ABC (or AZT) + 3TC + RAL <sup>2</sup>
Children weight 20kg to < 30kg	ABC + 3TC + DTG	ABC + 3TC + LPV/r	ABC (or AZT) + 3TC + EFV (or NVP) ABC (or AZT) + 3TC + RAL
Children weight ≥ 30kg	TDF + 3TC + DTG	TDF + 3TC + EFV 400	ABC (or AZT) + 3TC + DTG ABC (or AZT) + 3TC + EFV TDF + 3TC + ATV/r <sup>5</sup> (or LPV/r) TAF <sup>6</sup> + 3TC + DTG

<sup>1</sup>See Annex 5 for dosing of ART

<sup>1</sup>LPV/r (40mg/10mg) oral granule is recommended in infants and children 14 days of age and older, in combination with other ARVs and they should not be administered to premature neonates (born one month or more before expected date of delivery) until 14 days after their due date.

<sup>2</sup>Neonate starting ART with RAL-based regimen should transition to an LPV/r-based as soon as possible

<sup>3</sup>EFV could be used when the children aged ≥ 3 years and ≥ 10kg

<sup>4</sup>For age and weight group with approved DTG dosing

<sup>5</sup>ATV/r should be used when the child's weight is ≥ 35kg

<sup>6</sup>TAF may be considered for people with established osteoporosis and/or impaired kidney function.

# CHAPTER 10: ART IN HIV CO-INFECTION

## 10.1 ART and TB Treatment

### 10.1.1 When to start ART in children receiving TB treatment

- It is recommended that ART begin within two weeks of starting TB treatment.
- The child should have demonstrated initial stabilization on TB medications and be tolerating the regimen without adverse drug reactions before starting ART.

#### Box 9: When to start ART in children receiving TB therapy

Begin ART as soon as tolerated in the first 2 weeks of TB therapy, irrespective of the CD4 count or clinical stage.

### 10.1.2 Selecting an ART regimen in children receiving TB treatment

Rifampicin is a core component of first-line TB therapy. Rifampicin stimulates the activity of the cytochrome P450 (3A4) liver enzyme system, which metabolizes lopinavir, dolutegravir, nevirapine, and to a lesser extent, efavirenz, causing decreases in the blood levels of these drugs. PIs and NNRTIs can also modify this same enzyme system activity and lead to altered blood levels of rifampicin. Drug interactions may cause treatment failure or an increased risk of drug toxicity. Ritonavir *inhibits* the CYP 3A4 enzyme and is therefore able to “boost” blood levels of lopinavir when given together.

Specific interactions between rifampicin and ARV drugs are outlined below:

- **Lopinavir (LPV)**
  - Rifampicin reduces LPV AUC by >50% and trough concentrations by >90% in adults and children.
  - Standard-dose LPV/r CANNOT be used in patients also receiving rifampicin.
  - The addition of extra ritonavir “super-boosting” to standard LPV/r dosing results in sufficient therapeutic LPV concentrations in children receiving TB therapy.
  - Ritonavir is poorly palatable and adherence should be monitored carefully.
  - For children receiving LPV/r solution, extra ritonavir should be added. Older children receiving lopinavir/ritonavir tablets should also receive additional ritonavir while on rifampicin (See Table 16: Recommended ART regimens for children requiring TB treatment, page 61 and Annex 4: Anti-retroviral therapy dosing table, page 173).
  - Children should be monitored for medication intolerance and clinical hepatitis while receiving additional ritonavir boosting or double-dose LPV/r.
  - The “super-boosting” should be continued until 2 weeks after rifampicin discontinuation.
- **Ritonavir**

Ritonavir 100mg tablets are available in Cambodia, but these tablets must be swallowed whole and not crushed or chewed. If additional ritonavir is unavailable, children on LPV/r

may have their LPV/r dose doubled for the duration of TB therapy. Data on this approach are extremely limited. While studies of adult patients suggest this is an effective strategy, drug levels in children receiving rifampicin using double LPV/r dosing are lower. If ritonavir becomes available this should be given for super-boosting.

- Children should be monitored for medication intolerance and clinical hepatitis while receiving additional ritonavir boosting.
- The additional ritonavir “super-boosting” should be continued until 2 weeks after rifampicin discontinuation.

- ***Dolutegravir (DTG)***

Rifampicin reduces DTG Area Under the Curve (AUC) up to 85% when DTG used 50mg single dose. Data from the INSPIRING study in adults has shown that this reduction can be overcome by dosing DTG 50 mg twice daily. Adolescents receiving TLD can receive double dose DTG by giving TLD FDC once daily, and DTG 50 mg single 12 hours later. Using double dose DTG is currently being studied in children, and initial results suggest this is likely to be the same recommendation for children <30kg. This approach is not recommended for children 20 – 30 kg at present.

- ***Efavirenz (EFV)***

Rifampicin reduces EFV AUC by 22%. Most studies have suggested that trough levels remain in the therapeutic ranges in patients receiving both rifampicin and Efavirenz. For this reason:

- Efavirenz is the NNRTI of choice for use in patients receiving rifampicin-based TB therapy.
- It is not necessary to increase the daily dose of Efavirenz during rifampicin-based TB therapy. If lower than standard recommended doses of EFV are used, more intense monitoring (e.g. VL 3-months after starting ART should be performed).

- ***Nevirapine (NVP)***

- Rifampicin reduces NVP area under the curve (AUC) by 31%, although the clinical significance of this reduction is not clear. Small pediatric studies have variably suggested that trough levels are reduced to sub-therapeutic levels, although this reduction appears to be more dramatic in children of African origin than those from Asia.
- When possible, efavirenz should be used in place of NVP when co-administration with rifampicin is necessary.
- In the case of contraindications to efavirenz (age <3y, weight <10kg, or prior efavirenz intolerance), NVP may be used but should be dosed at the upper limit of 200 mg/m<sup>2</sup> per dose twice daily.

- o To measure body surface area (BSA):

$$BSA = \text{square root whole fraction } \sqrt{\frac{(\text{cm}) \times \text{wt (kg)}}{3600}}$$

- When NVP is begun in a child already receiving rifampicin, it should be initiated at the twice-daily maintenance dosing without a 14-day once-daily induction period.
- In children who remain on rifampicin and NVP, overlapping toxicities and drug-drug interactions warrant monthly assessment for signs of clinical hepatitis. ALT should be measured promptly if any evidence of hepatic injury arises.

- ***NRTIs***

There are no significant clinical interactions between rifampicin and the NRTI medications.

TB may be diagnosed before or after a child has started ART, or when the child is receiving second line therapy. Table 16 below describes the recommended dosing of ART and TB medication in these different scenarios. No adjustment to TB treatment is necessary.

**Table 16: Recommended ART Regimens for Children Requiring TB Treatment**

Age	ART after TB treatment initiated	TB develops during ART	When initial ART regimen failed	Comments
<3 years or <10 kg	ABC/AZT + 3TC + LPV/r, super-boost with extra ritonavir OR ABC/AZT + 3TC + NVP (dosed at 200 mg/m <sup>2</sup> )	Already on LPV/r-containing regimen, super-boost with extra ritonavir OR If child on NVP-based regimen increase dose of NVP to 200 mg/m <sup>2</sup>	ABC/AZT + 3TC + LPV/r, super-boost with extra ritonavir OR 3 <sup>rd</sup> line regimen recommended.	<ul style="list-style-type: none"> <li>• Use super boosted LPV/r for the duration of and 2 weeks after stopping TB treatment</li> <li>• If child on NVP, begin NVP at twice-daily maintenance dosing since CYP 3A4 already induced by rifampicin; close monitoring for NVP-related toxicity is advised</li> <li>• If this treatment regimen failed consult with 3<sup>rd</sup> line committee and discuss TB treatment options with CENAT.</li> </ul>
≥3 years and <10 years and <20 kg	ABC/AZT + 3TC + LPV/r, super-boost with extra ritonavir OR ABC/AZT + 3TC + EFV No dose adjustment	Already on LPV/r-containing regimen, super-boost with extra ritonavir OR If EFV-based regimen, continue EFV at the same dose	ABC/AZT + 3TC + LPV/r, super-boost with extra ritonavir OR 3 <sup>rd</sup> line regimen recommended	<ul style="list-style-type: none"> <li>• If on LPV/r, use super boosted LPV/R for the duration of and 2 weeks after stopping TB treatment</li> <li>• If this treatment regimen failed, consult with 3<sup>rd</sup> line committee and discuss TB treatment options with CENAT.</li> </ul>

20kg - < 30kg	ABC/AZT + 3TC +DTG No dose adjustment of DTG 50mg during TB treatment for this group	Continue DTG-based regimen. No dose adjustment of DTG 50mg during TB treatment for this group. No adjustment needed to ABC/3TC or AZT/3TC dosing. TDF is not given as children's weight < 30kg	AZT/ABC + 3TC + LPV/r, super boosted LPV/r for the duration of and 2 weeks after stopping TB treatment	<ul style="list-style-type: none"> <li>• If on LPV/r, use super boosted LPV/r for the duration of and 2 weeks after stopping TB treatment</li> <li>• No dose adjustment of DTG 50mg during TB treatment.</li> </ul>
≥ 30 kg	TDF + 3TC + DTG Dose DTG 50 mg twice daily, instead of once daily, for the duration of RIF-based TB treatment. This means one daily TDF/3TC/DTG fixed-dose tablet, and one daily DTG 50 mg	Continue DTG based regimen. Dose DTG 50 mg twice daily, instead of once daily, for the duration of RIF-based TB treatment. This means one daily TDF/3TC/DTG fixed-dose tablet, and one daily DTG 50 mg single tablet 12 hours later.	ABC/AZT + 3TC + LPV/r, super boosted LPV/R for the duration of and 2 weeks after stopping TB treatment	<ul style="list-style-type: none"> <li>• If on LPV/r, use super boosted LPV/R for the duration of and 2 weeks after stopping TB treatment</li> <li>• Dose DTG 50 mg twice daily, instead of once daily, for the duration of RIF-based TB treatment.</li> </ul>

## 10.2 ART in HIV Hepatitis B co-infection

HBV in children is frequently asymptomatic, although the impact of HIV infection on the natural progression of HBV is not well known. Children with HBV/HIV coinfection may have liver complications, which are related to flares in HBV activity, or they may develop liver toxicity if they are receiving ARV drugs.

The ultimate treatment goals in HIV/HBV co-infection are the same as for HBV mono-infection: to prevent disease progression and to reduce HBV mortality and morbidity.

- All HIV/HBV coinfecting adults, adolescents and children with evidence of chronic HBV should receive ART.
- Testing for hepatitis B surface antigen (HBsAg) and hepatitis C antibodies is recommended prior to initiation of ART if available.
- Formal diagnosis of chronic hepatitis B requires two HBsAg tests >6 months apart. However, any child with an indication for ART should be started on a regimen appropriate for HBV/HIV co-infection if the first HBsAg test is positive.

### Regimen selection in children with chronic hepatitis B

- All children and adolescents with HIV/HBV coinfection should receive Tenofovir Disoproxil Fumareate (TDF) based regimen, co-formulated with Lamivudine (TDF/3TC). However, TDF formulation is limited among those whose weight < 30kg. There is another option for using Tenofovir Alafenamide Fumareate (TAF) based regimen, co-formulated with Lamivudine (TAF/3TC) if available in Cambodia. These can be used for children weighing ≥ 25kg.
- ABC/3TC co-formulation is recommended as NRTI regimen backbone for children weighted < 30kg. The preferred 3<sup>rd</sup> drugs should be based on the recommendation of 1<sup>st</sup> line regimen, the same as for children without chronic hepatitis B.

**Table 17: Recommended ART Regimens for Children with Chronic Hepatitis B Infection**

Weight	Preferred initial regimen	Alternative Regimen
<20 kg	ABC + 3TC + LPV/r	AZT/ABC + 3TC + EFV <sup>2</sup> /NVP <sup>1</sup>
20 kg - < 30 kg	ABC + 3TC + DTG <sup>2</sup>	ABC (or AZT) + 3TC + LPV/r (or EFV <sup>2</sup> )
≥ 30kg	TDF + 3TC + DTG	TDF/ABC + 3TC + EFV <sup>2</sup>

\*Once appropriate dosing and pediatric formulation is available

<sup>1</sup> Follow LFTs monthly for 2 months, then every 6 months.

<sup>2</sup> EFV preferred, especially if baseline ALT is elevated ≥2N.

- HIV/HBV co-infected children may experience transient elevations of liver enzymes to ≤10 x normal during treatment initiation, which may be a sign of effective anti-HBV therapy. In general, medications should be continued with close monitoring through this period unless symptomatic hepatitis occurs.
- ALT should be measured monthly for 3 months, then 6 monthly (See Annex 7: Schedule of

routine clinical and laboratory monitoring for HIV-infected children not on ART, page 181).

### **10.3 ART in HIV Hepatitis C Co-infection**

The natural course of hepatitis C virus (HCV) infection in children is not well known. HCV infection may lead to liver cirrhosis; however, the process of liver damage is very gradual. Studies from adults have shown that patients with HCV/HIV co-infection progress 3 times more rapidly to liver cirrhosis than those patients who have HCV alone.

- ARVs used for the treatment of HIV have no activity against hepatitis C.
- Many of the drugs used to treat hepatitis C infection, have troublesome toxicities, and are not routinely available in Cambodia.
- New drugs such as sofosbuvir have not yet been approved for use in children.
- **Therefore, HCV treatment is not recommended for HIV/HCV co-infected children at this time.**
- HCV co-infected children on ART should have liver enzymes monitored for drug toxicity monthly for the first 2 months, then every 6 months.

## CHAPTER 11: DRUG TOXICITY

Healthcare workers need to be aware of the known side effects of the drugs they prescribe for patients and this needs to be communicated to the patients or caregiver. This may help with adherence, avoiding unnecessary drug interruptions, and will empower children/caregivers to know when an event is serious enough to warrant medical attention.

Children with HIV are frequently taking many different drugs, which sometimes have overlapping toxicity. Toxicities in children are similar to those observed in adults although observed less frequently.

Table 18 below serves as a guide to help make decisions about whether a patient experiencing toxicity needs a single drug switch or whether all drugs need to be stopped.

See Annex 5: Severity Grading of Selected Clinical and Laboratory Toxicities, page 176.

### Grading of adverse events

All adverse events are graded from grade 1 to grade 4 depending on the severity of the event as well as the age of the child.

Response to adverse events:

- **Grades 1 and 2:** Continue with treatment and repeat the test. Reassess the patient within 2 weeks.
- **Grade 3:** Requires that the test be repeated within 1 week and if it still remains at grade 3, all ARVs must be stopped and patient managed with the assistance of a specialist.
- **Grade 4:** Requires that all drugs be stopped immediately and be referred to hospital. The patient can restart therapy after getting better, with a different regimen (Please consult mentor or PAC TWG).

If there is a need to discontinue all ART, it is advisable to discontinue all ARVs rather than continuing with one or two agents alone. However, when a patient discontinues a NNRTI-containing regimen, attempt to continue the NRTI component for a week after stopping the NNRTI, this is to account for the longer half-life of the NNRTI.

It is preferable where possible to check that the viral load is suppressed prior to switching a single drug. This is not recommended if the toxicity occurs in the first few months after starting ART and should only be done if the toxicity is mild and the viral load result can be obtained within a month. If the viral load is >1000, follow the recommendations for treatment failure.

Some side effects can occur in the first weeks and months of treatment (rash, anemia or neutropenia, acute hepatitis) and require monitoring and close follow up as well, as they may require treatment changes (See Table 18 below). Other toxicities occur after months or years of antiretroviral treatment. These include lipodystrophy, peripheral neuropathy, hyperlactatemia and mitochondrial toxicity. These toxicities can be life threatening (lactic acidosis), disabling (neuropathy), or impact adherence (lipoatrophy in adolescents).

Toxicity can be monitored clinically on the basis of child and/or caregiver reports and physical examination and can also be assessed by means of a limited number of laboratory tests, depending on the toxicity and the specific ARV combination regimen used.

**Table 18: Management of ART-Related Toxicities with First- or Second-line Regimens**

First-line ARV drug	Most frequent significant toxicity	Comments	Suggested management
<b>Abacavir ABC</b>	Hypersensitivity reaction	Risk factor HLA-B*5701 Fever, rash (often maculopapular and mild), nausea, vomiting, diarrhea, fatigue, flank or abdominal pain, respiratory symptoms, myalgia, and arthralgia (1 <sup>st</sup> 6 wks of ART) (see Box 10, page 70).	Stop ABC and Switch to AZT or TDF (if the child is >10 years and >30 kg) NEVER reintroduce ABC as this could result in fatal hypersensitivity.
<b>Atazanavir ATV/r</b>	Indirect hyperbilirubinemia	Pre-existing hepatic disease. Usually benign indirect hyperbilirubinemia.	Indirect hyperbilirubinemia from ATV/r rarely requires a change in therapy. If liver enzymes are normal and there are no symptoms ATV/r may be continued. Review concurrent medications and substitute if possible Ensure adequate hydration Substitute with LPV/r if necessary.
	Electrocardiographic abnormality (PR and QT interval prolongations)	Pre-existing conduction system disorder or concurrent use of other drugs known to cause conduction disturbance	
	Nephrolithiasis	Usually associated with insufficient water intake	
<b>Zidovudine AZT</b>	Severe anemia <sup>1</sup> or neutropenia	If Hb drops by 25% or more from baseline Avoid AZT if baseline Hb <7.5 g/dl. If neutrophil count <500/mm <sup>3</sup> .	Stop AZT, switch to ABC or TDF (if the child is >10 years and >30 kg)  Mild nausea can be managed with frequent small meals and anti-emetics.
	Myalgia, myopathy	Creatine kinase (CK) >10; weakness	
	Severe gastrointestinal intolerance	Persistent nausea and vomiting that prevents ingestion of ARV. Minor nausea is common, but almost always improves during the first month of ART.	

	Lactic acidosis	Generalized fatigue and weakness GI symptoms (nausea, vomiting, diarrhea, abdominal pain, hepatomegaly, anorexia, poor weight gain and/or sudden unexplained weight loss) +/- hepatitis or pancreatitis Tachypnoea and dyspnoea Neurological symptoms Increased anion gap Lactic acidosis.	Stop all ARVs until symptoms disappear, switch to ABC or TDF (if the child is >10 years and >35 kg).
<b>Nevirapine NVP</b>	Hepatotoxicity	May be associated with underlying HBV or HCV infection  Mild- moderate: ALT 1.25 - <10 x normal  Severe hepatotoxicity ALT>10N	<b>Mild to Moderate:</b> investigate for other causes e.g. viral hepatitis. Continue treatment, monitor liver function daily, if no resolution change to LPV/r or manage as for severe hepatotoxicity <b>Severe:</b> stop all ARVs, restart when ALT 2xN, replace NVP with LPV/r or EFV or DTG (as appropriate for age/weight).
	Dry rash (mild or moderate rash – see Annex 6 for grading)	Dry rash: macules, papules, dry desquamation	<ul style="list-style-type: none"> <li>• Continue NVP same dose (continue once daily if lead in period).</li> <li>• Give anti-histamine drug. Switch to LPV/r or EFV or DTG (as appropriate for age/weight) if rash lasts more than 1 month<sup>2</sup></li> </ul>
	Wet rash or Erythema multiform (severe rash – see Annex 6 for grading)	Wet rash: vesicles, ulcers, limited moist desquamation, limited mucous membranes involvement.	Stop NVP and continue NRTI for 1 week, start with LPV/r or EFV or DTG (as appropriate for age/weight). when symptoms resolve

	Life-threatening rash (Stevens-Johnson syndrome or Lyell)	Extended moist desquamation, with mucous membranes involvement systemic signs, e.g. fever	Stop all ARVs, restart LPV/r or DTG (as appropriate for age/weight). Based HAART when symptoms resolve.
	Hypersensitivity reaction	Systemic symptoms of fever, myalgia, arthralgia, hepatitis, and eosinophilia with or without rash.	(EFV should be avoided)
<b>Efavirenz EFV</b>	Persistent and severe central nervous system toxicity Seizures	<ul style="list-style-type: none"> <li>• Persistent hallucinations or</li> <li>• Psychosis</li> <li>• Pre-existing neuropsychiatric disorder or epilepsy</li> </ul>	Switch to LPV/r or DTG (as appropriate for weight).
	Gynecomastia (enlarged breast tissue in adolescent boys)		
	Hepatotoxicity	May be associated with underlying HBV or HCV infection ALT>10N	Stop all ARVs, restart regimen with LPV/r or DTG (as appropriate for weight) when symptoms resolve.
	Dry rash	See management for NVP rash	
	Wet rash or life-threatening rash (Stevens-Johnson syndrome or Lyell)	See management for NVP rash	
<b>Tenofovir TDF</b>	Tubular renal dysfunction (Fanconi Syndrome)	<p>Underlying renal disease. Check creatinine clearance before starting TDF</p> <p>The modified Cockcroft-Gault equation: Creatinine clearance = <math>(140 - \text{age}) \times \text{ideal weight} / \text{serum creatinine}</math> (x 0.85 for females)</p>	<p>Substitute ABC or AZT for TDF</p> <p>Substitute AZT or ABC</p>

	Decrease in Bone mineral density (can lead to pathologic fractures)	This is usually detected by DEXA scan and may be not be available in Cambodia therefore only use if indicated (e.g. for HBV co-infection in children <10years and <35kg)	Vitamin D supplementation (1000 – 4000 IU daily) and ensure adequate dietary calcium intake (e.g. dairy products)
	Flatulence, Nausea, diarrhea, abdominal discomfort	TDF contains lactose and lactose intolerant individuals may suffer these symptoms	
<b>Lopinavir/ritonavir LPV/r</b>	Electrocardiographic abnormality (PR and QT interval prolongations)	Pre-existing conduction system disorder	If LPV/r first line treatment in children NVP or EFV or DTG (as appropriate for age/weight) can be substituted.  ATV/r may be substituted in children > 6 years of age and > 40 kg.
	Hepatotoxicity	Worse if underlying liver disease e.g. HBV or HCV	
	Dyslipidaemia or lipo-hypertrophy		
	Nausea, vomiting, diarrhea		
<b>Ritonavir (RTV)</b>	Nausea, vomiting, diarrhea, peri-oral numbness, headache, abdominal pain and anorexia		
<b>Dolutegravir (DTG)</b>	Insomnia, dizziness, anxiety, Skin hypersensitivity		Counsel patients (Usually mild and subside within a few months) Can consider switch to EFV or boosted PI

<sup>1</sup>Exclude malaria in areas of endemic malaria.

<sup>2</sup>If systemic signs and/or ALT>5N, stop all ART and restart with LPV/r

### Box 10: Clinical feature of Abacavir hypersensitivity (ABC HSR)

This is a multi-organ process manifested by at least two of the following groups of signs or symptoms:

- Fever is the most common manifestation occurring in 80% of cases. Chills have been reported to accompany fever.
- Rash is experienced by 70% of cases and pruritus can also occur. In contrast to NVP, the rash is often mild and may go unnoticed by patients. When rash occurs in the absence of other features of HSR, ABC should not be discontinued.
- Gastrointestinal symptoms such as nausea, vomiting, diarrhoea and abdominal pain are all features of HSR but may also occur in the absence of HSR, particularly when ABC is used with AZT. Therefore, as with rash, patients with isolated gastrointestinal symptoms should not discontinue ABC but should be followed closely for the development of other additional signs or symptoms.
- Constitutional symptoms include fatigue, myalgia and generalized malaise.
- Respiratory symptoms occur in 18% of cases and include dyspnoea, cough and pharyngitis. Symptoms may be difficult to distinguish from influenza and other respiratory viruses. Respiratory symptoms together with abdominal symptoms suggest HSR rather than influenza or other respiratory illness. Clusters and combinations of symptoms are important in the diagnosis of ABC HSR. An abnormal chest x-ray may be present, with interstitial findings.
- With ABC HSR, there is an accentuation of symptoms in the hours immediately after the dose and worsening of symptoms with each subsequent dose. Stopping therapy is followed by rapid improvement in the symptoms.
- If ABC is not stopped or is restarted after temporary cessation, the HSR will progress to hypotension, renal dysfunction and bronchospasm and ultimately, death. Resuming ABC therapy may lead to anaphylaxis and should be avoided even in cases where there was diagnostic uncertainty.
- Abnormal laboratory findings may include leukopenia, anaemia and thrombocytopenia, as well as elevations in transaminases, urea, creatinine and LDH. Eosinophilia is usually absent.

### Box 11: Management of Abacavir hypersensitivity

On commencement of ABC, patients should be counselled in detail about the possible signs of HSR and be advised to contact their care provider should any occur. Prior to starting ART, make sure that the child does not have any illness with similar features to ABC HSR, and that recovery from this illness has occurred before commencing ART.

- Encourage caregivers to contact clinic staff if they have concerns and not to stop medication on their own as once ABC has been stopped under circumstances of suspicion for HSR, it should NEVER be restarted.
- The vast majority of HSR cases occur in the first 6 weeks of therapy, with a median onset of 9 days. Non-specific symptoms beginning months after the initiation of ABC are unlikely to be related to HSR.
- Where possible, contact information for the usual ART physician should be provided in case the child needs admission as non-HIV trained staff may be less aware of the management of ART side effects
- Deciding whether to stop therapy in a patient with suggestive symptoms can be difficult given the non-specific nature of the presentation. A detailed medical history should be obtained.

The following should be considered:

- When was ABC initiated? (ABC HSR occurs typically within 6 weeks of starting ABC)
- Are two or more systems involved?
- Do the symptoms increase with each dose?
- Do the symptom exacerbate just after the dose?
- Are there other family members or close contacts who have similar symptoms, suggesting the possibility of a viral illness in the household?

Exacerbation of symptoms associated with dosing of ABC makes the diagnosis of ABC HSR more likely.

**If this is the case or there are 2 or more constitutional signs and symptoms as above, ABC may be stopped. AZT or TDF (if >10 years and >35kg) may be substituted.**

## **CHAPTER 12: 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.

Patients with advanced HIV disease, particularly those with a CD4 count <100 cells/ $\mu$ l, may become ill with IRIS, usually during the first 3 months of ART.

Opportunistic infections may present in atypical ways during this phase of immune reconstitution.

The development of IRIS is not usually a reason to stop ART, or to change the regimen. However, careful counselling is needed to ensure that the patient understands this.

TB is the most common cause of IRIS, which occurs in up to one third of patients who start ART shortly after TB diagnosis. Rashes (including zoster, herpes, molluscum and others), cryptococcal meningitis, and hepatitis due to hepatitis B/C that occur in the first weeks and months of ART initiation are other manifestations of IRIS

Two types of IRIS are summarized below:

### **12.1 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.

### **12.2 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.

## Box 12: BCG IRIS

### Manifestation

IRIS related to BCG immunization has been reported during immune reconstitution. These symptoms include:

- Abscess at the site of injection 10-15mm
- Lymphadenitis (>1.5cm) (lymphadenopathy may also occur at other sites, e.g. supraclavicular and cervical)
- Suppurative lymphadenopathy in association with BCG injection
- Disseminated BCG disease (indicated by failure to thrive, fever, hepatosplenomegaly)
- Osteitis
- Skin and eye reactions including erythema nodosum, lupus vulgaris and iritis.

### Management

If an abscess is present, it should be drained to avoid sinus formation.

Pus may be sent for TB culture and PCR for detection of *Mycobacterium bovis* - BCG should be requested.

Most infants with localized BCG reaction will get better without anti-mycobacterial drugs, especially if it is part of an immune reconstitution inflammatory syndrome (IRIS).

### Disseminated BCG disease

This may occur as an IRIS event but can also occur prior to starting ART. Clinically this may be indistinguishable from disseminated TB disease, with miliary pneumonitis, granulomatous hepatitis, soft tissue infections, bone marrow involvement, and sepsis. Diagnosis may be made on sputum specimens, abdominal ultrasound and other investigations as indicated. Case fatality may be as high as 70%.

Children with disseminated BCG disease should receive treatment with high-dose INH (20mg/kg/day), Rifampicin (15 mg/kg/day) and Ethambutol (25 mg/kg) for a period of 9 months. PZA is usually also added because BCG disease and TB may be difficult to differentiate, even though BCG is inherently PZA resistant. Some strains of BCG used for vaccination have low-level resistance to INH, hence the choice of drug regimen with higher doses of INH.

# CHAPTER 13: CLINICAL AND LABORATORY MONITORING

Clinical and laboratory assessments are required for all HIV infected children before ART is started and regularly after ART initiation, to determine response from baseline and to identify the development of any toxicities.

## 13.1 Baseline Clinical and Laboratory Assessment

- All children who are diagnosed with HIV infection should undergo baseline clinical and laboratory assessment to determine their WHO clinical stage, and baseline CD4 (See also Annex 1 and Annex 7, page 167 and page 181 respectively)
- Monitoring should also be performed during follow-up care for children regardless of eligibility to receive ART.
- The standard baseline clinical and laboratory assessment of children newly diagnosed with HIV is outlined below.

### Box 13: Baseline evaluation of children with newly diagnosed HIV infection

#### Clinical Assessment

- Clinical staging of HIV infection (Annex 1)
- Identification of concomitant and previous medical conditions (TB, other OIs, pregnancy, hepatitis, kidney disease)
- Detailing of concomitant medications such as CTX and others drugs for OI
- prevention or treatment as well as prior exposure to ART
- Traditional or herbal therapy use
- Weight, height, head circumference, and measures of growth (see Annex 15, page 195, for pediatric weight-for-age growth charts)
- Developmental status
- Nutritional status
- Assessment of children and parents or caregivers for preparedness for ART and psychosocial needs.

#### Laboratory Assessment

- Measurement of CD4 and %CD4
- Complete blood cell count, including white blood cells (WBC), Hemoglobin measurement, and platelets
- Hepatitis B surface Ag and Hepatitis C Ab if available
- Liver enzymes (LFTs)
- Pregnancy test (adolescent girls only)
- Urine dipstick and Creatinine if starting TDF.

## 13.2 Routine Monitoring of Children on ART

- Once the child is initiated on ART, ongoing clinical and laboratory monitoring should take place in the context of the routine clinical care of the child.
- Clinical and laboratory assessments of the child and caregivers should include assessing their understanding of ART, drug regimen and dosing, and drug side effects, as well as medication adherence and anticipated psycho-social and community support.
  - The routine clinical and laboratory monitoring of children receiving ART is outlined in Box 13: Baseline evaluation of children with newly diagnosed HIV infection, page 74 and Annex 7: Schedule of routine clinical and laboratory monitoring for HIV infected child not on ART, page 181.

### Box 14: Routine clinical and laboratory monitoring in children receiving ART

#### Clinical assessment

- Nutritional status and feeding
- TB symptoms screen
- Neurological and developmental assessment
- Weight, height, weight-for-height, head circumference\*, and growth assessment
- Evaluation of any interval illnesses and new medications
- Assessment of ARV dosing, side effects, toxicities and drug interactions
- Adherence to ART
- Disclosure and psychosocial needs assessment
- Developmentally appropriate counseling for prevention of secondary transmission, STIs and pregnancy, sharing needles or blood exposures
- Evaluate medication dosing and adjust as necessary for interval weight gain.

#### Laboratory assessment

- Measurement of CD4 and %CD4+ every year
- Hemoglobin measurement at week 8 (if on AZT)
- Viral load (VL) at month 6, 12 months, then annually
- Fasting lipid panel yearly in adolescents receiving EFV or LPV/r
- Urinalysis if available
- Creatinine, baseline, 3 months and then annually for children receiving TDF
- Other testing as symptomatically indicated.

*\*Under 2 years of age*

## CHAPTER 14: TREATMENT FAILURE

- Treatment failure initially occurs through virologic failure, then immunologic failure, and later presents as clinical failure see Table 19 below.
- The use of viral load testing is now strongly recommended by WHO to monitor for and diagnose treatment failure in all people.
- It is recommended to switch to second-line drugs before clinical failure occurs. Children with virologic failure who appear to be well generally have better outcomes if treatment is switched to second line rather than waiting for symptoms to appear.

**Table 19: Definition of Treatment Failure**

Failure	Definition	Comments
<b>Virological Failure</b>	Plasma viral load > 1000 copies /ml based on 2 consecutive measurements after 3 months with enhanced adherence counseling (EAC)	Patient should be taking ART at least 6 months before it can be determined that the regimen has failed.
<b>Immunological Failure</b>	Children <5 years Persistent CD4 levels < 15% or <200 cells/mm <sup>3</sup>  Children ≥5 years Persistent CD4 levels <100 cells/mm <sup>3</sup>	Without concomitant infection to cause transient drop in CD4. The patient must be taking ART for 1 year before immunological failure can be diagnosed. Children with immunological failure should have viral load performed to confirm failure.
<b>Clinical Failure</b>	New or recurrent event indicating advanced or severe immunodeficiency <sup>21</sup> after 6 months of effective treatment	Condition clinically distinct from immune reconstitution inflammatory syndrome (IRIS). <sup>22</sup> Children with clinical failure should have a viral load performed to confirm failure.

### 14.1 Causes of treatment failure

The causes for treatment failure with first-line drugs should be addressed before considering changing to second line. Some common causes for treatment failure are:

- Inadequate adherence:
  - Missing doses because of forgetfulness, non-disclosure, stigma, inconsistent caregivers.

<sup>21</sup> WHO stage 3 or 4 condition see Annex 1 for WHO staging in children

<sup>22</sup> See above section on immune reconstitution inflammatory syndrome (IRIS)

- Failing to refill medications on time.
  - Side effects
  - Inappropriate dose (misunderstanding, sharing drugs).
- Inadequate drug levels:
    - Under-dosing (failure to increase dose for weight gain)
    - Poor absorption (diarrhea)
    - Varying pharmacokinetics
    - Metabolic changes in a growing child
    - Drug-Drug interactions
    - Inadequate potency of the drugs chosen
    - Pharmacy errors.
  - Pre-treatment resistance to NNRTIs (as in the case of failed PMTCT).

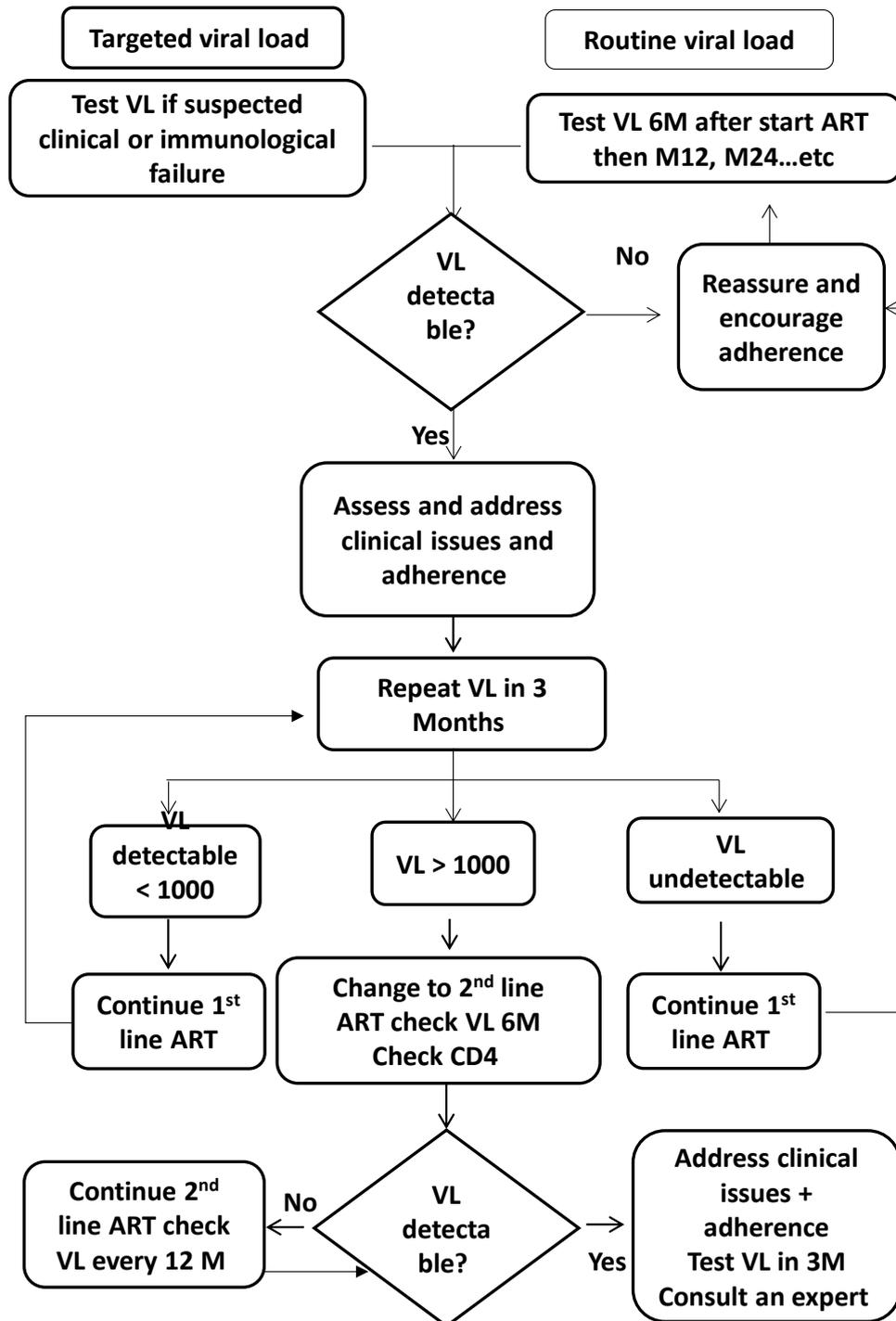
Before considering a change in treatment because of growth failure, it should be ascertained whether the child is receiving adequate nutrition.

Inadequate adherence is the most common cause of virologic failure. At each visit, adherence should be confirmed by pill counts and self-report and other methods as available (visual analogue scale, pharmacy refill records or other means). Proper dosing should be confirmed, and medication doses adjusted for any weight gain since the last visit. (Refer to adherence section below.)

## 14.2 Viral load testing

- The overall aim of treatment is to reduce viral load (VL) to levels below the lowest detection threshold given by the laboratory (in Cambodia this is 40 copies/mL) as rapidly as possible and to maintain undetectable levels for as long as possible.
- Viral load is now a routine test in Cambodia, and all pediatric patients should receive VL testing according to these guidelines.
- The recommended schedule is to determine the VL after 6 months of ART and again at 1 year after ART initiation in children (VL decrease may take longer especially in younger children).
- If the VL is undetectable, continued monitoring every 12 months thereafter is recommended.
- If the viral load is <1,000 copies/ml but >40 this should be repeated at the next visit to ensure that the viral load is undetectable. In case of persistent VL > 40 and < 1,000 copies/ml (after 2 times of EAC) then discuss with children expert.
- At any time, if there is a clinical indication such as clinical or immunological failure or reported poor adherence, a VL load test can be repeated even if this is before the scheduled time for VL to be checked
- If the VL is detectable, additional steps need to be taken to ensure adequate drug adherence (see Figure 8 below).

Figure 8: Viral load testing strategy



**Remark:**

All patients receiving ART using PIs-based and DTG-based 1<sup>st</sup> line regimen who have viral load detectable (VL ≥ 40 copies/ml), must receive enhanced adherence counseling and control VL after completion of 3 sessions of EAC (follow EAC SOP). If the control VL is still detectable (VL ≥ 40 copies/ml); clinicians should report the cases to TWG of NCHADS for further recommendation from experts. As PIs as well as DTG-based regimen are very potentials and have high barriers to

resistance<sup>8</sup>. Thus, it is unlikely that first-line PI-based or DTG-based are resistance within couple of year of using them.

### **14.3 CD4 testing for monitoring**

- The role of CD4 in monitoring for treatment failure is reduced when VL can be performed regularly.
- CD4 should be measured at baseline and is useful to determine disease severity.
- Thereafter CD4 may be tested annually in between viral load testing. If the CD4 drops this should indicate the need for a viral load test.
- Sometimes the CD4 may drop transiently even though the plasma VL is undetectable. Switching to 2<sup>nd</sup> line therapy will not improve the clinical or immunologic status of the child if the VL is undetectable, and alternative explanations for the child's low CD4 count, such as an acute infection, steroid use or bone marrow suppression, should be sought.

# CHAPTER 15: CHOICES FOR SECOND LINE TREATMENT

Children meeting the definition of treatment failure require modification of their ART regimen to control viral replication, avoid clinical disease progression and to prevent the further emergence of new more extensive viral resistance mutations.

## 15.1 Second line regimen options

### 15.1.1 VL >1000 copies/ml on PI-based first line therapy

- Infants will sometimes take longer than 6 months to fully suppress HIV on their initial regimen, therefore Enhanced Adherence Counseling (EAC) and repeat VL after 6 months.
- Development of PI mutations and TAMS occurs slowly, making persistent treatment with the same regimen a good option. With EAC support, children's VL may in many cases become suppressed again.
- Therefore, adherence support should be intensified and the VL reassessed after 6 months.
- Children who continue to have VL >1000 copies/ml despite EAC support after at least 6 months further may require genotyping if available and may need to be assessed in consultation with clinical mentors or the AIDS Care Unit at NCHADS.
- Please see the proposed 2<sup>nd</sup> line regimen in table 20 below.

### 15.1.2 VL >1000 copies/ml on NNRTI-based first line therapy

- Children on first line treatment with NNRTI-based therapy should be switched to a LPV/r-containing regimen when weight < 20kg or DTG-based when weight ≥ 20kg, repeat VL after 6 months, and if VL fails to suppress after 1 year on second line therapy the child may require genotyping, if available, and may need to be assessed by a clinical mentor or the AIDS Care Unit at NCHADS.

### 15.1.3 Considerations for NRTI's in second line therapy

- 3TC is always retained in second line treatment
- If ABC is used in first line, this should be switched to AZT If AZT is used in first line, this should be switched to ABC for or TDF (if child >30 kg).
- If TDF was used in first line, this should be switched to AZT.

#### **IMPORTANT: When switching to second-line treatment:**

- Never change EFV to NVP or NVP to EFV as they share the same resistance mutations and cross resistance will occur.
- *(This switch is possible when switching from first-line to alternative first-line for toxicity).*

## 15.2 Treatment failure in special circumstances

- *Active tuberculosis*

- When 2<sup>nd</sup> line is necessary during TB treatment, additional ritonavir must be added to co-formulated lopinavir/ritonavir to bring the lopinavir/ritonavir ratio to 1:1. This is referred to as “super-boosting.” (See above in section on treatment of TB/HIV co-infection).
- The additional ritonavir dose should be continued until 2 weeks after rifampicin is discontinued.
- ***Chronic Hepatitis B virus infection***
  - Abrupt discontinuation of hepatitis B treatment can precipitate a severe flare in hepatitis B activity.
  - Children or adolescents with chronic hepatitis B who require 2nd line therapy for HIV should not stop either 3TC/FTC or TDF if included in the first line, even if they are no longer effective for HIV treatment because of their continued activity on hepatitis B virus.

**Table 20: Recommended Second-line Regimens**

<b>Weight</b>	<b>If patient fails this 1<sup>st</sup> line regimen</b>	<b>Switch to this preferred 2<sup>nd</sup> line regimen</b>	<b>Comments</b>
<b>&lt; 20 kg</b>	<p>ABC (or AZT) + 3TC + NVP (or EFV)</p> <p>ABC (or AZT) + 3TC + LPV/r</p>	<p>AZT (or ABC) + 3TC + LPV/r</p> <p>AZT (or ABC) + 3TC + DTG (when pediatric DTG formulation becomes available).</p>	<p>If children are switched to NNRTI-based therapy, repeat VL after 6 months, if still elevated, switch back to LPV/r. Children remaining on LPV/r or who have switched back to LPV/r should have EAC and repeat viral load after EAC. If viral load remains elevated after 1 year and/or CD4 count decreasing or new stage 3 or 4 events occur, refer for genotyping if possible, and may require third line options if available (to be discussed with mentor or PAC TWG). Use AZT if ABC used first line or ABC if AZT used in first line therapy.</p>
<b>20kg - &lt; 30 kg</b>	<p>ABC (or AZT) + 3TC + NVP (or EFV or LPV/r)</p> <p>ABC (or AZT) + 3TC + DTG</p>	<p>AZT (or ABC) + 3TC + DTG</p> <p>ABC (or AZT) + 3TC + LPV/r</p>	<p>Use AZT if ABC used first line or ABC if AZT used in first line therapy.</p>
<b>≥ 30kg</b>	<p>TDF (or ABC) + 3TC + EFV (or NVP)</p> <p>AZT + 3TC + EVF (or NVP)</p> <p>TDF (or ABC) + 3TC + DTG</p> <p>AZT + 3TC + DTG</p>	<p>AZT + 3TC + DTG</p> <p>TDF (or ABC) + 3TC + DTG</p> <p>AZT + 3TC + PIs</p> <p>TDF (or ABC) + 3TC + PIs</p>	<p>Use AZT if TDF used first line or TDF if AZT used in first line therapy</p> <p>If &gt; 40kg, ATV/r is the best choice of PI, because the tablets burden can be reduced and the medication can be taken daily with TDF 300mg + 3TC 300mg.</p>

## CHAPTER 16: THIRD LINE TREATMENT

Treatment support as described below should be in place to ensure that most children succeed on their first-line ART regimen (See section on Psychosocial Support). Those patients failing first-line treatment should be identified early and offered EAC support to ensure durability of 2<sup>nd</sup> line treatment. Nevertheless, some children will require 3<sup>rd</sup> line options.

### 16.1 What to do when a patient on 2nd line regimen has a confirmed virological failure

Treatment failure defined as when children who are on ART but with viral load  $\geq 1,000$  copies/mL after 3-month Enhanced Adherence Counseling (EAC). Virological failure to 2<sup>nd</sup> line regimen may be due to ART resistance. Such patients may be eligible for third-line.

“salvage therapy.” Suspected cases of 2nd line resistance should be referred to NCHADS for discussion with the 3<sup>rd</sup> line Technical Working Group.

#### Refer suspected cases of 2<sup>nd</sup> line resistance to NCHADS if:

Patient has been on PI-based regimen for at least 12 months AND

Patient has had two consecutive VL results  $\geq 1000$  copies/mL, separated by Enhanced Adherence Counseling (1 time per month in 3 consecutive months, using the process of EAC).

These patients are experiencing a medical emergency. The clinician must:

#### Contact AIDS Care Unit

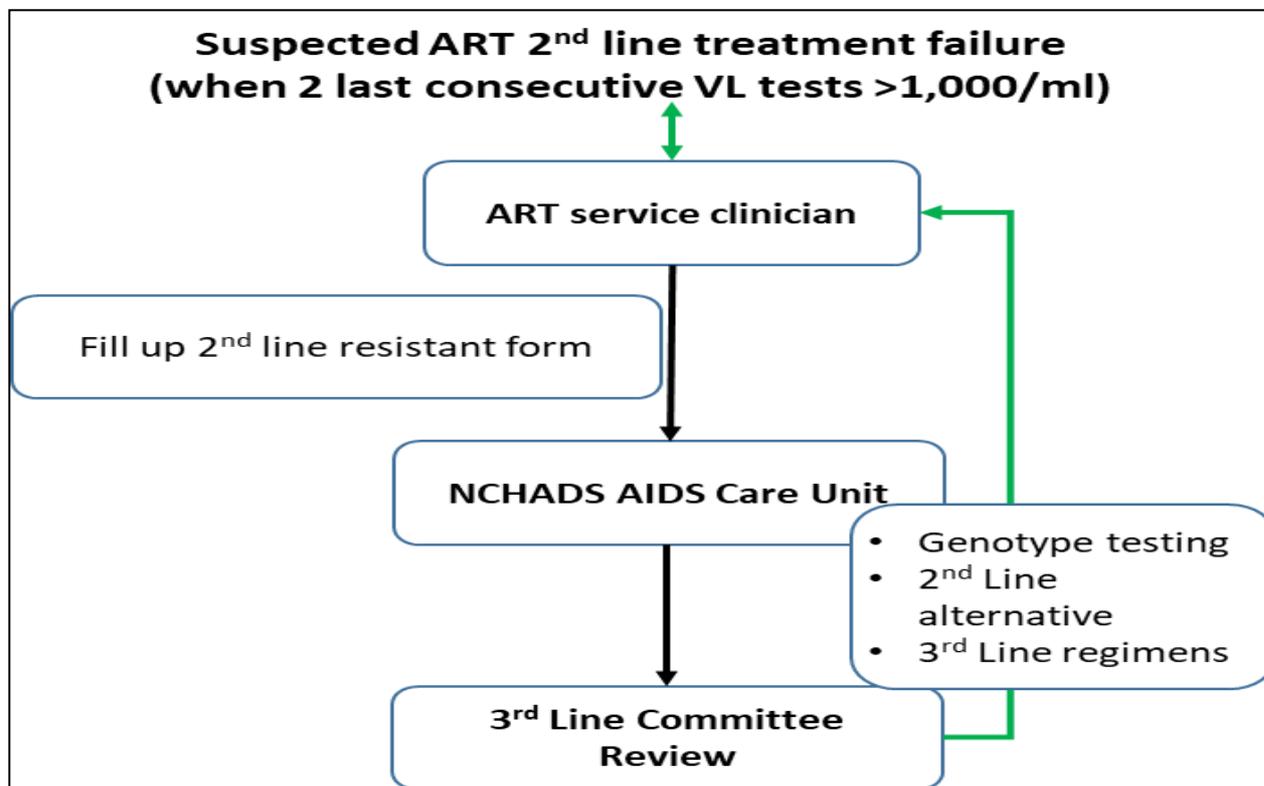
- E-mail address: [clinicalmentoring@nchads.org](mailto:clinicalmentoring@nchads.org)
- Dr. Ngauv Bora, AIDS Care Unit: [bora@nchads.org](mailto:bora@nchads.org)
- Dr Ky Sovathana, AIDS Care Unit: 077 811 189 / [kysovathana@nchads.org](mailto:kysovathana@nchads.org)

**Fully complete the ‘Suspected 2<sup>nd</sup> line resistance form’** see Annex 11, page 191.

The patient’s ‘Suspected 2<sup>nd</sup> Line Resistance Form’ will be reviewed by the 3<sup>rd</sup> line TWG composed of partners, experts and NCHADS. The Cambodian3L TWG will meet regularly to review all 2<sup>nd</sup> line suspected failure referrals and provide appropriate recommendations. NCHADS will feed back to the clinicians on site about the recommendations from the 3<sup>rd</sup> line TWG for each patient, especially about the need for an HIV genotype to further analyze HIV-1 gene mutations.

## 16.2 Process of following the suspicion of 2<sup>nd</sup> line virological failure

Figure 9: Procedure to manage the patients suspected failure on 2<sup>nd</sup> line treatment



regimen

Composition of TWG of 3<sup>rd</sup> Line regimen

- Director of NCHADS
- Chief/vice chief of Technical Bureau
- Chief/vice chief of AIDS Care Unit
- National mentors
- National and international HIV expert
- Experienced ART team leaders from sites
- Key partners: CHAI, US-CDC, WHO, AHF, FHI 360-LINKAGES, etc.
- Other relevant units: LMU, Lab unit

New generation and new class antiretroviral drugs have been developed and combinations of highly effective drugs are now available for 3<sup>rd</sup> line options and will be available for pediatric formulation and doses in Cambodia soon.

These drugs include:

- **Darunavir** (plus ritonavir – a new generation boosted PI that is very potent and has a high barrier against resistance).
- **Raltegravir and dolutegravir** (integrase inhibitors, a new class of antiretroviral).

- **Etravirine** (new generation NNRTI with a higher threshold for resistance).

The result from genotype resistance test will allow the HIV experts and TWG members to optimize ART regimen that is potential for the 3<sup>rd</sup> line candidates which is the best combination of ARVs drugs available within Cambodia. After best efforts to maintain first line and second line regimens, patients failing second-line therapy or who have failed a regimen containing LPV/r, should have genotyping in order to guide further management.

If healthcare workers identify children who may need third line treatment, they should contact the clinical mentors or the AIDS Care Unit at NCHADS and cases will be discussed on an individual basis. The ART clinician needs to fill up the data collection form and submit to TWG on 3<sup>rd</sup> line therapy (Annex 10: Data collection form for patient required third line ART, page 188).

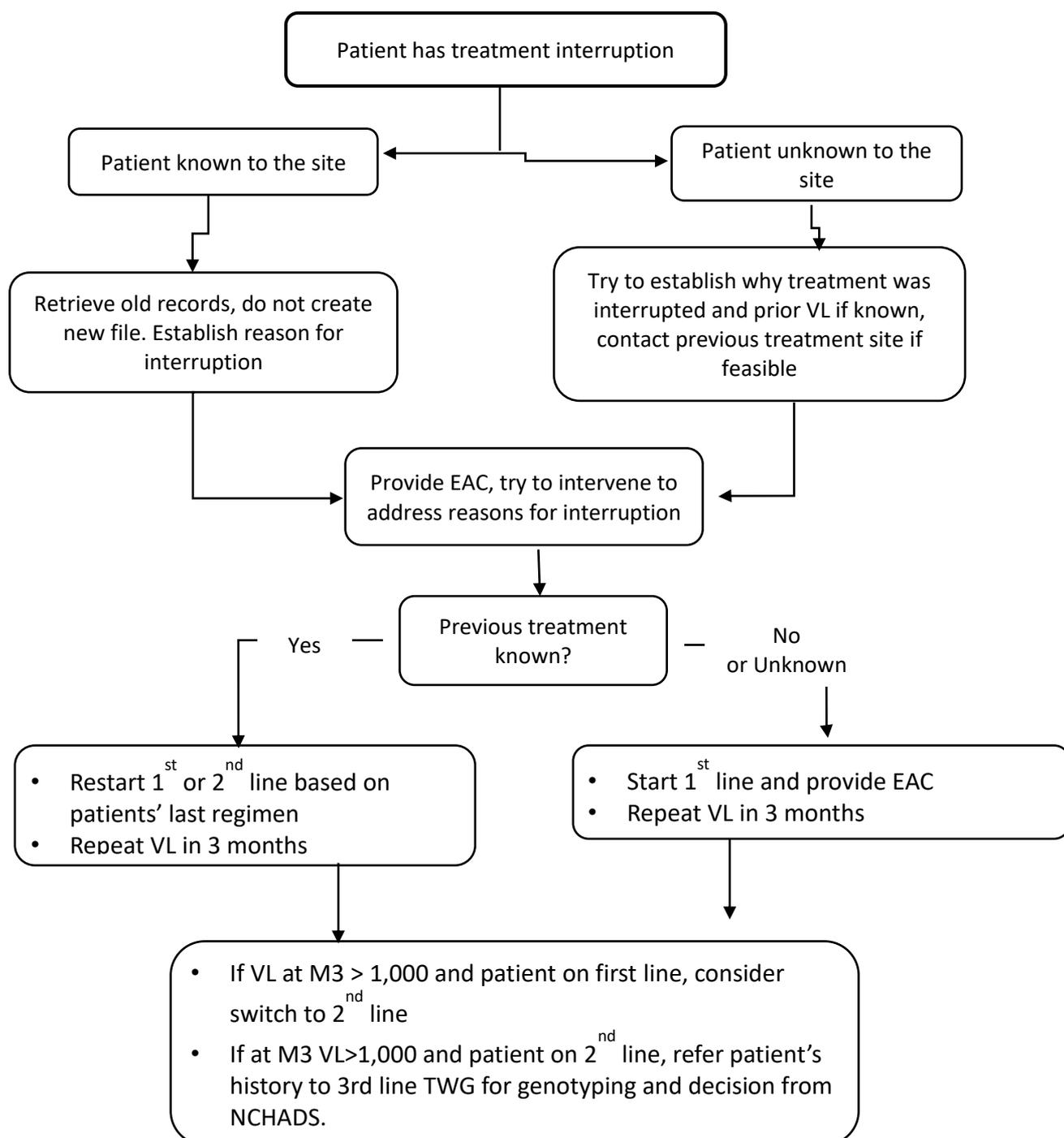
Once 3<sup>rd</sup> line regimen starts, patients need to be closely monitored clinically, laboratory as mentioned in section ART monitoring. Enhanced adherence counseling (EAC) must be strengthened regularly, until VL success (VL < 40 copies/ml) is obtained. Third-line treatment will not be widely available and should be prescribed at the public health facilities.

## CHAPTER 17: MANAGEMENT OF CHILDREN WHO ARE LOST TO FOLLOW UP

**Definition of Lost to follow-up (LFU):** When children with HIV missed their appointment for or more than 3 months (90 days) since last appointment.

Children who have a lapse or default during treatment should generally be restarted on the same regimen they discontinued unless treatment was discontinued due to severe intolerance and/or there was previous evidence of treatment failure. A viral load should be checked 3 months after restarting the same regimen, or, 6 months after a changed regimen, re-initiation of therapy (see Figure 10).

**Figure 10: Management of treatment interruption**



# CHAPTER 18: PSYCHOLOGICAL SUPPORT FOR INFANTS, CHILDREN AND ADOLESCENTS LIVING WITH HIV AND THEIR CAREGIVERS

Medical management of HIV/AIDS must run parallel to psychosocial support (PSS) to ensure emotional wellbeing for HIV infected patients and promote adherence to medication, which is life-long. PSS is a process of listening to and addressing a child or adolescent's emotional, mental, spiritual, and social needs. This includes providing counseling, emotional support, reduction of stigma and discrimination, and promotion of positive living.

PSS is needed throughout the course of treatment and should be adapted to the particular needs of the different stages of development through childhood and adolescence. Adolescents may have particular needs depending on their transmission route (perinatal or behavioral), and to support their safe transition to adulthood. Health care workers (HCW) need to be sensitive to the myriad of PSS issues children living with HIV face, as well as those that arise in caring for children with HIV, from parental shame/guilt, illness or loss, dealing with stigmatization, through disclosure to children, and support for adolescents living with HIV (ALHIV).

## 18.1 Individualized Assessment

Each child needs to have a standardized basic assessment at first presentation and this needs to be followed-up regularly (at least 6-monthly). Assessment forms can be found in Annex 12: Child well-being assessment tool, page 194. Each child should be assessed individually to provide more information and determine children who may be at risk and need support. Even at the same age, children have different levels of maturity and social circumstances, which may make some more vulnerable. This assessment will be invaluable for identifying children who are at risk and provide an indication for those who may need additional support.

## 18.2 Who can provide PSS?

In Cambodia, PSS can be offered by many people caring for the child: doctors, nurses, case management supporters, mmm volunteers, programs helping orphans and other vulnerable children, and community volunteers, NGOs and support groups, such as mmm (Mondul Mith Chuoy Mith or Friends Helping Friends groups).

### Why PSS is important:

- By providing opportunities for social connectedness and coping skills, PPS promotes resilience in children and adolescents.
- Children and adolescents often require grief support; infected families often have to deal with the loss of family members.
- Many myths surround HIV and patients require accurate information as well as skills and commodities for applying desired behaviours (e.g., re-infection and onward transmission prevention, medication adherence).
- Stigma is widespread and HIV-infected patients are vulnerable in their communities.
- Successful treatment is lifelong and depends on excellent adherence.

Define roles and responsibilities for providing PSS:

- Doctors and nurses – provide support for disclosure, adherence, sexual and reproductive health, healthy living, and referral to specialized services (i.e., psychological services).
- Case Management Supporter – provides support for transition, lost to follow-up linked with CSV and CMA.
- MMM volunteers/groups – provides individual and group counseling and social networking opportunities to find support among peers. This will support those adolescents who want to transition in a group.

PSS training and job aides should be provided to these specific groups providing care for children and adolescents living with HIV and the resource can be outsourced in Cambodia e.g. NGOs who is expertise in psychology.

### **18.3 When is PSS necessary?**

Children may need more intensive support at specific times such as at the time of diagnosis, ART initiation, loss of a parent or caregiver, disclosure, through adolescence, and during the transition to adult care see Table 21.

**Table 21: Psychosocial Support Required for HIV-infected Children at Different Developmental Stages**

Development stage	Key elements relating to development stage	PSS needs	Actions needed
Pregnancy, early infancy and diagnosis	<ul style="list-style-type: none"> <li>• Women require appropriate support antenatally in order to achieve a healthy pregnancy and safeguard their unborn infants from transmissible diseases as well as other pregnancy complications e.g. prematurity.</li> <li>• Newborn infants and babies are dependent on mothers or caregivers for all their needs.</li> <li>• Early infancy is a time of rapid neurological development and when strong bonds form between infant and primary caregiver (“attachment”)</li> </ul>	<ul style="list-style-type: none"> <li>• HIV-infected pregnant women require support and education prevention of HIV transmission, where and when the baby will be diagnosed as well as optimal feeding</li> <li>• Infants need a stable caregiver who understands HIV and ART and the need for adherence</li> <li>• Attention must be paid to food and nutritional requirements for infants</li> <li>• Caregivers should understand the reasons for urgent access to ART if HIV infected (for both infant and mother)</li> <li>• Infants need appropriate neurocognitive stimulation from their caregivers</li> <li>• Infants require a safe environment; caregivers need to be taught how to provide this.</li> </ul>	<ul style="list-style-type: none"> <li>• HCT should be provided for all pregnant women</li> <li>• Provide HIV/AIDS counseling support for mother and father after learning about their diagnosis of HIV</li> <li>• Educate parents about ART (Option B+) and its benefit for themselves and how this helps prevent HIV transmission to infants</li> <li>• Provide infant feeding education and support (promote exclusive breast feeding, but support safe replacement feeding as necessary (see section on infant feeding)</li> <li>• Help parents understand process of early infant diagnosis, provide support if the infant is diagnosed with HIV and the advantages of early ART.</li> <li>• Educate parents:             <ul style="list-style-type: none"> <li>– How to create safe environment</li> <li>– The importance of early childhood development (ECD) and how to stimulate infants and children.</li> </ul> </li> </ul>

<p>Infancy and pre-school children (3-5 years)</p>	<ul style="list-style-type: none"> <li>• Children are dependent on their caregivers for all requirements of daily living and medication/accessing services.</li> <li>• This is a time of rapid neurological development.</li> </ul>	<ul style="list-style-type: none"> <li>• Children need a stable caregiver who understands HIV disease and their role in ensuring adherence and retention in care.</li> <li>• They require a safe environment.</li> <li>• Children need stimulation to support cognitive and motor development.</li> <li>• Children can be taught about their own bodily hygiene and safety without mentioning the word HIV (can be taught about danger of blood).</li> <li>• Children are curious about where they come from, and the differences in genitalia between males and females.</li> </ul>	<ul style="list-style-type: none"> <li>• The caregiver needs education on HIV, how medication works and importance of adherence and attending clinic appointments.</li> <li>• Caregiver education and support is also needed on: <ul style="list-style-type: none"> <li>– How to create a safe environment</li> <li>– Early childhood development (ECD) and how to stimulate infants and children</li> <li>– How to manage blood spills (universal precautions)</li> </ul> </li> <li>• Assessment at every visit for identifying children at risk and points of intervention.</li> <li>• Children may be curious about sex and their bodies, this should be discussed in an open, age-appropriate manner, and anatomically correct terms should be used for genitalia.</li> </ul>
<p>School age children (6-10 years)</p>	<ul style="list-style-type: none"> <li>• Children become more independent.</li> <li>• Children can take some responsibility e.g. can learn to remember when to take their medication.</li> <li>• Children start attending school.</li> <li>• Still dependent on family but start making social ties</li> </ul>	<ul style="list-style-type: none"> <li>• Children need for stable caregiver who understands HIV disease and their role in ensuring adherence and retention in care.</li> <li>• It is best that children learn their HIV status- with intensive counseling and support through the process.</li> <li>• Children require a stable and safe environment.</li> <li>• Education support if the child is developmentally delayed</li> </ul>	<ul style="list-style-type: none"> <li>• Prepare caregiver for the process of disclosure of the child's and caregiver's HIV status, once child knows their status, education of child about HIV and how medication works and importance of adherence and attending clinic</li> <li>• Continue support of caregiver to promote child adherence,</li> <li>• Assessment at every visit for identifying children at risk and points of intervention.</li> <li>• Provide safe spaces at clinic, provide an accepting non-judgmental atmosphere, group support if possible, for caregivers and children.</li> </ul>

			<ul style="list-style-type: none"> <li>• Increase children’s involvement in taking their medication.</li> <li>• Provide education for children on how to keep themselves safe.</li> </ul>
Pre/young adolescents (11-14 years)	<ul style="list-style-type: none"> <li>• This is usually when puberty starts.</li> <li>• Emotional changes begin.</li> <li>• Risk-taking behaviour may start.</li> <li>• Adherence may decrease.</li> <li>• Children develop stronger connections to peers.</li> </ul>	<ul style="list-style-type: none"> <li>• A stable caregiver continues to be needed.</li> <li>• Adherence support is required.</li> <li>• Provide sexual and reproductive health information including understanding about physical changes that are occurring.</li> <li>• Positive prevention – support and education about having safe and healthy romantic relationships; avoid sharing injection equipment.</li> </ul>	<ul style="list-style-type: none"> <li>• Support HIV disclosure if this has not occurred earlier.</li> <li>• Support adolescents in developing life and relationship skills.</li> <li>• Counsel adolescents about how to disclose to significant others.</li> <li>• Provide or refer for family planning or STI management.</li> <li>• Assessment for high risk behavior and intensify counseling.</li> <li>• Peer support and provide support groups if possible.</li> </ul>
Older adolescents (15-19 years)	<ul style="list-style-type: none"> <li>• This is the time of transition to adult services.</li> <li>• Adolescents develop autonomy.</li> <li>• Sexual activity may begin.</li> <li>• Risk-taking-behaviour may increase.</li> </ul>	<ul style="list-style-type: none"> <li>• Education about risks of substance abuse (alcohol, glue sniffing, etc).</li> <li>• Access to family planning STI if sexually active.</li> <li>• Preparation and support through transition.</li> </ul>	<ul style="list-style-type: none"> <li>• Develop a transition plan.</li> <li>• Familiarize adolescent with adult ART site and staff.</li> <li>• Case Management Supporter to assist adolescents through transition. Case Management Assistants as part of ACM can assist to link with community to follow –up with lost cases.</li> <li>• Follow up adolescent transition and assess adherence to visits and medication after transition.</li> <li>• Intensified counseling for those who become non-adherent.</li> </ul>

# CHAPTER 19: ADHERENCE SUPPORT FOR ART IN CHILDREN

Good clinical and virological outcomes depend on excellent adherence to ART (>95%). **All children eligible for ART should be initiated without delay**, preferably within 2 weeks of HIV diagnosis. And to ensure the best outcomes for children who start ART, **treatment must never be interrupted without a valid medical reason.**

Infants, children, and adolescents require adult supervision of medication. In older children or adolescents, knowledge about their HIV status may impact medication adherence (see section on disclosure below). An assessment of the child should be performed at every visit in order to identify children in need of the greatest support for adherence. A good relationship between the healthcare providers (i.e., counselors, nurses, and doctors), the child and the caregiver also help to optimize adherence.

## 19.1 What is adherence to treatment?

- Taking all medication (including ARVs and other medicines such as CTX) correctly, as prescribed, even if the person feels healthy.
- Not taking any breaks from treatment
- Not missing appointments.

Adherence support consists of the following:

- **Education sessions** should be given by doctors and nurses at the time of ART initiation to the child/adolescent (if old enough) and the caregiver. Components of these sessions should:
  - Explain the basics of HIV and its natural history, the benefits and side effects of the prescribed ARVs, how the medications should be taken, and the importance of adhering to medicines (>95%).
  - Identify adherence barriers and assist families to solve potential problems.
  - Develop a treatment plan and explain when clinic visits will be scheduled and what will happen at the visits.
  - Encourage disclosure to family or friends who can support the treatment plan.
  - Encourage caregiver and/or child participation in a support group, if available.
  - Identify food insecurity and actively address this through several available programs (e.g. UNICEF and Foundation for International Development/Relief (FIDR), Cambodia Children's Fund (CCF), or World Vision for support if there is food insecurity).
  - Provide contact details of key clinic staff and take patients contact details to facilitate communication between clinic visits should these be necessary.

**Note:** One educational session may suffice and if parents or caregivers are receiving ART themselves, the child may be able to start immediately or at a subsequent visit where education and initiation of ART may occur simultaneously.

## 19.2 Adherence support at routine follow-up visits

- Use pill counts, self-reports or other methods such as visual analogue scales to measure adherence as available.

- Provide adherence support at every visit for the first few months, with discussion of medication and any problems that the patient may be experiencing. Thereafter, depending on the individual requirements a shorter session with the patient may be sufficient.
- Identify and provide additional adherence support to patients with adherence <80%.
- Discuss any missed appointments with the client. Such appointments are a powerful predictor of poor adherence and should indicate the need for immediate questions about issues that may affect attendance and adherence.
- Avoid being judgmental about adherence lapses.
- Identify food insecurity and actively address this through NGO-support programs,
- Update phone number of key clinic staff and patient's phone numbers and addresses to facilitate communication between clinic visits should these be necessary.

If it becomes evident that adherence is poor:

- Try to determine a reason for poor adherence (e.g. caregiver illness or death).
- Try to intervene if feasible (refer caregiver for treatment, identify another adult who may provide support, use phone reminders for appointments).
- Mobilize community support volunteers to provide a home visit
- Update the adherence plan
- More frequent appointments at the healthcare facility may be required.

## **19.3 Techniques to improve adherence**

### **19.3.1 Infants and young children**

- Practice measurement of liquids with the caregiver and train the children in pill swallowing.
- Provide tools which may be available through NGOs, community, (e.g. pill boxes, calendars with stickers, drawings or pictures of the drugs, labelled syringes, story books, toys, involving the child in his/her own treatment starting by giving him information about the virus and the aim of the treatment, and fitting the ARVs into the child's (and/or caregiver's) lifestyle.)
- Match drug regimens for children and adults in the same family, if possible.
- Prepare children and caregivers for common, non-severe adverse effects.
- Self-report methods for monitoring such as diary cards, medication checks, counting of remaining pills and other measures may be advised.
- The dose should preferably be given at the same time every day, however, if this time is missed, the dose should rather be given than missed entirely.
- If the baby or child vomits within 30 minutes of taking medication, re-dose the medication. This is not necessary after 30 minutes.
- Refusal to take medication may occur. See below for tips on how to prevent against medication refusal. Re-dose if the child spits up the medication.

### **19.3.2 Older children and adolescents**

- As above for younger children; adherence support tools e.g. pillboxes, calendars.
- Help develop plans for privacy, such as formulating excuses for reasons to get away for a few minutes to take medication.
- Try to take medications at the same time as something else they do every day (such as brushing your teeth), if the timing is right.
- Set alarms at times medicine needs to be taken.

- Engage a trusted friend or adult to help remind them.
- Adherence support may also be provided by community support volunteers (CSVs) by reminding and encouraging caregivers and children to go to regular appointments and to maintain adherence to medication.

### **Box 15: Practical tips for giving medicines to infants, children and adolescence**

#### **Babies**

- Use a syringe or spoon for medicine mixed with food
- Hold the baby close to you to avoid movement
- Put the medicine in the corner of his mouth along the side of the tongue. It will be more difficult for him to spit it out.
- Keep the baby's mouth gently closed until he/she swallows
- Be sure the baby swallows the medicine well
- do not mix medicine with bottle feed in case the baby does not finish the feed and insufficient dose will be given
- Try to comfort the baby rather, getting angry may make things worse.

#### **Toddlers**

- Make drug-taking routine
- Let the child understand you know it is not easy but you are there to support.
- Improve the taste of the medication with something the child likes (juice, jam, peanut butter).
- Do not mix medicine with essential food, (e.g. eggs, fish, meat, vegetables, rice). The child could link the bad taste with it and refuse taking the essential food, even when there is no medicine in it.
- Offer the child a choice of how to take the medicine (with juice, jam, etc.) This will give him/her some feeling of control.
- Some children prefer taking the medicine at once and then to drink something else quickly afterwards. Others will prefer to take the medicine one step at a time with a drink in between. This can be the choice of the child.
- Be sure the child swallows the medicines.
- Help the child to be proud of taking his/her medicines well. Congratulate him/her every time, rewards in the form of stickers may work for toddlers
- Connect the child's health improvement to taking medication well.

#### **Older children and Adolescents**

- It is important to disclose the HIV status to the child and adolescence so that they better understand why they need to take their medication (see below section on disclosure)
- Encourage more autonomy by teaching the child/adolescent to:
- Incorporate dosing into daily routines and take medication at the same time each day (e.g., after brushing teeth, before a meal).
- Keep a tally sheet of doses, mark a calendar, or use a pillbox.
- Engage an adult family member or trusted friend to help them remember
- Use visual reminders (e.g., notes on the medicine cabinet or refrigerator).
- Use alarms from clock/watch /cell phone.
- Children/adolescent may still respond to a reward system, e.g. pocket money, cell

airtime and phone.

**Box 16: Tools for re-enforce adherence**

***Open questions that can be asked to reinforce adherence***

“Your mum told me you can take you drugs by yourself? That’s great! Can you tell me when you are taking them?” (Positive reinforcement).

Some children tell me taking drugs is not always easy. “Can you give me an example of when it was difficult for you?” (allow disclosure of difficulties with adherence);

“Tell me about the last three days. What have you done? Do you remember about when you took the drugs?” (three days recall)

“I know sometimes in the beginning this medicine makes you feel nauseous or unwell: how has it been lately?” (identify side effects)

“What do you do to remember that you have to take the medicine?” (Encourage positive linking strategies).

# CHAPTER 20: HIV DISCLOSURE FOR CHILDREN AND ADOLESCENTS

Disclosure is the process by which the patients learn about their HIV/AIDS status. Disclosure should be viewed as a gradual process. Initially this may be partial, where a young child learns that they have an unnamed infection, about its treatment, and universal precautions to keep themselves and others safe. As they approach puberty, they should be fully disclosed to and learn about their HIV status.

Disclosing their HIV status to the child or adolescent is important for a number of reasons (see text box): it is a child's right to know about their own health status. According to Article 17 of the United Nations Convention on the Rights of the Child, every child should have: "access to information and material from a diversity of national and international sources, especially those aimed at the promotion of his or her social, spiritual and moral well-being and physical and mental health".

Disclosing HIV/AIDS status includes disclosure to the child about their own HIV status, the parent's HIV status as well as support for older children and adolescents, to disclose to significant others.

## 20.1 When to disclose?

Disclosure is a highly individualized process requiring consideration of many factors including age, developmental stage, family dynamics, caregiver preparedness and clinical situation. Do not disclose until the caregivers are fully prepared and supportive.

- **Younger children should be informed incrementally** to accommodate their cognitive skills and emotional maturity, in preparation for full disclosure. Avoid using the words "HIV" or "AIDS" in front of a child under 6 years.
- **The moment of full disclosure should occur between the ages of 6 - 12 years.** Signs of readiness for disclosure include curiosity about their health/treatment, and the ability to maintain privacy/confidentiality.
- **If disclosure occurs after puberty has started, usually after the age of 12,** there may be negative consequences, such as a treatment non-adherence and depression.

## 20.2 Who should do the disclosure?

- Someone whom the child trusts and respects should conduct the disclosure process. Usually, this will be the caregiver. Counsellors should support the caregiver through the disclosure process by giving relevant tips, information, answering questions, providing psychosocial support and/or practicing disclosure through role plays.

### Reasons for disclosing to children:

- Disclosure empowers the child to participate more actively in his/her health care.
- Disclosure is a necessary part of good health because it relieves the stress of secrecy.
- Disclosure communicates respect for the child and reflects his/her right to know.
- With emotional support, a child can cope as well as an adult with being HIV positive if told at a young age.
- Disclosure enables choices and self-protection against further infection.
- Children (especially adolescents) can make smart decisions about their lifestyle and participate more fully in their care if they fully understand their condition.

- Caregivers may be reluctant to disclose a child's status, in which case, with the consent of the caregiver, the counselors or healthcare workers, may disclose the HIV status to the child or adolescent. The choice of whom should disclose should be guided by what is in the best interest of the child.

Based on evidence of the health and life planning benefits to the children who are aware of their parents'/caregivers' HIV status and the lack of harm to caregivers, WHO also recommends caregivers' disclose their own HIV status to their children (see box 17).

### **Box 17: Caregivers' disclose their status to their children**

#### **Caregiver discloses at home**

Caregivers should ideally be the ones to disclose the HIV diagnosis to the child. If the caregiver feels ready and strong enough to disclose the status to the child at home, help them by discussing the information the child should know about the disease and treatment. Also explain the normal child's reactions such as sadness, anger, and how to deal with them. Disclosure at home can be done naturally when any opportunity arises or more formally if the caregiver prefers to sit down with the child for an open discussion. The clinic staff should reassure the caregiver that they will provide support if needed at the time or at future sessions after disclosure at the health facility.

#### **Caregiver and counselor disclose together**

The caregiver might not feel strong enough to disclose by themselves. They often feel under-confident and fear the child's possible reactions.

In this case, there is a risk that caretakers may not provide appropriate information and support. Practically, either the caregiver can disclose the diagnosis to the child and the counsellor can provide emotional support and basic explanations to reassure the child (based on disclosure tools), or the counselor provides all in the presence of the caregiver who may wish to intervene whenever he/she feels comfortable.

The presence of the caregiver demonstrates to the child that he/she is open for discussion on this topic. It is helpful for the caregivers to learn from the counselors so that they can continue the discussion later on in the same way.

## **20.3 Partial vs complete disclosure**

- Partial disclosure refers to informing the child about their illness without using the words HIV or AIDS.
- Full disclosure involves using the terms HIV and AIDS and also includes information about how the disease is transmitted and treated. Full disclosure ideally should occur before onset of puberty, if not, it is a priority to disclose to the adolescent as soon as possible.

## **20.4 Disclosing a caregiver's HIV status to the child**

- School age children (from 6 years)<sup>23</sup> should be told of their caregivers' HIV status.

<sup>23</sup> In this document, school-age children are defined as those with the cognitive skills and emotional maturity of a normally developing child of 6-12 years. WHO Guideline of HIV on HIV disclosure counselling for children up to 12 years of age.

- Younger children should be informed incrementally to accommodate their developing cognitive skills and emotional maturity.
- Children may need to be reassured about the health of the parent/caregiver and have fears and concerns addressed.

It is important to be aware of the negative consequences that disclosure may have on the child/adolescent and their family caused by discrimination and stigma. Health care workers and counselors should help support the families through this and should work with their local communities (e.g. schools, religious bodies or NGOs working on HBC) to educate them about HIV and to try and mitigate against the stigma associated with HIV.

### **Box 18: Things to say to children and adolescents during disclosure**

#### **PRE-SCHOOL CHILDREN**

- You have to see the nurse so she can check your blood.
- The nurse takes your blood to make sure you stay well.
- You need to take medicine because there's a germ in your blood that can make you sick.

#### **PRIMARY SCHOOL CHILDREN**

- Going to the doctor will help you stay well.
- You have a virus in your blood called HIV. It attacks the germ fighters in your body. This is why you get sick sometimes.
- You and I both have HIV in our bodies (parent telling the child)
- You have to take medicine so the germ fighters can work and you won't get sick so much.
- You (and I) take medicine to keep us strong.
- You cannot give the sickness to anyone else by playing with them, touching or hugging them, eating from the same plate, or using the same toilets.
- HIV is nothing to be ashamed of, but it is something private. You don't have to tell other people if you don't want to.
- Maybe we should keep this in the family for now?

#### **ADOLESCENTS**

- You have the HIV virus. A virus is something that gets into your blood and can make you sick.
- Having HIV does not mean that you are sick all the time.
- You can control the virus by taking your medication every day. But, there is no way you can get rid of HIV completely.
- Knowing that you have HIV gives you a special responsibility to take extra good care of yourself and not to pass HIV to other people.
- Even with HIV, if you take your treatment as prescribed you may live a long life, have relationships, and get married and have children.
- If you are in a relationship and want to have sex, it is important for you to protect your partner. You can do this in a number of ways. It is very difficult but important to discuss your HIV status. We will help you prepare for this discussion. You and your partner should use condoms.
- You can have long-term relationships, get married and have children, although you will need to take special precautions not to transmit HIV to your partner or baby. There are many things you could do to lower these chances. We can talk more

about this whenever you like.

## 20.5 Tips on communicating about disclosure

- Find out how much the child knows about his/her illness and what they want to know
- Children need to know that they are loved and will be cared for.
- Assure the child that his/her HIV status or the parent's HIV status is not a punishment for any wrongdoing.
- Educate them on how HIV is transmitted.
- Disclosure must be age appropriate; use age-appropriate language in line with developmental and emotional readiness.
- Be honest. If you don't know the answer to the child's questions, say so.
- Be led by the child in terms of the amount of information he/she requires.
- Anticipate possible responses by the child and plan for the future.
- Anticipate the impact of the disclosure on other family members, friends, the school and the community and plan for this.
- Monitor the child's behaviour after disclosure (sleeping, school problems, and withdrawal). Changes in behaviour can indicate a need for more support and intervention.
- Be respectful of the child's needs, feelings and responses.

## 20.6 Disclosure process

Disclosure should not be seen as a once off event, but rather a process that will require several sessions.

### 20.6.1 Pre-disclosure

- Health professionals are taught to support caregivers' decisions whether to disclose the HIV diagnosis, and they respect the family's timing. They do not rush the disclosure process but instead stay alert and sensitive to the families' feelings and needs as they evolve through the phases of disclosure.
- The health professionals are taught to respect caregivers' reasons to fear and resist the disclosure process.
- The family receives a detailed explanation of the disclosure model before disclosure.
- During educational sessions, the staff member prepares family members to answer embarrassing or painful questions that children are likely to ask (e.g. about sexual practices or drug use).
- The team of health professionals assists caregivers in revealing other family secrets first, such as adoption.
- If caregivers are reluctant to disclose, counsellors should investigate the reasons for this and help to solve the issue. The time frame for disclosure depends on the child and situation, the counsellor may need to exercise patience in dealing with the family.

### 20.6.2 During disclosure

- Staff members must consider the stage of HIV and the child's medical condition because fear, pain and fatigue further compromise the child's and family's emotional energy levels during the disclosure process. They avoid disclosure during a medical crisis or acute illness.
- Emphasizing confidentiality, the staff member engages the patient in a "partnership" based on confidence and trust.

- Throughout the sessions, the staff member ensures that the child seems curious and ready to learn more about his/her medical condition.

### **20.6.3 After Disclosure**

- Disclosure is an ongoing process. There may be many questions and several sessions should be scheduled to support the family and child to ensure that there is sufficient time for children's questions or concerns to be addressed.

## CHAPTER 21: ADOLESCENT CARE AND PREPARATION FOR SUCCESSFUL TRANSITION TO ADULT SERVICES

Adolescence is defined by WHO as the period from 10 to 19 years of age. Healthcare providers working with adolescents should be familiar with the physical stages of puberty (see Annex 12: Sexual maturity rating (Tanner staging index) for adolescents, page 192). As children mature into adolescence, their medical requirements change, and clinicians should be prepared to meet their medical needs, or be familiar with referral services that they might need, (e.g. birth spacing, or treatment for STIs).

Adolescence is generally a turbulent time as children begin to establish autonomy and transition into adulthood. Adolescents may become rebellious and defiant and risk-taking behavior often peaks in this period. This may be exacerbated among youth living with HIV, because of stigma associated with the disease. Adherence to medication may deteriorate, putting them at risk of treatment failure. Adolescents may react differently during this period, and therefore require support in different ways. The threat of poor adolescent adherence to treatment success and the rising numbers of HIV-infected adolescents who are perinatally infected as well as those who are infected horizontally through risk-taking behavior have created a substantial public health challenge. Responding to this challenge requires a deeper understanding of the developmental processes and potentially modifiable risk factors for treatment non-adherence among these adolescents. If possible, care for adolescents should contain the components of Youth Friendly services, including more flexible hours, adolescent-only clinics, peer support groups, transportation support, informational materials, and use of cell phone messaging for support. See Annex 13: Child well-being assessment tool, page 194, for a list of components of youth friendly services, where feasible, at least some components of youth friendly services should be adopted.

Psychosocial support should be tailored to the needs of these youth:

- By the time they reach adolescence, many **perinatally infected children** have faced the stigma of chronic illness, including stunted growth and development and poor school performance because of frequent absences. They may be orphaned or live in a household with chronically ill parents or caregivers who does not show empathy to their status. They may have delayed puberty, which leads to poor self-esteem.
- **Adolescents who have acquired HIV through horizontal means** also have distinct needs; they may be from key populations e.g. MSM, transgender, PWID and/or engaged in sex work. This group is generally prone to risk-taking behaviour, which is likely to make medication adherence a challenge. They also have a need for family planning and STI services.

Cambodia offers PAC services for children up to the age of 15, and thereafter, adolescents will be transferred to an adult ART clinic. The transition should be planned and monitored carefully from both PAC and adult site staff with the goal to support youth to:

- Remain adherent to ART.
- Disclose their HIV status to sexual partners and take measures to reduce reinfection and onward HIV transmission.
- Receive psychosocial support:
  - Identifying and address crises (i.e., suicidal behaviour, homelessness).
  - Reproductive health and sexuality and promotion of safer sex behaviours.

- Providing access to benefits, entitlements, and services.
  - Supporting youth in self-care and life-enhancing practices.
  - Identifying and treating chronic problems (i.e., depression, substance abuse).
  - Promoting skills to live independently and to make the transition to adulthood.
- Receive all needed services in an integrated/linked quality manner by skilled providers.
  - Successfully transition to adult care where they receive quality services from health care workers.

## **21.1 Support for Adolescents living with HIV/AIDS**

If the adolescent does not yet know their HIV status it is crucial that this be disclosed (see above). Disclosure to the child should take place prior to transition to adult services.

Counseling for adolescents includes; sexual and reproductive education, support for intimate romantic relationships, as well as disclosure to partners and significant others. Group counseling should be used to help these teenagers develop better self-esteem. By providing a meeting space in the clinic and inviting skilled individuals, health care workers can help facilitate the process and foster the formation of a forum where adolescents can get together and through which they can develop some of these skills.

## **21.2 Transition from PAC site to adult ART site**

### **Definition of transition**

The process of transition happens when an adolescent patient is moved from PAC sites to Adult ART sites for HIV care and treatment.

### **21.2.1 Challenges and barriers to a successful transition**

Many young patients experience worry and anxiety about transitioning to Adult ART sites and have a difficult time adjusting to the increased responsibility and expectations. Issues specific to HIV-infected youth may make the transition more difficult for this population compared with adolescents with other chronic illnesses.

### **21.2.2 Preparing for transition in the adolescent care setting**

The adolescent care provider should:

- Develop a transition plan.
- Ensure that HIV-infected youth understand their chronic illness and its management.
- Assess patients, in an individualized manner, for development of sufficient skills and understanding for successful transition. Please see Annex 13: Child well-being assessment tool, page 194.

#### **A. DEVELOPING A TRANSITION PLAN**

- The PAC provider should collaborate with the patient and/or family (if possible) to develop a transition plan.
- For adolescents who do not yet know their HIV status, disclosure should be a primary goal of the transition plan.
- As part of the transition plan, arrangements should be made for transitioning patients to meet their new providers well in advance of their final appointment with their PAC provider.

## **B. EDUCATION AND SKILLS TRAINING FOR ADOLESCENT PATIENTS**

- The PAC provider should offer education support to patients to explain what patients will need to know in the Adult sites and evaluate the patient progress toward readiness for transition.
- The adolescent should be able to do the following before transitioning:
  - Know when to seek medical care for symptoms or emergencies
  - Identify symptoms and describe them
  - Make, cancel, and reschedule appointments
  - Arrive to appointments on time
  - Call ahead of time for urgent visits
  - Make sure that they have enough medication at home before medications run out before appointment date.
  - Understand the importance of health care follow up.

## **C. IDENTIFYING THE ADULT CARE PROVIDER**

When possible, the pediatric/adolescent healthcare team should assist the adolescent in choosing an adult clinic that best suits the individual. Some adolescents may feel that location is the most important factor due to time and transportation restrictions.

## **D. PREPARING FOR TRANSITIONING PATIENTS IN THE ADULT CARE SETTING**

The adult care provider should:

- Meet the patient, with or without family members, before the change in care
- Assign one clinic staff member as point person and have his/her contact information available, including hours when contact is possible
- Have an orientation plan in place to acquaint the newly transitioned patient to the new clinic environment.

The adult provider or PLHIV volunteers should have a plan in place to help newly transitioning adolescents adjust to the adult site. The clinic and/or the provider's expectations of the newly transitioned patient should be explained during or before the first visit. The policy for late arrivals and walk-ins should be clearly explained to the adolescent.

### **D1. WHEN TO TRANSITION**

The transition plan should be implemented when the patient:

- Demonstrates understanding of his/her disease and its management
- Demonstrates the ability to make and keep appointments
- Knows when to seek medical care for symptoms or emergencies.

*Whenever possible, transition should be implemented when the patient's disease is clinically stable.*

Most HIV-infected adolescent transition to adult care between **15 and 20 years of age**. Adolescents who demonstrate independence in making their own decisions and show responsibility for their own care may be ready sooner. The goals and challenges of transition, as well as the support that will be needed during the process, should be individualized for each patient.

## **D2. COMMUNICATION BETWEEN THE PEDIATRIC AND ADULT CARE PROVIDER:**

Direct communication between providers is essential. When the pediatric care team is informed about the transition plan in the adult clinic, it allows them to provide the transitioning patient with realistic expectations and helps them to prepare the patient with the necessary skills for managing their new Adult site.

## **D3. ROLES USE OF TRANSITION FOCAL POINT**

The adult service should designate one member of the healthcare team such as an NGO volunteer, mmm volunteer, AUA, social worker, MAGNA, CPN+, to oversee transition planning and be someone who the patient can contact with questions or concerns. The focal person can guide the patient to appropriate services and also alert providers if there are any concerns. In some programs, a PLHIV, who may be someone who has recently transitioned successfully, works with the patient to create and track progress on an individualized transition plan. PLHIV may accompany patients to the initial adult medical appointments and then provide support while they gain the independence and confidence to attend later appointments by themselves.

## **E. EVALUATION BEFORE TRANSITION OCCURRED**

### **E1. PRE-TRANSITION ASSESSMENT**

The team of pediatric care provider should devise a plan to achieve the following on an ongoing basis:

- Assessment of whether an individual patient is adequately caring for his/her own health.
- Assessment of barriers that the patient is facing, what support is needed, and who will provide this support.

### **E2. CHECKLIST FOR SUCCESSFUL TRANSITION**

- Patient has accepted his or her HIV status.
- Patient has learned how to negotiate appointments and has been introduced to the adult ART clinic.
- Patient is able to assume responsibility for his or her treatment and participate in decision-making.
- Psychosocial support needed after the transition occurred.
- Know who to call in case of an emergency, and that the patient should carry this information with them.
- Speak up and ask the physician or nurse counselor questions. If they don't understand the answer, please ask again.
- Be sure that patient understands the medications that they are taking e.g. "What are their names and when do you take them".

## **F. POST-TRANSITION ASSESSMENT**

After transitioning to an adult site, patients may continue to have contact with their PAC site, which may reinforce a successful transition or may create challenges in maintaining ongoing care at the adult site facility. Communication between PAC and adult providers is important to a successful transition process.

Both the patient and their care giver may want to "check in" with their PAC clinic as they start to transition. This is normal and can help lower the patient's sense of loss. Patients in transition may continue to rely on their pediatric care provider for emotional support. The pediatric

provider should defer clinical management decisions to the adult site and should be alert to the risk of hindering the patient from establishing a trusting relationship with the new adult site.

Young patients who withdraw from care in an adult clinic will often return to their PAC site. When this happens, the PAC provider should be prepared to help the patient identify services that can provide increased support and should encourage re-engagement at adult site.

### **Model for transition (modified from MAGNA Children at Risk)**

Transitioning adolescents from pediatric care to adult-oriented services is a process that requires flexibility and interaction between services and prior planning devised by the pediatric team in conjunction with patients themselves, their family members, and care providers in the receiving team. The timing of transition should not be determined by age alone, but by the preparedness and maturity of the young patient, which can be assessed by specific parameters.

Adolescents living with HIV/AIDS need special attention due to the unique care needed, including such as safer sex issues, disclosure of HIV status to partners, early experiences of loss in the family, constant struggling with the possibility of severe illness and/or death, and exposure to discrimination and prejudice, which makes this population even more vulnerable to the usual challenges of this turning point in life.

#### **At pediatric service**

- Start preparation for transition **up to one year before the transfer**
- Help adolescents join mmm support groups for children or adolescents where transition is discussed
- Support groups for caregivers
- Assign case manager (case management supporter) over transition period – NGOs, mmm volunteer, AUA social worker, MAGNA, CPN+
- Help contact with Adult Site for the transfer and set up an appointment for the adolescent
- Help to complete the transfer form
- Explain to the Adolescent and caretaker where Adult services location (take them there for an initial visit).

#### **After Transition**

- Book the appointment in Adult Services
- Help with the registering the patient in Adult Services and transferring patient file
- Nurse counsellor or PLHIV volunteer to accompany patient for to the first visit in Adult sites
- Explain the patient about the new registration and pharmacy system at Adult site
- Reminders to the Adolescent about the next appointment date
- Nurse counsellor or PLHIV volunteer to link with community support volunteer (CSV) care to find the lost case
- Active Case Management can be used to follow-up with lost cases
- Case management supporter /Community support volunteer can visit adolescent (2 times per month ) for first 6 months
- Case management supporter /Community support volunteer can visit adolescent (1 time per month) after 6 months
- Evaluation after 9 months.



# CHAPTER 22: COMMON NON-OPPORTUNISTIC ILLNESS IN HIV INFECTED CHILDREN

## 22.1 Key points

- Common childhood infections such as diarrhea, pneumonia, and upper respiratory tract infection are more frequent and more severe in HIV-infected children.
- Infection with pneumococcus, *haemophilus*, and *salmonella* species are common in HIV-infected children and may occur even in those children with a high CD4 count and on ART.
- Immunization and CTX 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.

## 22.2 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.

## CHAPTER 23: FEVER

### 23.1 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°C axillary
- > 38°C oral
- > 38.5°C rectal.

### 23.2 Etiology

Fever may be caused by:

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

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

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

### 23.3 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 °C and no identifiable source should receive the following:
  - Complete blood count (CBC)
  - Blood and urine cultures
  - Chest radiograph
  - Lumbar puncture.

### 23.4 Management

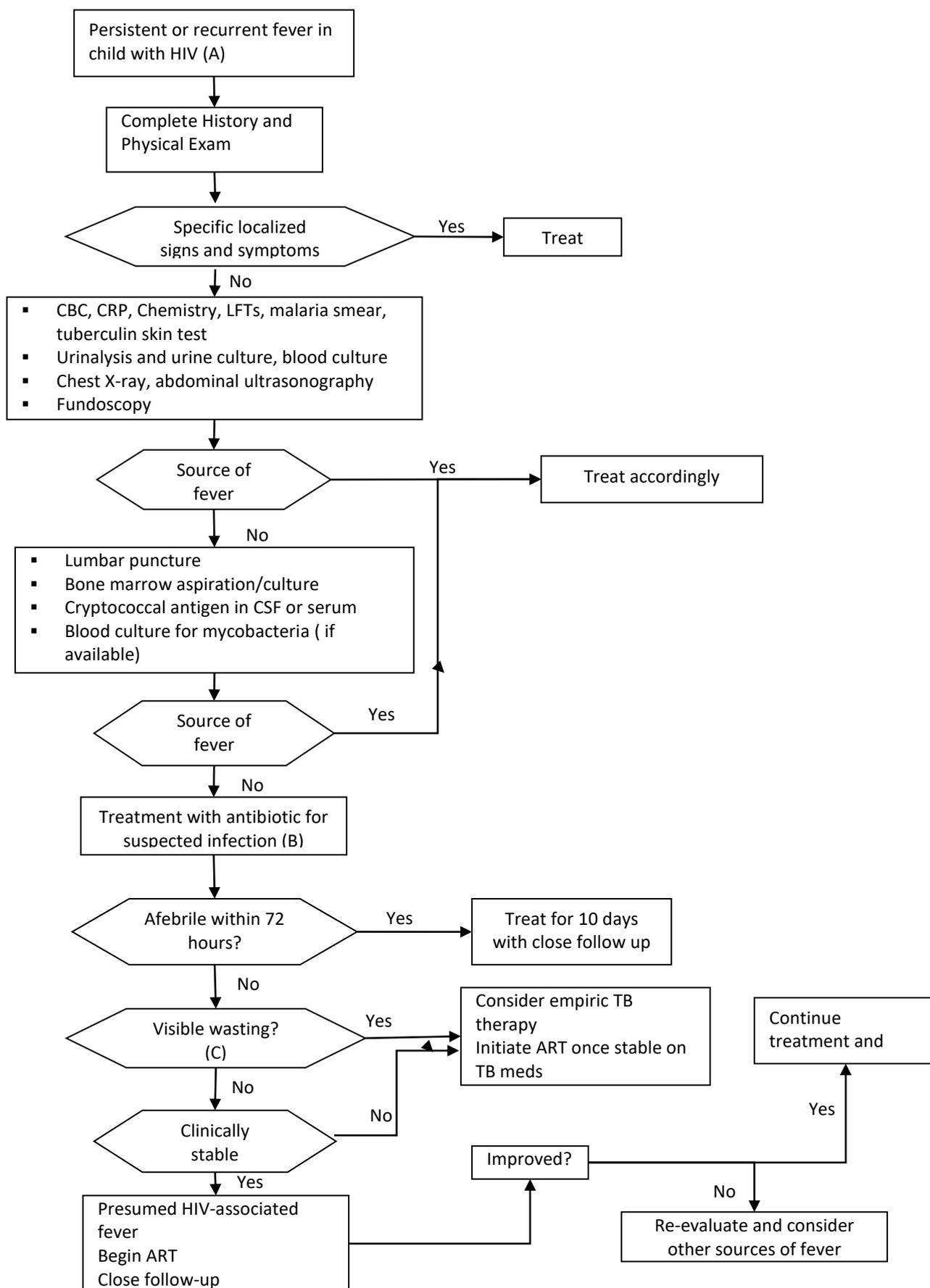
Treatment with antibiotics is indicated when:

- 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 (absolute neutrophil count <500) is present
- < 3 months of age and febrile without a source.

### **23.5 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 ( $\geq 14$  days of unexplained fever). For persistent fever of  $\geq 14$  days without a source, please see algorithm below.

**Figure 11: Algorithm for investigation and management of persistent fever in children with HIV infection**



**Annotations:**

- A. **Persistent fever:** daily fever for  $\geq 14$  days; **Recurrent fever:** fever on the majority of days for  $\geq 14$  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.

# CHAPTER 24: UPPER RESPIRATORY TRACT INFECTION

## 24.1 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.

## 24.2 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 acid fast bacilli (AFB) testing and fungal stain and/or culture where available.

## 24.3 Mastoiditis

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

## 24.4 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.

## **24.5 Parotid Enlargement**

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

## **24.6 Persistent Generalized Lymphadenopathy (PGL)**

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

## **24.7 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 25: ORAL MANIFESTATIONS IN HIV INFECTED CHILDREN

## 25.1 Key points

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

## 25.2 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.

## 25.3 Clinical manifestations

### 25.3.1 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 deficiencies may also cause angular cheilitis.
- Oral candidiasis is often seen in conjunction with candida 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.

### 25.3.2 Oral hairy leukoplakia (OHL)

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

### 25.3.3 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.

### 25.3.4 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.

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

### 25.3.6 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.

### 25.3.7 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 (See Annex 14: Photos of oral and skin lesions in HIV-infected children, page 194). 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.

## 25.4 Treatment

**Table 22: Treatment of oral lesions**

Oral lesions	Treatment	Comments
Oral candidiasis	<p><b>Topical</b></p> <ul style="list-style-type: none"> <li>- Nystatin suspension 200,000-400,000 units/day divided in 4-6 doses for 14 days.</li> <li>- Gentian violet 1% aqueous solution painted in the affected area q8h</li> </ul> <p><b>Systemic</b></p> <ul style="list-style-type: none"> <li>- Fluconazole 6 mg/kg on day 1 then 3 mg/kg daily x 7-14 days (oral) or 21 days (esophageal)</li> </ul> <p><b>Prophylaxis</b></p> <ul style="list-style-type: none"> <li>- Consider prophylaxis for severe/recurrent disease until established on ART</li> <li>- Nystatin 100,000-400,000 units PO q12h for long period</li> <li>- Fluconazole 3 mg/kg PO daily.</li> </ul>	<ul style="list-style-type: none"> <li>- Topical treatment preferred for mild oral thrush</li> <li>- Systemic therapy necessary for severe oral thrush interfering with feeds or for esophageal candidiasis</li> <li>- Amphotericin B may rarely be needed for azole-resistant infections.</li> </ul>
Angular Cheilitis	<p><b>Topical</b></p> <ul style="list-style-type: none"> <li>- Nystatin-triamcinolone ointment applied on the affected areas after meals and at bedtime, or</li> <li>- Miconazole 2% cream applied q12h on the affected areas, for 1-2 weeks</li> <li>- Multivitamin supplementation if evidence of malnutrition.</li> </ul>	<ul style="list-style-type: none"> <li>- Lesions tend to heal slowly because of the repeated opening of the mouth.</li> </ul>
Herpes Simplex Virus (HSV) Infection	<p><b>Systemic</b></p> <ul style="list-style-type: none"> <li>- Acyclovir 10 mg/kg PO q4h or q6h for 5-7 days</li> <li>- Acyclovir 10 mg/kg IV q8h for severe disease</li> <li>- CMV and histoplasmosis may mimic HSV in children with very low CD4; consider biopsy if lesions do not respond to IV acyclovir.</li> </ul>	<ul style="list-style-type: none"> <li>- Patients taking acyclovir should be instructed to drink plenty of fluids.</li> </ul>
Lineal Gingival Erythema (LGE)	<p><b>Local</b></p> <ul style="list-style-type: none"> <li>- Scaling and root planning</li> <li>- 0.12% Chlorhexidine gluconate (Periogard, Peridex) 0.5 oz q12h rinse, for 30 sec. and spit.</li> </ul>	<ul style="list-style-type: none"> <li>- Prophylaxis with regular brushing, flossing, and use of mouth rinses.</li> <li>- Treat concomitant oral thrush if present.</li> </ul>

Parotid Enlargement	<b>Systemic</b> <ul style="list-style-type: none"> <li>- Non-steroidal anti-inflammatories</li> <li>- Analgesics</li> <li>- Antibiotics (for superinfection only, usually due to staphylococcus).</li> </ul>	<ul style="list-style-type: none"> <li>- Surgical removal of the parotid gland should be avoided.</li> <li>- Symptoms may improve with provision of ART.</li> </ul>
Oral Hairy Leukoplakia (OHL)	<b>No treatment</b>	<ul style="list-style-type: none"> <li>- OHL is rare in children.</li> <li>- Consider ART if severe symptoms.</li> </ul>
Necrotizing Ulcerative Gingivitis (NUG), Necrotizing Ulcerative Periodontitis (NUP), Necrotizing Stomatitis (NS)	<b>Local</b> <ul style="list-style-type: none"> <li>- Debridement of affected areas</li> <li>- Irrigation with povidon-iodine (10% Betadine) or 0.12% chlorhexidine gluconate (Peridex, Periogard) mouth rinse q12h.</li> </ul> <b>Systemic</b> <ul style="list-style-type: none"> <li>- Clindamycin 20–30 mg/kg PO q6h, for 7 days, or</li> <li>- Amoxicillin clavulanate (Augmentin) 40 mg/kg PO q8h, for 7 days, or</li> <li>- Metronidazole 15-35 mg/kg PO q8h, for 7-10 days.</li> </ul>	<ul style="list-style-type: none"> <li>- Prolonged use of chlorhexidine may cause staining of teeth, altered taste, and gum irritation.</li> <li>- Metronidazole may cause peripheral neuropathy when used for prolonged periods or with ddl, d4T.</li> </ul>
Recurrent Aphthous Ulcers	<b>Topical</b> <ul style="list-style-type: none"> <li>- Triamcinolone 0.1% paste applied in a thin layer q6h daily, or</li> <li>- Dexamethasone liquid (0.5 mg/5ml) rinse and spit</li> </ul> <b>Systemic</b> <ul style="list-style-type: none"> <li>- Prednisone 2 mg/kg q6h, for 5–7 days</li> </ul>	<ul style="list-style-type: none"> <li>- Major aphthous ulcers usually require systemic steroids.</li> <li>- Iron, vitamin B12, and folate deficiencies should be ruled out.</li> <li>- Dexamethasone liquid may be used for multiple ulcers or ulcers not accessible for topical application.</li> </ul>
Oral Warts	<b>Topical</b> <ul style="list-style-type: none"> <li>- Podophyllin resin 25% applications q6h for long period</li> <li>- Cryotherapy with liquid nitrogen.</li> </ul>	<ul style="list-style-type: none"> <li>- Recurrence rate is high.</li> <li>- ART decreases recurrence.</li> </ul>

# CHAPTER 26: DERMATOLOGIC MANIFESTATIONS IN HIV INFECTED CHILDREN

## 26.1 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.

## 26.2 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 23 lists common dermatologic manifestations in HIV-infected children.

**Table 23: Causes of skin diseases in HIV**

Category	Causes
Infections	<ul style="list-style-type: none"> <li>- Varicella zoster</li> <li>- Herpes simplex virus</li> <li>- Superficial fungal infection (e.g. Tinea)</li> <li>- Disseminated fungal infection</li> <li>- Cryptococcosis</li> <li>- Penicilliosis</li> <li>- Histoplasmosis</li> <li>- Human papillomavirus</li> <li>- Impetigo</li> <li>- Mycobacterial infection</li> <li>- Secondary syphilis</li> <li>- Furunculosis</li> <li>- Folliculitis</li> <li>- Pyomyositis</li> <li>- Verucca planus.</li> </ul>
Neoplasia	<ul style="list-style-type: none"> <li>- Kaposi's sarcoma</li> <li>- Lymphoma</li> <li>- Squamous and basal cell carcinoma</li> <li>- Sarcoma.</li> </ul>

## Others

- Pruritic papular eruption
- Seborrheic dermatitis
- Drug eruptions
- Vasculitis
- Eczema
- Psoriasis
- Granuloma annulare
- Thrombocytopenic purpura
- Telangiectasia
- Hyperpigmentation.

## 26.3 Common Skin Diseases in Children Living with HIV

Common cutaneous manifestations of HIV are summarized below.

### 26.3.1 Herpes simplex virus

- Stomatitis is the most common manifestation of HSV in children (See Annex 15: Photos of oral and skin lesions in HIV-infected children, page 197).
- 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.

### 26.3.2 Chickenpox (Primary Varicella Zoster Virus)

- 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.

### 26.3.3 Herpes zoster (shingles)

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

- Treat superinfection with cloxacillin as above.

### 26.3.4 Molluscum Contagiosum

- Commonly found in persons with advanced HIV infection and is due to a virus.
- Molluscum contagiosum lesions are pearly or flesh-colored, round papules 3-5 mm in size with a central dimple.
- In children who are ill appearing or with very low CD4 cell count, the differential diagnosis includes cryptococcus, penicillium, or histoplasma.
  - Serum cryptococcal antigen testing is recommended in children with possible molluscum and very low CD4 count
  - If negative, biopsy may be needed to rule-out invasive fungal infection
- Giant molluscum lesions often occur on the face when immunosuppression is severe, and can be disfiguring. See Annex 15: Photos of oral and skin lesions in HIV-infected children, page 197.
- 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.

### 26.3.5 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 24 summarizes the bacterial causes of skin disorders seen in HIV infected children, including a brief description and suggested initial treatment.

**Table 24: Causes and management of bacterial skin infections**

Bacterial skin infection	Causative organism	Description	Treatment
Folliculitis	<i>Staphylococcus aureus</i>	Inflammation, infection of the hair follicles	Warm compress Cleansing Cloxacillin in severe cases.
Cellulitis	<i>Streptococcus, Staphylococcus aureus, Haemophilus influenzae</i>	Inflammation of skin and subcutaneous tissues, characterized by edema, erythema, and pain	Cloxacillin 100-200 mg/kg daily divided q6 hourly.
Skin abscess	<i>Staphylococcus aureus, Haemophilus influenzae</i>	Localized collection of pus in a cavity formed by disintegration of tissue; may complicate untreated cellulitis	Surgical drainage Systemic antibiotics if cellulitis

Impetigo	<i>Staphylococcus aureus</i> , <i>Streptococcus</i>	Vesicles or bullae with characteristic honey-colored crusting	Topical mupirocin Cloxacillin for disseminated lesions
Furunculosis (boil)	<i>Staphylococcus aureus</i> , <i>Streptococcus</i>	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	<i>Staphylococcus aureus</i>	Infection involving the folds of tissue surrounding the fingernail or toenail	Surgical drainage Cloxacillin for 5-7 days
Bacillary angiomatosis	<i>Bartonella henslae</i>	Disseminated vascular lesions that may mimic Kaposi's sarcoma	Azithromycin or erythromycin Consult expert
Staphylococcal Scalded Skin Syndrome	<i>Staphylococcus aureus</i>	Diffuse bullous lesions starting on face, most common in infants; may mimic Stevens Johnson Syndrome but without precipitating exposure and NO mucosal involvement.	Cloxacillin 200 mg/kg/day IV divided q6 hours Surgical consultation Aggressive wound care and attention to hydration status.

### 26.3.6 Fungal skin infections

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

#### A. 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.

#### B. 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.

### 26.3.7 Scabies

- Highly contagious mite infection of the skin characterized by pruritic papular lesions found most commonly in the webs of the fingers and toes, folds of the wrist, antecubital area, and axilla.
- Infants may also have lesions on the palms and soles of the feet.
- Generalized scabies occurring in patients with advanced HIV is called Norwegian scabies and is highly contagious.

#### Treatment

- Benzyl Benzoate 25% lotion: apply over the body except head/face, leave in place 12 hours, then wash off for 2-3 consecutive days.
- Permethrin 5% cream applied head to toe for 12 hours followed by bath is preferred where available. Toxicity is minimal, treatment effective, and it may be used in infants.
- Pruritis can persist for 1-2 weeks due to persistent antigen in the skin even when treatment has been effective in older children, 0.3% gamma-benzene hexachloride (lindane) applied from neck to toe may be used, but has been associated with neurotoxicity so is not preferred
- Oral antihistamines may be given to relieve itching.
- All household members should be treated along with the child, regardless of symptoms.
- All contaminated clothes and bedsheets should be washed and hung to dry in the sun.

### 26.3.8 Drug Eruptions

- Medications commonly causing drug eruptions include CTX, penicillins, cephalosporins, dapson, 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 re-challenge.
- 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.

### **26.3.9 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.

### **26.3.10 Pruritic Papular Eruption**

- Chronic eruption of papular lesions on the skin (See Annex 15, page 197).
- May be related to disordered inflammatory response to common antigens such as those due to repeated mosquito bites.
- Itching is intense.
- Usually evenly distributed on the trunk and extremities
- May become superinfected with *Staphylococcus* or *Streptococcus* organisms.

**Generally refractory to treatments other than ART; when severe, strongly consider early initiation of ART.**

# CHAPTER 27: HEMATOLOGIC MANIFESTATIONS OF HIV INFECTED CHILDREN

## 27.1 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.

## 27.2 Anemia

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

**Table 25: Causes and etiology of anemia in HIV infection**

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

### 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.

### 27.3 Neutropenia

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

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

**Table 26: Causes and etiology of neutropenia in HIV infection**

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

#### Clinical presentation

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

### 27.4 Thrombocytopenia

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

### **Clinical presentation**

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

### **Causes**

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

# CHAPTER 28: HIV ASSOCIATED MALIGNANCIES IN CHILDREN

## 28.1 Key points

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

## 28.2 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.

### 28.2.1 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 27: Site-dependent symptoms of NHL**

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

### **28.2.2 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.

### **28.2.3 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.

## **28.3 Primary CNS Lymphoma**

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

### **28.3.1 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.

### **28.3.2 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.

## **28.4 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 29: RESPIRATORY MANIFESTATIONS IN HIV INFECTED CHILDREN

## 29.1 Key Points

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

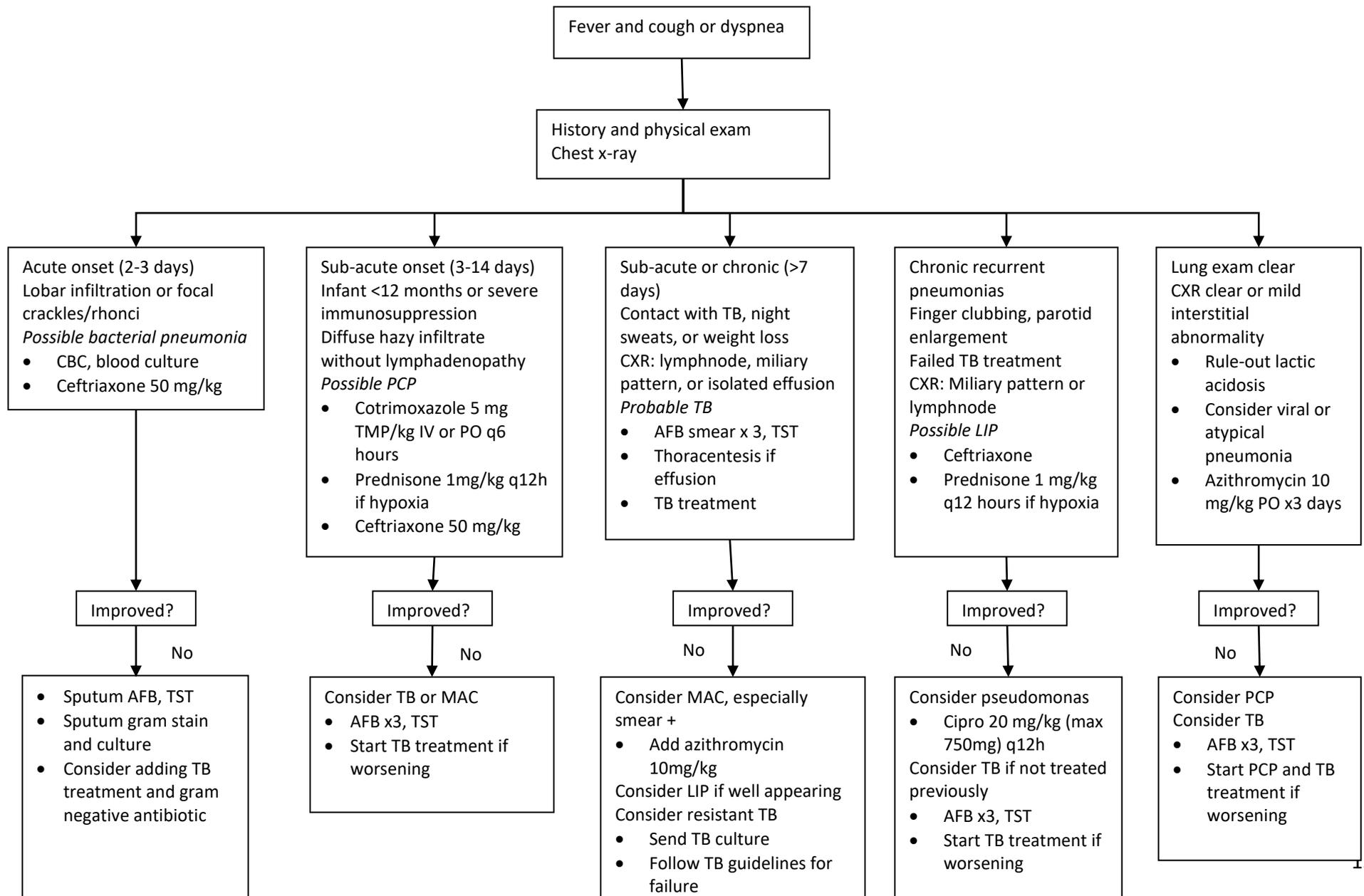
## 29.2 Introduction

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

**Figure 12: Evaluation of respiratory complaints in children with HIV**



## 29.3 Bacterial Pneumonia

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

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

Recurrent bacterial pneumonia ( $\geq 3$  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.

### 29.3.1 Clinical Presentation

Clinical presentation of pneumonia includes the following:

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

### 29.3.2 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.

### 29.3.3 Treatment

#### A. 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.

#### B. SEVERE PNEUMONIA

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

##### B.1 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.

## B.2 SPECIFIC THERAPY

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

## B.3 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.

## 29.4 Pneumocystis jiroveci pneumonia (PCP)

### 29.4.1 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.**

### 29.4.2 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%.

### 29.4.3 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 O<sub>2</sub> levels frequently below 85%.

### 29.4.4 Diagnosis

- Diagnosis of PCP in Cambodia is usually made on clinical grounds on the basis of abnormal chest x-ray with typical interstitial infiltrates, hypoxia, and a response to PCP therapy.

- Treatment **MUST NOT** be delayed as definitive diagnosis is rarely possible.
- If PCP is in the differential diagnosis, it should be treated immediately.
- Chest radiographs may show bilateral diffuse parenchymal infiltrates with 'ground-grass' or reticulogranular appearance, **but may be normal**.
- Definitive diagnosis is difficult in children. The organism can be demonstrated in pulmonary tissues or fluids by silver or fluorescent antibody staining where available, collected as follows:
  - induced sputum analysis (nebulized 3% hypertonic saline), *or*
  - bronchoscopy with bronchoalveolar lavage.

#### 29.4.5 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*).

#### 29.4.6 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 CTX.**
  - 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 CTX, or clinical treatment failure after 5–7 days of CTX therapy.
  - With clinical improvement after 7–10 days of intravenous therapy with pentamidine, an oral regimen (e.g., atovaquone) might be considered to complete a 21-day course.
  - Adverse drug reaction: renal toxicity, severe hypotension (particularly if infused rapidly), prolonged QT, cardiac arrhythmias.
- Atovaquone 30-40 mg/kg/d, 2 divided doses with fatty food (3-24 months, 45 mg); data limited for children.
  - Adverse reactions: skin rashes (10%–15%), nausea, and diarrhea can occur.
- Others treatments in adults:
  - Clindamycin/primaquine: data for children are not available
  - Dapsone/trimethoprim: data on toxicity and efficacy among children are not available.
- Corticosteroids
  - Indication:
    - Room-air PaO<sub>2</sub> value of <70 mmHg, or alveolar-arterial gradient of >35 mmHg
    - When blood gas not available: O<sub>2</sub> 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.

### **29.4.7 Cotrimoxazole Prophylaxis**

All children diagnosed with PCP should begin CTX prophylaxis as soon as treatment-dose CTX has been completed, and should continue through the age of 5 years regardless of immune reconstitution on ART (Please see Chapter 6: sub-section 6.2: Prevention of opportunistic infection, page 36).

## **29.5 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.

### **29.5.1 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.

### **29.5.2 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 X-ray 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.

### **29.5.3 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 CTX 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.

## **29.6 Bronchiectasis**

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

### **29.6.1 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.

### **29.6.2 Clinical Presentation**

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

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

### **29.6.3 Diagnosis**

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

### **29.6.4 Treatment**

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

### **29.6.5 Prevention**

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

# CHAPTER 30: TUBERCULOSIS IN HIV INFECTED CHILDREN

## 30.1 Key Points

- Tuberculosis (TB) is the leading cause of death in HIV infected patients
- Cambodia has a high incidence of TB
- Children with HIV must be screened for symptoms of active TB at every visit
- Diagnosing TB in children is difficult and should follow the *National Clinical Guidelines 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 Guidelines 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 TPT based on the eligible regimens, (see chapter 8: Treatment Prophylaxis for TB, page 47).

## 30.2 Epidemiology

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

Table 28 shows the effect of HIV infection on lifetime risk of an *M. tuberculosis* infected individual developing TB.

**Table 28: Lifetime risk of active TB with and without HIV**

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

## 30.3 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 19.

**Box 19: 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.

**30.4 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 sites. TB culture is an important part of the evaluation of HIV-infected children suspected of tuberculosis, and should be obtained whenever possible.

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

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

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

### 30.5 Treatment regimens

2 months RHZE/4 months RH for new cases:

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

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

**Table 29: Recommended doses for TB medication in children**

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

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

#### Additional considerations for HIV-infected children

- Pyridoxine supplementation during TB treatment should always be given as follows:
  - Age <5 years, 12.5 mg daily
  - Age ≥5 years, 25 mg daily.
- Children with active TB should be given CTX prophylaxis for the duration of TB therapy, regardless of the CD4 count.

## 30.6 Common side-effects of TB medications

Table 30: Management of anti-tuberculosis drug side-effects

Side-effects	Drug(s) probably Responsible	Management
<b>Minor side effects</b>		<b>Continue anti-TB drugs</b>
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
<b>Severe side effects</b>		<b>Stop drug(s) responsible</b>
Deafness	Streptomycin	Stop streptomycin, give ethambutol instead
Dizziness, vertigo, or nystagmus	Streptomycin	Stop streptomycin, give ethambutol instead
Jaundice	Most anti-TB drugs	Stop all anti-TB drugs until jaundice resolves
Vomiting and confusion (consider drug-included liver failure if jaundice present)	Most anti-TB drugs	Stop all anti-TB drugs, urgent liver function tests
Visual impairment	Ethambutol	Stop ethambutol
Shock, purpura, acute renal failure	Rifampicin	Stop rifampicin

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

## 30.7 Severe forms of tuberculosis

### 30.7.1 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 Guidelines for the Management of TB/HIV Co-infection* and the *National Guidelines for the Diagnosis and Treatment of TB in Children*.
- Steroids are not usually indicated in the routine management of miliary TB unless signs or symptoms of TB meningitis are present.
- TB treatment 2 RHZS/4 RH.

### 30.7.2 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<sup>3</sup> with predominance of lymphocytes
  - Protein usually very elevated and glucose very low
  - Rarely, bacilli in CSF smear.
- Treatment is as follows:
  - 2 RHZS/ 10 RH
  - Prednisone 2-4 mg/kg (max 60mg) daily x 28 days then tapered over 2 weeks
  - Can use dexamethasone 0.6 mg/kg in place of prednisone
  - For children intolerant of streptomycin, replace with ethionamide 20 mg/kg daily
  - Ethionamide has excellent CNS penetration, is available in an oral form, and is safe in small infants.

### 30.8 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 are as follows:
  - All PTB retreatment cases such as failures, relapse, loss-to-follow-up, and others, month 1 and 2 non-converters of FLD treatment
  - MDR-TB close contacts, and
  - PLHIV
  - For management of suspected MDR TB, refer to the National Guidelines for MDR TB management.
- Patients who are clinically worsening need to 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.

# CHAPTER 31: BCG IMMUNIZATION

## 31.1 What is BCG

- BCG is an immunization of live mycobacteria derived from *M. bovis*.
- BCG reduces the risk of disseminated TB in immunocompetent infants and young children.

## 31.2 When to provide BCG

- 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 TPT has been completed and HIV testing is negative.

## 31.3 BCG complications

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

# CHAPTER 32: NEUROLOGICAL MANIFESTATION IN HIV INFECTED CHILDREN

## 32.1 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.

## 32.2 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.

### 32.2.1 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.

#### A. 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.

## **B. 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 13 and 14 below).

## **C. 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.

## **D. PREVENTION**

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

### **32.2.2 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:

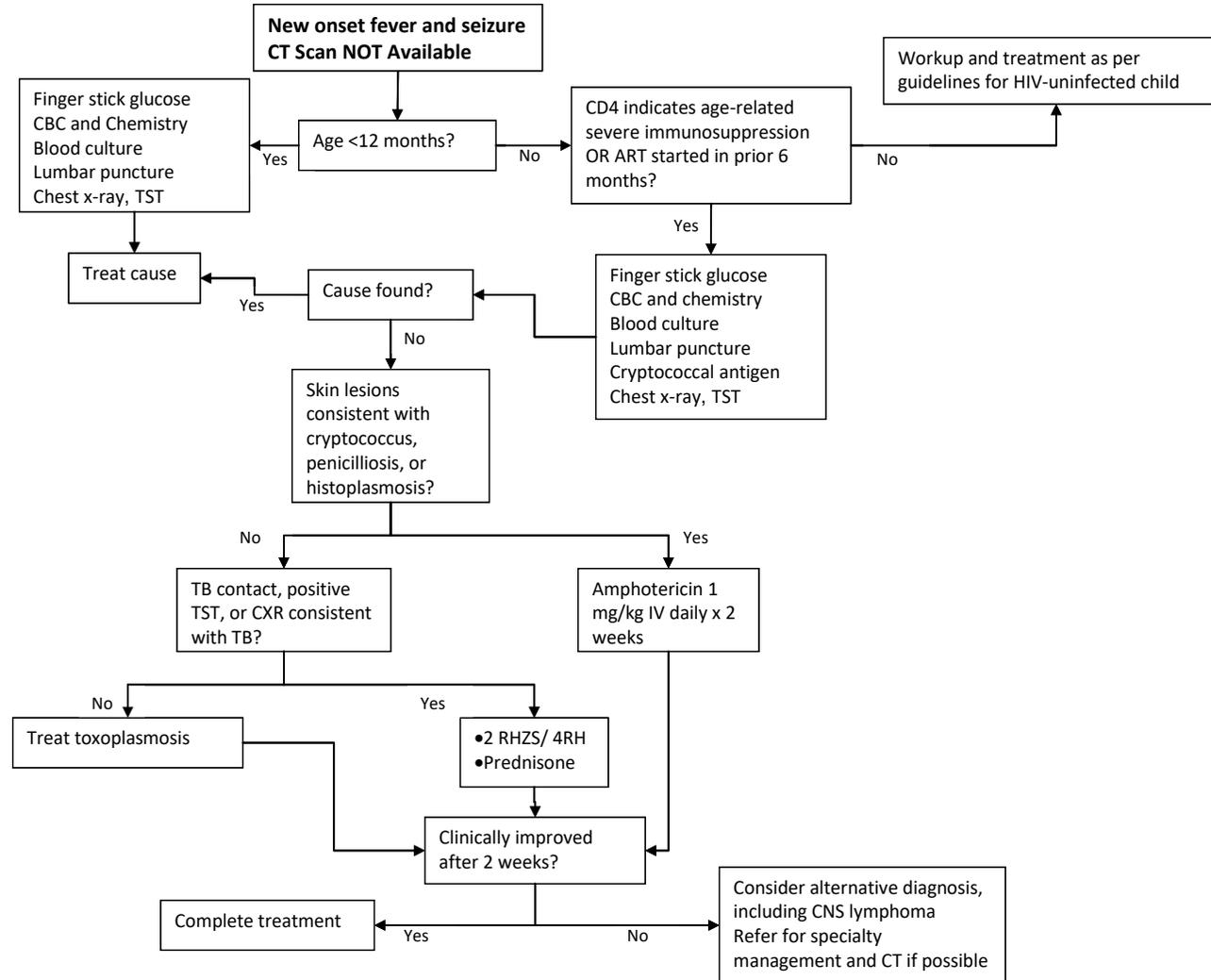
- Space-occupying lesions, including toxoplasmosis, tuberculoma, fungal infection, and lymphoma
- Meningitis or meningoencephalitis (cryptococcal, TB, bacterial, viral)
- Cerebral malaria
- Febrile convulsions (age 6 months – 5 years)
- Metabolic disturbances (e.g. hypoglycemia)
- Epilepsy.

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 13 and 14 for the evaluation of new seizures in children with HIV. New focal neurologic deficit and fever should be evaluated using the same algorithms.**

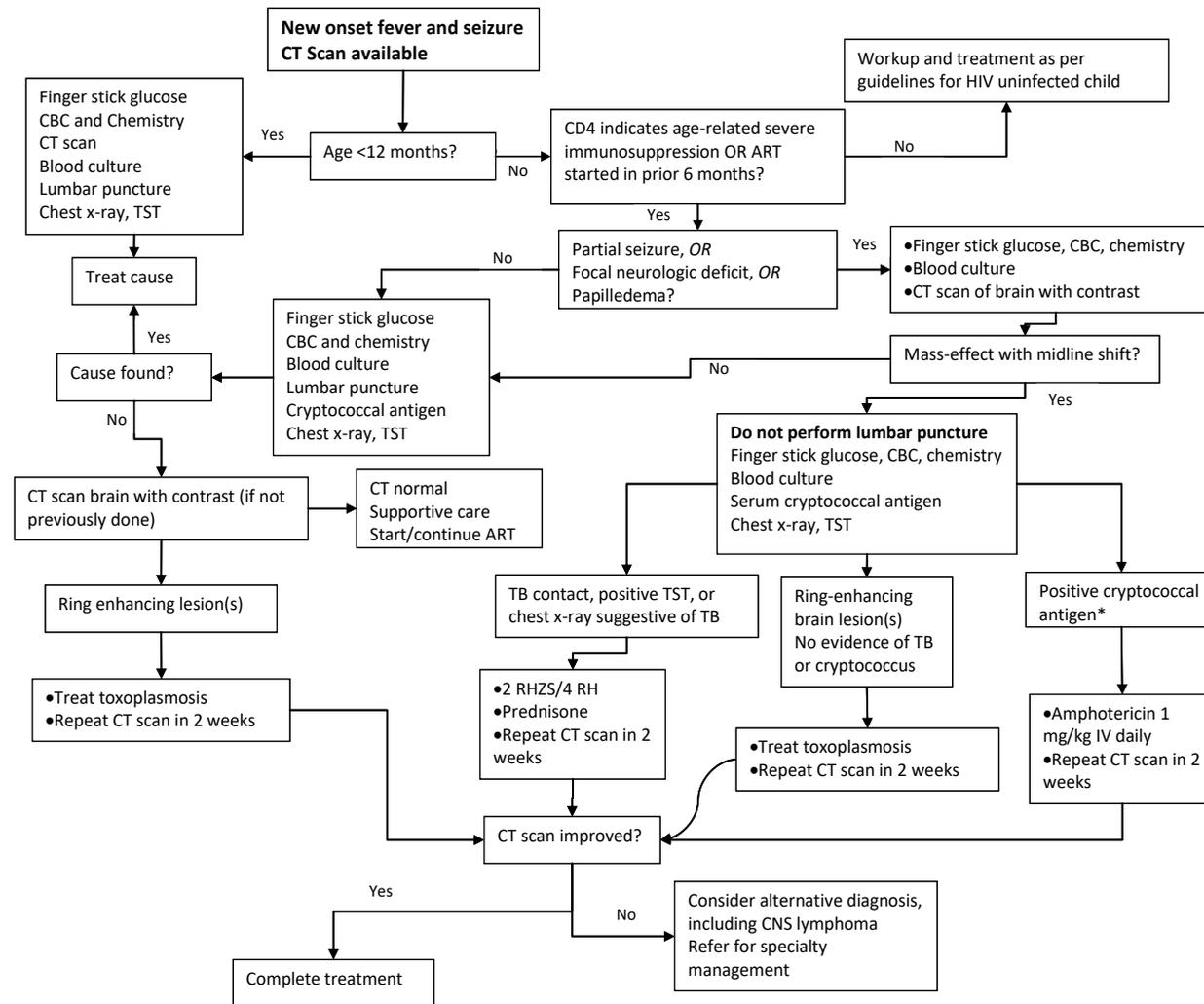
Many anti-epileptic agents interact with ARVs, which may result in either abnormally low or high serum concentrations of the anti-seizure drug. Valproate is the preferred agent in children with seizures who are receiving ART.

**Figure 13: Workup of seizure and fever when CT scan is NOT available**



**Figure 14: Workup of seizure and fever when CT scan is available**

and fever when CT



# CHAPTER 33: INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

Infections of the central nervous system (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.

## 33.1 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

### 33.1.1 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.

#### 33.1.1.1 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 X-Ray
  - If lumbar puncture fails, cryptococcal antigen testing of the blood.

See Table 32 for typical CSF findings in cryptococcal meningitis.

### 33.1.1.2 Treatment

#### A. INDUCTION THERAPY

*i. Recommended Option:*

A short-course (one-week) induction regimen with Amphotericin B deoxycholate (1.0 mg/kg/day) and flucytosine (100 mg/kg/day, divided into four doses per day), followed by 1 week of fluconazole (12 mg/kg/day, up to a maximum dose of 800mg daily), is the preferred option.

*ii. Alternative options:*

- Two weeks of fluconazole (12 mg/kg/day + flucytosine (100 mg/kg/day, divided into four doses per day) OR
- Two weeks of amphotericin B deoxycholate (1.0 mg/kg/day) + fluconazole (12 mg/kg/day up to a maximum of 800 mg daily).
- Pre-emptive fluids to minimize renal toxicity<sup>24</sup>
- If creatinine doubles, decrease dose of amphotericin B to 0.7 mg/kg/day.

*iii. Therapeutic Lumbar Puncture*

- 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.

#### B. CONSOLIDATION THERAPY

- Fluconazole 6-12 mg/kg x 8 weeks.

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<sup>24</sup> One litre of normal saline solution with one ampoule (20 mmol) of KCL at 10-15 ml/ kg over 2-4 hours before each controlled infusion of amphotericin B (other intravenous rehydration solutions that contain potassium can be used e.g. Darrow's or Ringer's Lactate solutions)

Monitor:

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

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

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

### C. MAINTENANCE TREATMENT (SECONDARY PROPHYLAXIS)

- Fluconazole 6mg/kg/day (maximum 200mg), continued until age ≥5 years and CD4 >100 cells/mm<sup>3</sup> for >6 months on adherent ART.

### D. PRIMARY PROPHYLAXIS:

Fluconazole prophylaxis is no longer recommended for adults or children with HIV as primary prophylaxis. See Chapter 6: sub-section 6.2.2: Cryptococcus infection, page 38.

**Table 31: Amphotericin: Administration, toxicity prevention, monitoring and management**

<b>Administration of Amphotericin – toxicity prevention, monitoring and management<sup>25</sup></b>
<p><b>Pre-emptive hydration and electrolyte supplementation (adolescent only)</b></p> <ul style="list-style-type: none"><li>• One liter of normal saline solution with one ampoule (20 mmol) of KCL over 2-4 hours before each infusion of amphotericin B (with one liter of 5% dextrose)</li><li>• One to two 8mEq KCL tablets orally twice daily.</li><li>• An additional one 8mEq KCL tablet twice daily may be added during the second week.</li><li>• If available, add two 250mg tablets of magnesium trisilicate twice daily.</li><li>• Potassium replacement should be avoided if renal impairment or hyperkalaemia.</li><li>• A test dose for amphotericin B is not recommended.</li></ul>
<p><b>Administration of Amphotericin B</b></p> <ul style="list-style-type: none"><li>• Amphotericin powder (50mg vials) refrigerate at 2-8°C and protect from light. Reconstitute each 50mg vial into 10ml sterile water and injected into 1liter bag of 5% dextrose and shaken. <b>(Never use saline).</b></li><li>• Use within 24 hours of reconstitution</li><li>• Infuse through peripheral IV cannula over ≥ 4 hours. After infusion remove the infusion bag and flush line with normal saline. Monitor the IV cannula for phlebitis and change as necessary.</li></ul> <p><b>Monitoring during the infusion</b></p> <ul style="list-style-type: none"><li>• Pulse, BP, temperature every 30 mins during the first 2 hours then every hour.</li><li>• In case of fever and shivers - hydrocortisone 50mg</li><li>• If BP &lt; 70mmHg cease the infusion and give IVI fluids, clinical assessment</li></ul>
<p><b>Monitoring for toxicities</b></p> <ul style="list-style-type: none"><li>• Serum potassium and creatinine (baseline and twice weekly), especially in the second week of amphotericin B administration.</li><li>• Haemoglobin (baseline and weekly)</li><li>• Careful attention to fluid monitoring of intake and output, and <i>daily weight</i></li></ul>

<sup>25</sup> Rapid Advice Diagnosis, Prevention and Management of Cryptococcal Disease in HIV –infected Adults, Adolescents and Children. WHO December 2011.

**Management of toxicities**

- If K <3.3mmol/l, increase potassium supplementation to two KCL ampoules (40 mmol), or one or two 8mEq KCL tablets three times daily. Monitor potassium daily.
- If hypokalaemia remains uncorrected, double magnesium oral supplementation.
- Renal impairment at baseline is not a contraindication to standard dose of amphotericin B ensure well hydrated and if creatinine increases by >2 fold from baseline value, either temporary omission of an amphotericin B dose, or increase pre-hydration to one liter 8 hourly. Once improved, restart at 0.7 mg/kg/day and consider alternate day amphotericin B.
- If creatinine remains elevated, discontinue amphotericin and continue with fluconazole at 1200mg/day (see notes on fluconazole below). Monitor creatinine daily.

**Table 32: CSF Findings in HIV-infected patients with CNS disease**

Disease	Appearance	Opening Pressure	WBC/mm <sup>3</sup>	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 Guidelines for resource poor settings, MSF, 2006*

**33.1.2 Toxoplasma encephalitis****33.1.2.1 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.

### 33.1.2.2 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.

### 33.1.2.3 Diagnosis

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

### 33.1.2.4 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
  - Folic acid 5-20 mg 3 times weekly
  - All for 6 weeks.
- 2nd line therapy:
  - High dose CTX (10-15/50-75 mg/kg daily) for 6 weeks, then CTX 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.

### 33.1.2.5 Primary prophylaxis

- Cotrimoxazole 6/30 mg/kg/day per the indications (see Chapter 6, sub-section 6.2.1: Prevention of severe bacterial infection and malaria, page 35).

### 33.1.2.6 Secondary prophylaxis

- In patients with prior toxoplasmosis, CTX may be discontinued when age  $\geq 5$  years *and* CD4  $>350$  cells/mm<sup>3</sup> for  $>6$  months on adherent ART.

## 33.2 Viral encephalitis

Viral encephalitis may be caused by a wide-variety of agents, including CMV, HSV, enteroviruses, and Japanese encephalitis virus. Encephalitis is defined as evidence of

inflammation of the brain or meninges by CSF analysis or MRI imaging *and* alteration in mood, personality, or mental status. Suspect viral meningitis in patient with:

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

### 33.2.1 Further evaluation

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

### 33.3 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 X-Ray 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 13 unless an alternative diagnosis is confirmed.

### 33.4 Peripheral neuropathy

- Causes of peripheral neuropathy in children with HIV infection include:
  - HIV-related autoimmune effects
  - Vitamin deficiencies
  - CMV-related polyradiculoneuropathy

- Symptoms of peripheral neuropathy range from mild numbness or tingling to debilitating pain.
- Children with peripheral neuropathy should be provided with multivitamin supplementation and ART.
- Children receiving d4T should be changed to AZT when neuropathy is noted, as severe medication-related neuropathy is not always reversible.
- Children receiving 2<sup>nd</sup> line ART with ddi should be referred to an expert for ART adjustment.

# CHAPTER 34: GASTROINTESTINAL MANIFESTATIONS IN HIV INFECTED CHILDREN

## 34.1 Key Points

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

## 34.2 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 33: Classification of dehydration**

	Mild dehydration	Moderate dehydration	Severe dehydration
<b>Older child</b>	<b>3% (30 ml/kg)</b>	<b>6% (60 ml/kg)</b>	<b>9% (90 ml/kg)</b>
<b>Infant</b>	<b>5% (50 ml/kg)</b>	<b>10% (100 ml/kg)</b>	<b>15% (150 ml/kg)</b>
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
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*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 34: Rehydration**

Indication	Route	Fluid choice	Dose*
Plan A: Prevention of dehydration in the setting of diarrhea. No current dehydration	Oral	ORS (oral rehydration salts) solution **	<ul style="list-style-type: none"> <li>• Children &lt;2 years: 50-100 ml after each loose stool</li> <li>• Children 2-10 years: 100-200 ml after each loose stool.</li> <li>• Children &gt; 10 years and adults: as much fluid as desired after each loose stool.</li> </ul>
Plan B: Mild to moderate dehydration	Oral	ORS solution	<ul style="list-style-type: none"> <li>• Children &lt; 2 years: 5 ml every 1-2 minutes by spoon. Total volume over 4 hours should equal about 75 ml x weight (kg)</li> <li>• Children &gt; 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).</li> </ul>
Plan C: Severe dehydration	Intravenous	LR, Normal saline (0.9% NaCl)	<ul style="list-style-type: none"> <li>• Infants: 30 ml/kg for 1 hour+, then 70 ml/kg over 5 hours (total of 100 ml/kg over 6 hours)</li> <li>• Older children and adults: 30 ml/kg over 30m, then 70ml/kg over 2.5 hours (total of 100 ml/kg over 3 hours).</li> </ul>
Plan C: Severe dehydration	Nasogastric (only if IV therapy is not available)	ORS	<ul style="list-style-type: none"> <li>• 20 ml/kg/h* for 6 hours (total of 120 ml/kg).</li> </ul>
Plan C: Severe dehydration	Oral (only if alert and when IV/NG are not possible)	ORS	<ul style="list-style-type: none"> <li>• Children &lt; 2 years: 5 ml/minute by spoon.</li> <li>• Children &gt; 2 years and adults: 20 ml/kg/h for 6 hours (total of 120 ml/kg).</li> </ul>

\*Decrease the rate if there is vomiting or abdominal distension

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

### 34.3 Acute Diarrhea

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

Children should be admitted to inpatient care if:

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

#### 34.3.1 Watery diarrhea

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

#### 34.3.2 Bloody diarrhea

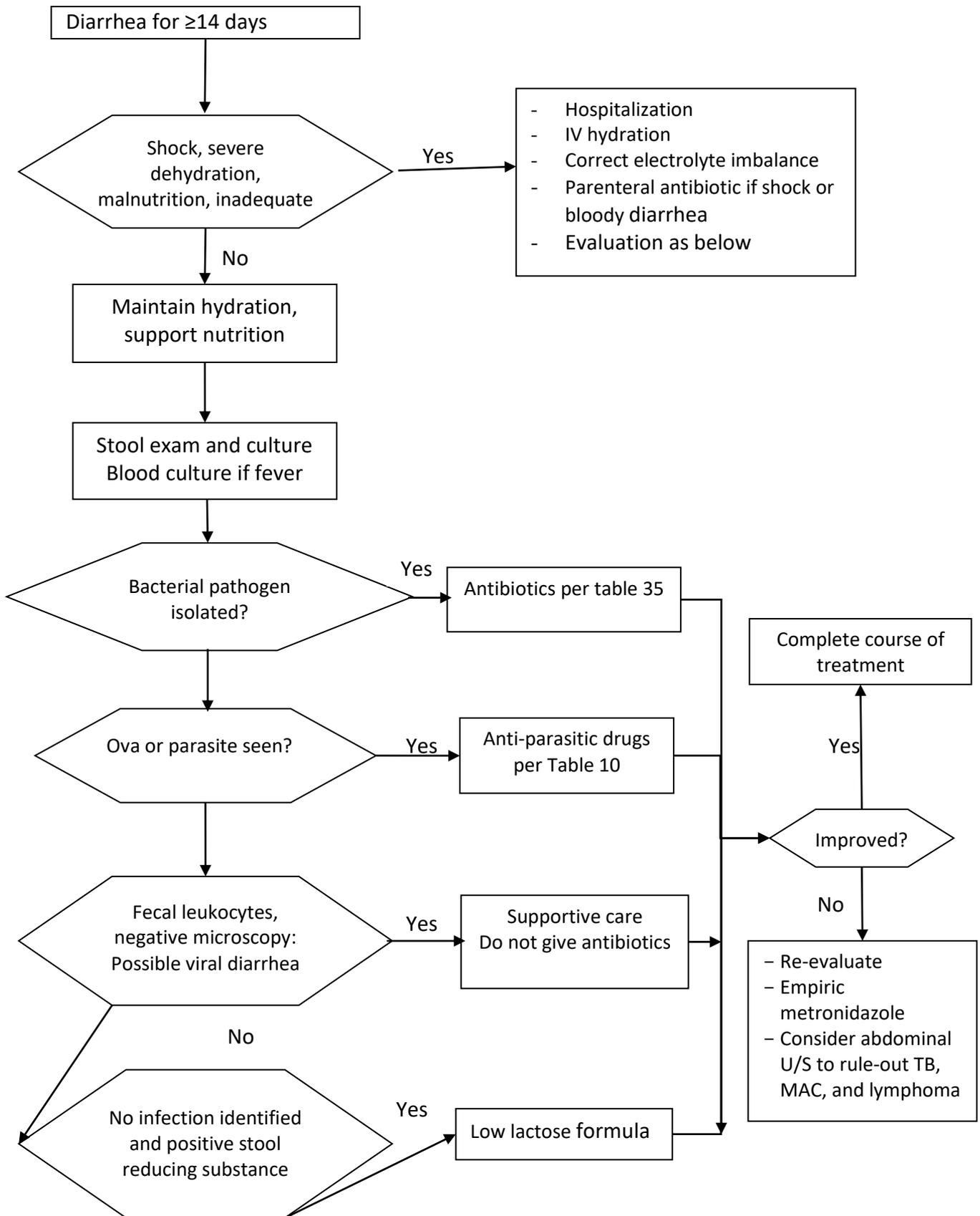
- Dysentery, or bloody diarrhea, may be caused by:
  - Shigella
  - Typhoid and non-typhoidal salmonella
  - Yersinia, campylobacter, enterohemorrhagic and enteroinvasive *E. coli*, and the parasite *Entamoeba histolytica*.
- Dysentery may be accompanied by systemic symptoms such as fever and an elevated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

- Provide mother or caregiver oral rehydration salts for home use until diarrhea stops
- Follow up in 2-3 days, or earlier if symptoms worsen.

### **34.4 Chronic diarrhea**

- Chronic diarrhea that persists for >14 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 35 below.
  - Consider empiric treatment for giardia with metronidazole 7.5 mg/kg/dose q8 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 15 outlines the approach to an HIV infected child with chronic diarrhea.

**Figure 15: Approach to the child with chronic diarrhea**



**Table 35: Treatment of diarrhea**

Etiology	Treatment
<b>Bacteria</b>	
<i>Salmonella</i> (non-typhoidal)	<ul style="list-style-type: none"> <li>• Ciprofloxacin 15mg/kg PO twice daily for 3-7 days</li> </ul>
<i>Salmonella typhi</i>	<ul style="list-style-type: none"> <li>• Ceftriaxone 50-75mg/kg OD, IV for 7 days <i>Or</i></li> <li>• Ciprofloxacin for 15mg/kg PO BID for 7 days</li> </ul>
<i>Shigella</i>	<ul style="list-style-type: none"> <li>• Ciprofloxacin 15mg/kg PO BID for 3 days</li> </ul>
<i>Escherichia coli</i>	<ul style="list-style-type: none"> <li>• No antibiotic</li> </ul>
<i>Campylobacter jejuni</i>	<ul style="list-style-type: none"> <li>• Erythromycin 10mg/kg PO QID for 5 days <i>Or</i></li> <li>• Ciprofloxacin 15 mg/kg PO BID for 5 days</li> </ul>
Cholera	Erythromycin 20mg/kg/dose, 4 times daily for 3 days
<i>Mycobacterium avium</i> Complex	<ul style="list-style-type: none"> <li>• Clarithromycin 15mg/kg/day BID <i>Or</i></li> <li>• Azithromycin 10mg/kg OD <i>PLUS</i></li> <li>• Ethambutol 15-25 mg/kg OD <i>PLUS</i></li> <li>• Rifabutin 10-20mg/kg OD <i>Or</i></li> <li>• Ciprofloxacin 20-30mg/kg OD</li> </ul>
Tuberculosis	<ul style="list-style-type: none"> <li>• 2RHZE/4RH</li> </ul>
<i>Yersinia enterocolitica</i>	<ul style="list-style-type: none"> <li>• TMP-SMZ (TMP 8mg/kg/day) divided BID for 5 days.</li> </ul>
<b>Protozoa</b>	
<i>Cryptosporidium</i>	<ul style="list-style-type: none"> <li>• No therapy proven efficacious</li> <li>• Spontaneous resolution may occur after ART</li> <li>• Azithromycin 10mg/kg OD for 1 day, follows by 5 mg/kg OD for 9 days may be useful</li> <li>• If no response, azithromycin 10mg/kg OD for 2 weeks may be tried</li> </ul>
<i>Isospora belli</i>	<ul style="list-style-type: none"> <li>• TMP-SMZ (TMP 5mg/kg/dose) qid for 10 days then bid for 3 weeks.</li> </ul>
<i>Giardia lamblia</i>	<ul style="list-style-type: none"> <li>• Metronidazole 20mg/kg/day PO divided tid for 10 days</li> </ul>
<i>Entamoeba histolytica</i>	<ul style="list-style-type: none"> <li>• Metronidazole 35-50mg/kg/day PO divided tid for 10 days</li> </ul>
<i>Microsporidia</i>	<ul style="list-style-type: none"> <li>• Albendazole 20mg/kg/day bid x 4 weeks</li> </ul>
<i>Cyclospora</i>	<ul style="list-style-type: none"> <li>• TMP-SMZ (TMP 5mg/kg/dose) qid for 10 days then bid for 3 weeks</li> </ul>

## CHAPTER 35: VIRAL HEPATITIS

### 35.1 Signs and symptoms

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.

### 35.2 Hepatitis A and E viruses

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

### 35.3 Hepatitis B virus (HBV)

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

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

### **35.4 Hepatitis C virus (HCV)**

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

# CHAPTER 36: OTHER SYSTEMIC OPPORTUNISTIC INFECTION

## 36.1 Key points

- Disseminated *Mycobacterium avium* complex occurs in children with severe immunosuppression and presents as non-specific fever, weight loss, anemia, and elevated liver enzymes.
- Disseminated MAC and tuberculosis are often indistinguishable.
- *Penicillium marneffe* is endemic in Southeast Asia and causes disseminated fungal infection in severely immunosuppressed hosts.
- Characteristic skin lesions may indicate disseminated penicilliosis.
- Histoplasmosis has been reported in Cambodia and causes disseminated infection with skin lesions similar to those of *Penicillium*.
- Itraconazole is the azole of choice for treatment of penicilliosis and histoplasmosis
- CMV frequently causes retinitis in children with very low CD4 counts and may worsen rapidly when ART is initiated.
- Children with CMV retinitis should receive intraocular or systemic ganciclovir to preserve vision while being immune-reconstituted on ART.
- Annex 18 summarizes common opportunistic infections occurring in children and management of these conditions.

## 36.2 Disseminated Mycobacterium Avium Complex (MAC)

### 36.2.1 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<sup>3</sup>
- Children 12-24 months: <500 cells/mm<sup>3</sup>
- Children 2 – 5 years: <75 cells/mm<sup>3</sup>
- Children ≥6 years: <50 cells/mm<sup>3</sup>

### 36.2.2 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.

### 36.2.3 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 colonize the epithelial lining of the GI tract without causing invasive disease
- Microscopy (without culture) does not differentiate between MAC and TB
- Definitive diagnosis requires isolation in mycobacterial culture from a sterile site, including blood, bone marrow, lymph node aspiration, tissue, or urine
- See Annex 17: Table of opportunistic Infection Symptoms, Diagnosis and treatment, page 200, for workup of MAC and other systemic OIs.

### 36.2.4 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.

### 36.2.5 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.

## CHAPTER 37: PENICILLIOSIS

### 37.1 Epidemiology

- Penicilliosis is an invasive fungal disease cause by the organism *Penicillium marneffe* which is endemic in Southeast Asia
  - Highest prevalence in Northern Thailand
- CD4 counts in adults below 100 cells/mm<sup>3</sup> increase the risk of infection; age related thresholds for children < 5 years are not known.

### 37.2 Clinical Manifestations

- Usually presents as disseminated disease with fever, anemia, weight loss, lymphadenopathy, pneumonia, and/or hepatosplenomegaly
- Papular, umbilicated or ulcerating skin lesions are common and may be mistaken for Molluscum contagiosum or *Cryptococcus* (See Annex 15: Photos of oral and skin lesions in HIV-infected children, page 197)
- CNS disease with brain abscess has been reported.

### 37.3 Investigations

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

### 37.4 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.

### 37.5 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<sup>3</sup> after 6 months of adherent ART.

## CHAPTER 38: HISTOPLASMOSIS

### 38.1 Epidemiology

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

### 38.2 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 and respiratory distress.

### 38.3 Investigations

- Pancytopenia, elevated transaminases, and very elevated LDH may be seen
- Chest X-Ray 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.

### 38.4 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.

#### 38.4.1 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<sup>3</sup> 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.

## CHAPTER 39: CYTOMEGALOVIRUS 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.

### 39.1 Epidemiology

- Prior to the availability of ART, 20-30% of adult patients with CD4 <100 cells/mm<sup>3</sup> could be expected to develop cytomegalovirus (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.

### 39.2 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.

### 39.3 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<sup>3</sup>
- 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.

### 39.4 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.

### 39.5 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<sup>3</sup> should be attempted whenever possible.

# ANNEXES

## Annex 1: WHO clinical staging of HIV/AIDS for children with confirmed HIV infection

Stage 1	Stage 2
<ul style="list-style-type: none"> <li>• Asymptomatic</li> <li>• Persistent generalized lymphadenopathy</li> </ul>	<ul style="list-style-type: none"> <li>• Unexplained* persistent hepatosplenomegaly</li> <li>• Papular pruritic eruptions</li> <li>• Extensive wart virus infection</li> <li>• Extensive molluscum contagiosum</li> <li>• Fungal nail infections</li> <li>• Recurrent oral ulcerations</li> <li>• Unexplained persistent parotid enlargement</li> <li>• Lineal gingival erythema</li> <li>• Herpes zoster</li> <li>• Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis or tonsillitis)</li> </ul>
Stage 3	Stage 4
<ul style="list-style-type: none"> <li>• Unexplained* moderate malnutrition not adequately responding to standard therapy</li> <li>• Unexplained* persistent diarrhoea (14 days or more)</li> <li>• Unexplained* persistent fever (above 37.5°C intermittent or constant, for longer than one month)</li> <li>• Persistent oral candidiasis (after first 6-8 weeks of life)</li> <li>• Oral hairy leukoplakia</li> <li>• Acute necrotizing ulcerative gingivitis or periodontitis</li> <li>• Lymph node tuberculosis</li> <li>• Pulmonary tuberculosis</li> <li>• Severe recurrent bacterial pneumonia</li> <li>• Symptomatic lymphoid interstitial pneumonitis</li> <li>• Chronic HIV-associated lung disease including brochiectasis</li> <li>• Unexplained* anaemia (&lt;8.g/dl), neutropaenia (&lt;0.5 x 10<sup>9</sup> per liter) and/or chronic thrombocytopenia (&lt;50 x 10<sup>9</sup> per liter)</li> </ul>	<ul style="list-style-type: none"> <li>• Unexplained* severe wasting, stunting or severe malnutrition not responding to standard therapy</li> <li>• Pneumocystis pneumonia</li> <li>• Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection or meningitis but excluding pneumonia)</li> <li>• Chronic herpes simplex infection (orolabial or cutaneous of more than one month's duration or visceral at any site)</li> <li>• Extrapulmonary tuberculosis</li> <li>• Kaposi sarcoma</li> <li>• Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)</li> <li>• Central nervous system toxoplasmosis (after one month of life)</li> <li>• HIV encephalopathy</li> <li>• Cytomegalovirus infection: retinitis or cytomegalovirus infection affecting another organ, with onset at age older than one month</li> <li>• Extrapulmonary cryptococcosis (including meningitis)</li> </ul>

	<ul style="list-style-type: none"><li>• Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis, penicilliosis)</li><li>• Chronic cryptosporidiosis</li><li>• Chronic isosporiasis</li><li>• Disseminated non-tuberculous mycobacterial infection</li><li>• Cerebral or B-cell non-Hodgkin lymphoma</li><li>• Progressive multifocal leukoencephalopathy</li><li>• Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy</li></ul>
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\* Unexplained refers to where the condition is not explained by other causes such as tuberculosis or cryptosporidiosis

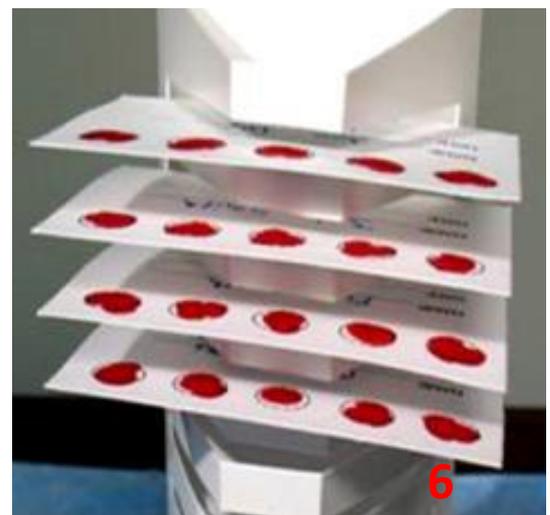
## Annex 2: Principals for managing child victims of sexual assault

Principal	Action
Promote the child's best interest	<ul style="list-style-type: none"> <li>• Secure physical and emotional safety (well-being) throughout care and treatment</li> <li>• Evaluate positive and negative consequences of actions with participation of the child and caregiver (as appropriate)</li> <li>• The least harmful course of action is always preferred</li> <li>• All actions should ensure that the child's rights to safety and ongoing development are not compromised.</li> </ul>
Ensure the safety of the child	<ul style="list-style-type: none"> <li>• Ensure physical and emotional safety</li> <li>• All actions should safeguard the child's physical and emotional well-being in the short and long term.</li> </ul>
Comfort the child	<ul style="list-style-type: none"> <li>• Offer comfort, encouragement, and support</li> <li>• Assure that service providers are prepared to handle the disclosure of sexual violence and exploitation appropriately</li> <li>• Believe the child when they have chosen to disclose sexual violence and exploitation</li> <li>• Never blame the child in any way for the sexual violence and exploitation they have experienced</li> <li>• Make the child feel safe and cared for as they receive services.</li> </ul>
Ensure appropriate confidentiality	<ul style="list-style-type: none"> <li>• Information about the child's experience of sexual violence and exploitation should be collected, used, and stored in a confidential manner</li> <li>• Ensure the confidential collection of information during all aspects of care including interviews and history taking</li> <li>• Share information only according to local laws and policies and on a need-to-know basis, after obtaining permission from the child and/or caregiver</li> <li>• Store all case information securely</li> <li>• If mandatory reporting is required under local law, inform the child and caregiver at the time they are seen</li> <li>• If the child's health or safety is at risk, there may be limits to confidentiality to protect the child.</li> </ul>
Involve the child in decision making	<ul style="list-style-type: none"> <li>• Children have a right to participate in decisions that have implications in their lives</li> <li>• The level of a child's participation in decision making should be appropriate to the child's level of maturity and age, and local laws</li> <li>• Although service providers may not always be able to follow the child's wishes (based on best-interest considerations), they should always empower and support children and deal with them in a transparent, open manner with respect</li> <li>• If a child's wishes are not able to be followed, then the reasons behind not being able to follow them should be explained.</li> </ul>

<p>Treat every child fairly and equally</p>	<ul style="list-style-type: none"> <li>• Use the principle of non-discrimination and inclusiveness for all children</li> <li>• All children should be offered the same high-quality care and treatment, regardless of their ethnicity, religion, sex, ability/disability, family situation, status of their parents or caregivers, cultural background, or financial situation, affording them the opportunity to reach their full potential</li> <li>• No child should be treated unfairly for any reason.</li> </ul>
<p>Strengthen children’s resiliencies</p>	<ul style="list-style-type: none"> <li>• Each child has unique capacities and strengths, and possesses the capacity to heal</li> <li>• Identify and build upon the child’s and family’s natural strengths as a part of the recovery and healing process</li> <li>• Factors that promote the child’s resilience should be identified and built upon during the episode of care</li> <li>• Children who have caring relationships and opportunities for meaningful participation in family and community life and who see themselves as strong will be more likely to recover and heal from sexual violence and exploitation (Perry 2007).</li> </ul>
<p>Health care providers should be appropriately trained and skilled in managing children who have experienced sexual violence and exploitation</p>	<p>All providers responsible for caring for children who have experienced sexual violence and exploitation should:</p> <ul style="list-style-type: none"> <li>• Undergo training and orientation to the sexual violence/post-rape care clinic and referral protocols</li> <li>• Have specialized training on the medical forensic examination</li> <li>• Have advanced training on and understanding of emergency contraception based on national laws and protocols, where applicable and legal, as well as HIV, Post-exposure prophylaxis (PEP), STI prophylaxis, hepatitis B vaccination, and the importance of timely intervention</li> </ul> <p>Health care centers should:</p> <ul style="list-style-type: none"> <li>• Identify and train dedicated practitioners (doctors, forensic nurses, or clinic officers) to provide post-rape care and services for children.</li> </ul>
<p>The health and welfare of the child takes precedence over the collection of evidence</p>	<ul style="list-style-type: none"> <li>• Crisis intervention; treatment of serious injuries; and assessment, treatment, and prevention of HIV, pregnancy, and STIs are of primary importance</li> <li>• The welfare of the child ensures that they are able to maintain their dignity after sexual violence and exploitation, and do not feel coerced, humiliated, or further traumatized by the process of seeking services</li> <li>• Children should NEVER be forced to undergo the medical forensic examination against their will unless the examination is necessary for medical treatment (WHO 2003).</li> </ul>

<p>Reporting to police should not be a prerequisite for obtaining medical care</p>	<ul style="list-style-type: none"> <li>• The child’s decision regarding police involvement should be respected at all times</li> <li>• The child should not be pressured, coerced, or forced to report the sexual violence and exploitation as a condition of receiving their medical care</li> <li>• It is common for health care workers to tell the child that a police report must be made and they must obtain the report form before the facility will conduct the examination</li> <li>• Reporting is often tied to payment of fee, the hospital may only agree to provide free services if the patient has reported the violence to the police and is in possession of the official documentation forms. In most cases, these are procedural rather than legal requirements and should be changed at the facility level.</li> <li>• Efforts should be made by the facility to have a clear policy on reporting, consistent with national policy, that affords the most patient-centered approach</li> <li>• Police forms should be kept ideally at the facility for children who present to the facility first and should be available free of charge</li> <li>• The child should be offered all available services including emergency contraception (EC) where legal, HIV PEP, and other needed health services even if there is no physician available to sign medico-legal forms, or if the child chooses not to report to the police.</li> </ul>
<p>Use the person-first approaches to care</p>	<ul style="list-style-type: none"> <li>• Professionals working with children who have experienced sexual violence and exploitation must have a strong understanding of current approaches to inclusive care of all patients regardless of ability</li> <li>• Recognize that children with disabilities (physical as well as mental/emotional) are at increased risk for sexual violence and exploitation, and have equal right to care and access treatment</li> <li>• Ensure that someone who is trained is available when necessary for communication alternatives (e.g., sign language) for patients who may require this approach.</li> </ul>

### Annex 3: Job Aid for Dried Blood Spot



1. Warm up the puncture area
2. Firmly press the lancet to puncture the fingertip
3. Wap out the first drop of blood
4. Drop the blood on the paper
5. Apply cotton pad in puncture area until stop bleeding
6. Dry the blood

#### Annex 4: Antiretroviral therapy dosing table

Singles			Number of tablets by weight band morning and evening													
Drug	Type	Strength	3–5.9 kg		6–9.9 kg		10–13.9 kg		14–19.9 kg		20–24.9 kg		25–29.9 kg		30–34.9 kg	
			AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
ABC	Tablet (dispersible)	60 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	–	–	–	–
ABC	Tablet (dispersible)	300 mg	–	–	–	–	–	–	–	–	–	–	1	1	1	1
AZT	Tablet (dispersible)	60 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	–	–	–	–
AZT	Syrup	10mg/mL	6ml	6ml	9ml	9ml	12ml	12ml	–	–	–	–	–	–	–	–
EFVa	Tablet (scored)	200 mg	–	–	–	–	1 (once daily)		1.5 (once daily)		1.5 (once daily)		2 (once daily)		2 (once daily)	
LPV/rb	Tablet (heat stable)	100/25 mg	–	–	–	–	2	1	2	2	2	2	3	3	3	3
LPV/rb	Tablet (heat stable)	200/50 mg	–	–	–	–	–	–	1	1	1	1	2	1	2	1
LPV/rb	Syrup	80/20 mg/ml	1ml	1 ml	1.5 ml	1.5 ml	2 ml	2 ml	2.5 ml	2.5 ml	3 ml	3 ml	–	–	–	–
LPV/r	Granules	40/10 mg	2	2	3	3	4	4	5	5	6	6	–	–	–	–
NVPc	Syrup	10 mg/ml	5 ml	5 ml	8 ml	8 ml	10 ml	10ml	–	–	–	–	–	–	–	–
DTG	Tablet	50 mg	–	–	–	–	–	–	–	–	1	-	1	-	1	-
RAL	Tablet (chewable/dispersible)	25mg	1	1	2	2	3	3	4	4	6	6	–	–	–	–
RAL	Tablet (chewable/dispersible)	100mg	–	–	–	–	–	–	1	1	1.5	1.5	–	–	–	–
RAL	Tablet	400mg	–	–	–	–	–	–	-	-	–	–	1	1	1	1

<sup>a</sup> EFV is not recommended for children younger than 3 years and weighing less than 10 kg. FDA approval for use in children less than 3 years weighing more than 3.5 kg was granted during the finalization of these guidelines (3.5-5 kg two 50 mg capsules; 5-7.5 kg three 50 mg capsules; 7.5-15 kg one 200 mg capsule),

however more data are urgently needed to inform recommendations for use of EFV in this age group.

<sup>b</sup> LPV/r liquid requires a cold chain during transport and storage. The LPV/r heat-stable tablet formulations must be swallowed whole and should not be split or crushed.

<sup>c</sup> NVP dose escalation with half dose for 2 weeks when initiating ART is still recommended to avoid toxicity from high initial NVP levels. However, secondary analysis from the (CHAPAS-1) trial recently suggested that younger children have a lower risk of toxicity, and consideration can be given to starting with a full dose (Fillekes Q et al. Is nevirapine dose escalation appropriate in young, African, HIV-infected children? AIDS, 2013, ahead of press (<http://www.ncbi.nlm.nih.gov/pubmed/23595153>, accessed 17 July 2013). doi: 10.1097/QAD.0b013e3283620811) More definitive evidence is expected from an ongoing trial.

Fixed Dose Combinations			Number of tablets by weight band morning and evening													
Drug	Type	Strength	3–5.9 kg		6–9.9 kg		10–13.9 kg		14–19.9 kg		20–24.9 kg		25–29.9 kg		30–34.9 kg	
			AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
ABC/3TC	Tablet (dispersible)	60/30 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	–	–	–	–
ABC/3TC	Tablet (dispersible)	600/300 mg	–	–	–	–	–	–	–	–	–	–	1 (once daily)		1 (once daily)	
ABC/3TC	Tablet (dispersible)	120/60 mg	1 once (or 0.5 twice) daily		1.5 once (or 0.5 AM and 1 PM) daily		2 once (or 1 twice) daily		2.5 once (or 1 AM and 1.5PM) daily		3 once (or 1.5 twice) daily		–	–	–	–
AZT/3TC	Tablet (dispersible)	60/30 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	–	–	–	–
AZT/3TC	Tablet (dispersible)	300/150 mg	–	–	–	–	–	–	–	–	–	–	1	1	1	1
TDF/3TC	Tablet	300/300 mg	–	–	–	–	–	–	–	–	–	–	–	–	1	–
AZT/3TC/NVP	Tablet (dispersible)	60/30/50 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	–	–	–	–
AZT/3TC/NVP	Tablet (dispersible)	300/150/200 mg	–	–	–	–	–	–	–	–	–	–	1	1	1	1
TDF/3TC/EFV400	Tablet	300/300/400 mg	–	–	–	–	–	–	–	–	–	–	–	–	1	–
TDF/3TC/DTG	Tablet	300/300/50 mg	–	–	–	–	–	–	–	–	–	–	–	–	1	–

**Important Points to Note:**

- 1) As suggested in the guidelines, TDF based regimens can be prescribed to children and adolescents under 30 kg in special circumstances. Please refer to the guidelines for details.
- 2) The dosage for the certain ARVs is decided on a case-by-case basis and clinicians are advised to consult with an expert prior to prescribing DRV/r, RAL and RTV

Raltegravir granule dosing is complex as it depends on both weight and age, and thus requires more detail than permitted in the above tables. This is the recommended dosing for RAL granules.

DOSING FOR RALTEGRAVIR GRANULES							
Birth to 1 Week: Once-Daily Dosing	Approximately 1.5 mg/kg/dose	1–4 Weeks: Twice-Daily Dosing	Approximately 3 mg/kg/dose	>= 4 Weeks: Twice-Daily Dosing	Approximately 6 mg/kg/dose	>= 4 Weeks: Twice-Daily Dosing	Approximately 6 mg/kg/dose
2 to <3	0.4 mL (4 mg) once daily	2 to <3	0.8 mL (8 mg) twice daily	3 to <4	2.5 mL (25 mg) twice daily	8 to <11	6 mL (60 mg) twice daily
3 to <4	0.5 mL (5 mg) once daily	3 to <4	1 mL (10 mg) twice daily	4 to <6	3 mL (30 mg) twice daily	11 to <14	8 mL (80 mg) twice daily
4 to <5	0.7 mL (7 mg) once daily	4 to <5	1.5 mL (15 mg) twice daily	6 to <8	4 mL (40 mg) twice daily	14 to <20	10 mL (100 mg) twice daily

## Annex 5: ARV toxicity severity grading

	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
<b>Parameter</b>	<b>Mild</b>	<b>Moderate</b>	<b>Severe</b>	<b>Severe and potentially life-threatening</b>
<b>General guidance on estimating severity grade</b>				
Characterization of symptoms and general guidance on management	Symptoms causing no or minimal interference with functional activities No therapy needed, monitor	Symptoms causing greater than minimal interference with usual social and functional activities: may require minimal Intervention and monitoring	Symptoms causing inability to perform usual social and functional activities; requires medical care and possible hospitalization	Symptoms causing inability to perform basic self-care functions: require medical or operative intervention to prevent permanent impairment, persistent disability or death.
<b>Haematology standard international units are listed in italics</b>				
Absolute neutrophil count	750 <1000/mm <sup>3</sup> 0.75 x 10 <sup>9</sup> <1x10 <sup>9</sup>	500-749/mm <sup>3</sup> 0.5x10 <sup>9</sup> - 0.749x10	250-500/mm <sup>3</sup> 0.25 x10 <sup>9</sup> - 0.5x10 <sup>9</sup> /l	<250/mm <sup>3</sup> <0.250x 10 <sup>9</sup> /l
Hemoglobin (child>60day of age)	85-10.0g/dl 1.32-1.55mmol/l	75-<8.5g/dl 1.16-<1.32mmol/	6.5-<7.5 g/dl 1.01-<1.16 mmol/l	<6.5 g/dl <1.01 mmol/l Or severe clinical symptoms attributable to anaemia (e.g. cardiac failure), refractory to supportive therapy.
Platelets	100000 - < 125000/mm <sup>3</sup> 100x10 <sup>9</sup> 125x10 <sup>9</sup> /l	50000 - <100000/mm <sup>3</sup> 50 x 10 <sup>9</sup> -<100 x 10 <sup>9</sup> /l	25000 - < 50000/mm <sup>3</sup> 25 x 10 <sup>9</sup> -<50 x 10 <sup>9</sup> /l	<25000/mm <sup>3</sup> <25 x 10 <sup>9</sup> / or bleeding
<b>Gastrointestinal</b>				
Laboratory				
ALT (SGPT)	1.25-2.5 X ULN	2.6-5.0x ULN	5.1-10.0 x ULN	>10.0 x ULN
AST (SGOT)	1.25-2.5 X ULN	2.6-5.0x ULN	5.1-10.0 x ULN	>10.0 x ULN
Bilirubin (>2 week of age)	1.1-1.5x ULN	1.6-2.5 x ULN	2.6-5.0 x ULN	>5.0 x ULN
Lipase	1.1-1.5x ULN	1.6-3.0 x ULN	3.1-5.0 x ULN	>5.0 x ULN
Pancreatic	1.1-1.5x ULN	1.6-2.0 x ULN	2.1-5.0 x ULN	>5.0 x ULN

amylase				
<b>Clinical</b>				
Diarrhea  ≥1 year of age  ≤1 year of age	Transient or intermittent episodes of unformed stools OR Increase of ≤3 stools over baseline per day liquid stools (more unformed than usual) but usual number of stools	Persistent episodes of unformed to watery stools OR increase of 4-6 stools over baseline per day liquid stools OR mild dehydration	Grossly bloody diarrhea OR increase of ≥7 stools per day OR intravenous fluid replacement indicated liquid stools with moderate dehydration	Life-threatening consequences (e.g. hypotensive shock) liquid stools resulting in severe dehydration with aggressive rehydration indicated OR hypotensive shock.
Nausea	Transient (≤24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24- 48 hours	Persistent nausea resulting in minimal oral intake for >48 hours OR aggressive rehydration indicated (e.g. intravenous fluids)	Persistent nausea with no or minimal oral intake resulting in dehydration with aggressive rehydration indicated
Pancreatitis	Not applicable	Symptomatic AND hospitalization not indicated (other than emergency treatment)	Symptomatic AND hospitalization not indicated (other than emergency treatment)	Life-threatening consequences (e.g. circulatory failure, haemorrhage, sepsis)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR aggressive rehydration indicated (e.g. intravenous fluids)	Life-threatening consequences (e.g. hypotensive shock)

**Annex 6: Classification of grading adverse events**

	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
<b>Parameter</b>	<b>Mild</b>	<b>Moderate</b>	<b>Severe</b>	<b>Severe and potentially life-threatening</b>
<b>Allergic/dermatological</b>				
Acute systemic allergic reaction	Localized urticarial (weals) lasting a few hours	Localized urticarial with medical intervention indicated OR mild angioedema	Generalized urticarial OR angio-oedema with medical intervention indicated OR symptomatic mild bronchospasm.	Acute anaphylaxis OR life-threatening bronchospasm or laryngeal oedema
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number or bullae OR superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions Or Stevens Johnson syndrome OR ulceration or mucous membrane involving two or more distinct mucosal sites OR toxic epidermal necrolysis (TEN).
<b>Neurological</b>				
Alteration in personality, behavior or mood	Alteration causing no or minimal interference with usual social and functional activities	Alteration causing greater than minimal interference with usual social and functional activities	Alteration causing inability to perform usual social and functional activities AND intervention indicated	Behavior potentially harmful to self or others OR life-threatening consequences
Altered mental status	Changes causing no or minimal interference with usual social and functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social and functional activities	Onset of confusion, memory impairment, lethargy, or somnolence causing inability of perform usual social and	Onset of delirium, obtundation or coma

			functional activities.	
Neuromuscular weakness (including myopathy and neuropathy)	Asymptomatic with decreased strength on examination OR minimal muscle weakness causing no or minimal interference with usual social and functional activities.	Muscle weakness causing greater than minimal interference with usual social and functional activities	Muscle weakness causing inability to perform usual social and functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR respiratory muscle weakness impairing ventilation
Neurosensory alteration (including painful neuropathy)	Asymptomatic with sensory alteration on examination OR minimal paraesthesia causing no or minimal interference with usual social and functional activities.	Sensory alteration or paraesthesia causing greater than minimal interference with usual social and functional activities	Sensory alteration or paraesthesia causing inability to perform usual and functional activities	Disabling sensor alteration or paraesthesia causing inability to perform basic self-care functions.
<b>Other laboratory parameters standard international units</b>				
Cholesterol (fasting, paediatric <18 years old).	170-<200 mg/dl 4.40-5.15 mmol/l	200-300 mg/dl 5.16-1.77 mmol/l	>300 mg/dl >7.77 mmol/l	Not applicable
Glucose, serum, high non-fasting	116-<161 mg/dl 6.44-<8.89 mmol/l	161-<251 mg/dl 8.89-<13.89 mmol/l	251-500 mg/dl 13.89-27.75 mmol/l	>500 mg/dl >27.75 mmol/l
Glucose, serum, high non-fasting	110-<126 mg/dl 6.11-<6.95 mmol/l	126-<251 mg/dl 6.95-<13.89 mmol/l	251-500 mg/dl 13.89-27.75 mmol/l	>500 mg/dl >27.75 mmol/l
Lactate	<2.0 x ULN without acidosis	≥2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences or related condition present	Increased lactate with pH 7.3 with life-threatening consequences (e.g. neurological findings, coma) or related condition present

Triglycerides (fasting)	Not applicable	500-<751 mg/dl 5.65-<8.49 mmol/l	751-1200 mg/dl 8.49-13.56 mmol/l	>1200 mg/dl >13.56 mmol/l
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*Source: Adapted from Division of AIDS, National Institute of Allergy and Infectious Diseases, Table for grading the severity of adult and pediatric adverse events, Bethesda, Maryland, USA; December 2004.*

<sup>a</sup> *Usual social and functional activities in young children include those that are appropriate to their age and culture (e.g. social interactions, play activities, learning tasks).*

<sup>b</sup> *Activities that are appropriate to age and culture (e.g. Feeding self with culturally appropriate eating implement, walking or using hands).*

<sup>c</sup> *Values are provided for children in general except where age groups are specifically not*

**Annex 7: Schedule of routine clinical and laboratory monitoring for the HIV-infected child not on ART**

	Baseline	Month 1	Month 2	Month 3	Every 3 months	Every 6 months	Every 12 months	Symptom directed
<b>Clinical</b>								
Clinical Evaluation (a)	X	X	X	X	X	X	X	X
Weight, Height, and Growth Charts	X	X	X	X	X	X	X	X
Nutritional status and feeding	X	X	X	X	X	X	X	X
ARV dosing and side effects, toxicity	X	X	X	X	X	X	X	X
Need for OI medication and doses	X	X	X	X	X	X	X	X
<b>Laboratory</b>								
WBC and Hb (b)	X							X
CD4 % and CD4 count	X						X	X
Transaminase: ALT, ASAT (c)	X							X
HBsAg and HBCAb if available	X							X
Pregnancy test (d)	X							X

- (a) Includes history-taking, physical examination and assessment of neurodevelopment.*
- (b) Adolescents of reproductive age, provide counseling on family planning, prevention of STIs, prevention of transmission of HIV to others, and the risk of transmitting HIV to their infants. Pregnancy test should be given at baseline and as indicated from counseling.*
- (c) TB symptoms screen should be performed at every visit.*
- (d) As indicated by history or symptoms in adolescent females.*

**Annex 8: Schedule of routine clinical and laboratory monitoring for the HIV-infected child on ART**

Items	Baseline	Week 2	Month 1	Month 2	Month 3	Month 6	Every 3 months	Every 6 months	Every 12 months	Symptom Directed
<b>Clinical</b>										
Clinical Evaluation (a)	x	x	x	x	x	x	x			x
Weight, Height, and Growth Charts	x	x	x	x	x	x	x			
Nutritional Status and Feeding	x	x	x	x	x	x	x			
ARV dosing and side effects, toxicity	x	x	x	x	x	x	x			
Need for OI medication and doses	x	x	x	x	x	x	X			
Counseling for Prevention of STIs and Pregnancy (a)	X				X	X	X			X
<b>Laboratory</b>										
WBC and Hb (b)	X			X(b)						X
Transaminase: ALT, ASAT (c)	X		X(c)	X(c)		X(c)		X(c)		X
CD4 % and CD4 count	X					X			X	X
Viral Load						X			X	X
Creatinine Clearance if on TDF	X				X	X		X		

Urine dipstick if on TDF	X				X	X	X			
Fasting cholesterol, triglycerides and glucose (d)	X(d)								X(d)	X

- (a) Includes history-taking, physical examination and assessment of neurodevelopment.*
- (b) Adolescents of reproductive age, provide counseling on family planning, prevention of STIs, prevention of transmission of HIV to others, and the risk of transmitting HIV to their infants. Pregnancy test should be given at baseline and as indicated from counseling.*
- (c) TB symptoms screen should be performed at every visit.*
- (d) As indicated by history or symptoms in adolescent females*

Annex 9: Pediatric Weight-for-Age Growth Charts

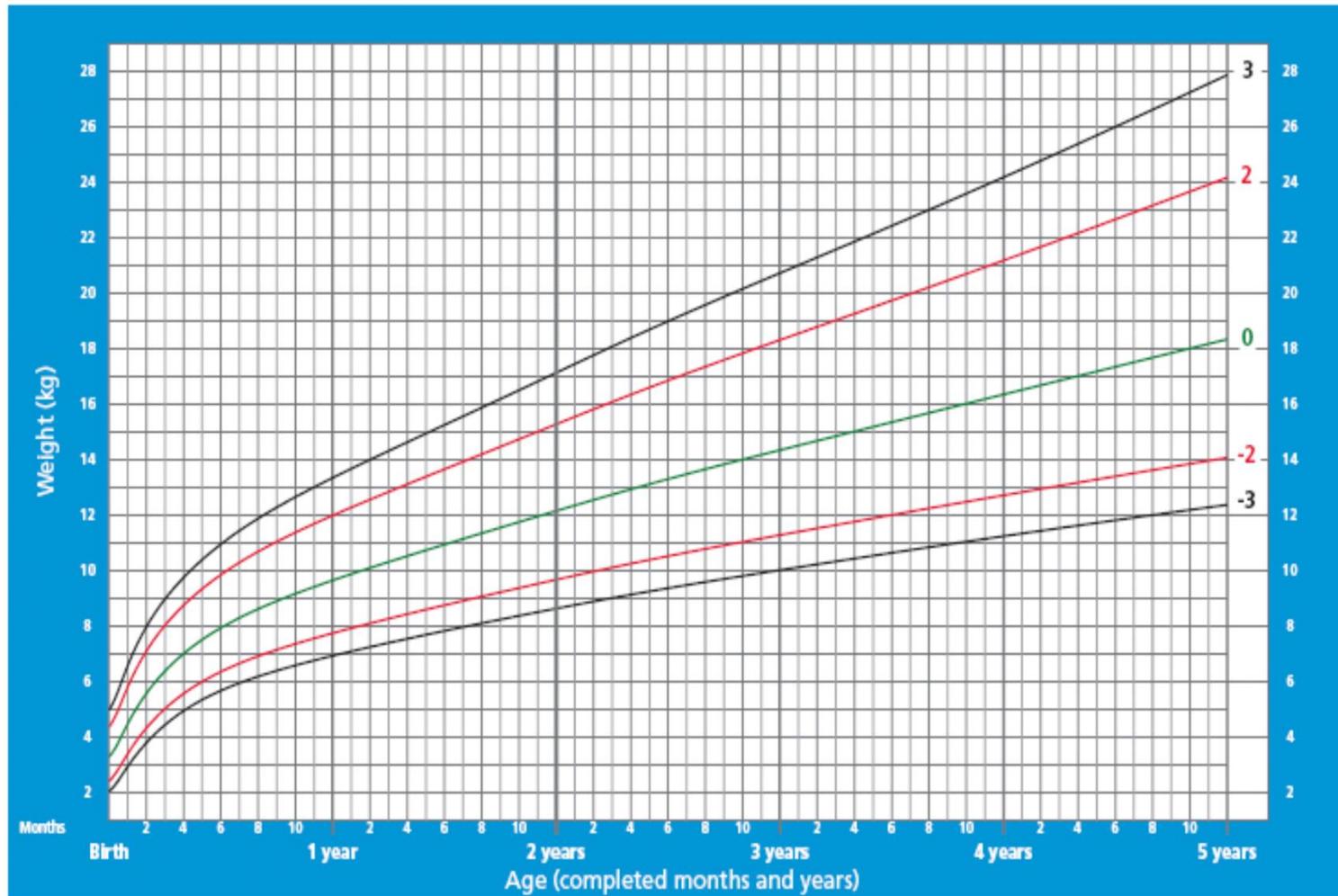
## Weight-for-age GIRLS

Birth to 5 years (z-scores)



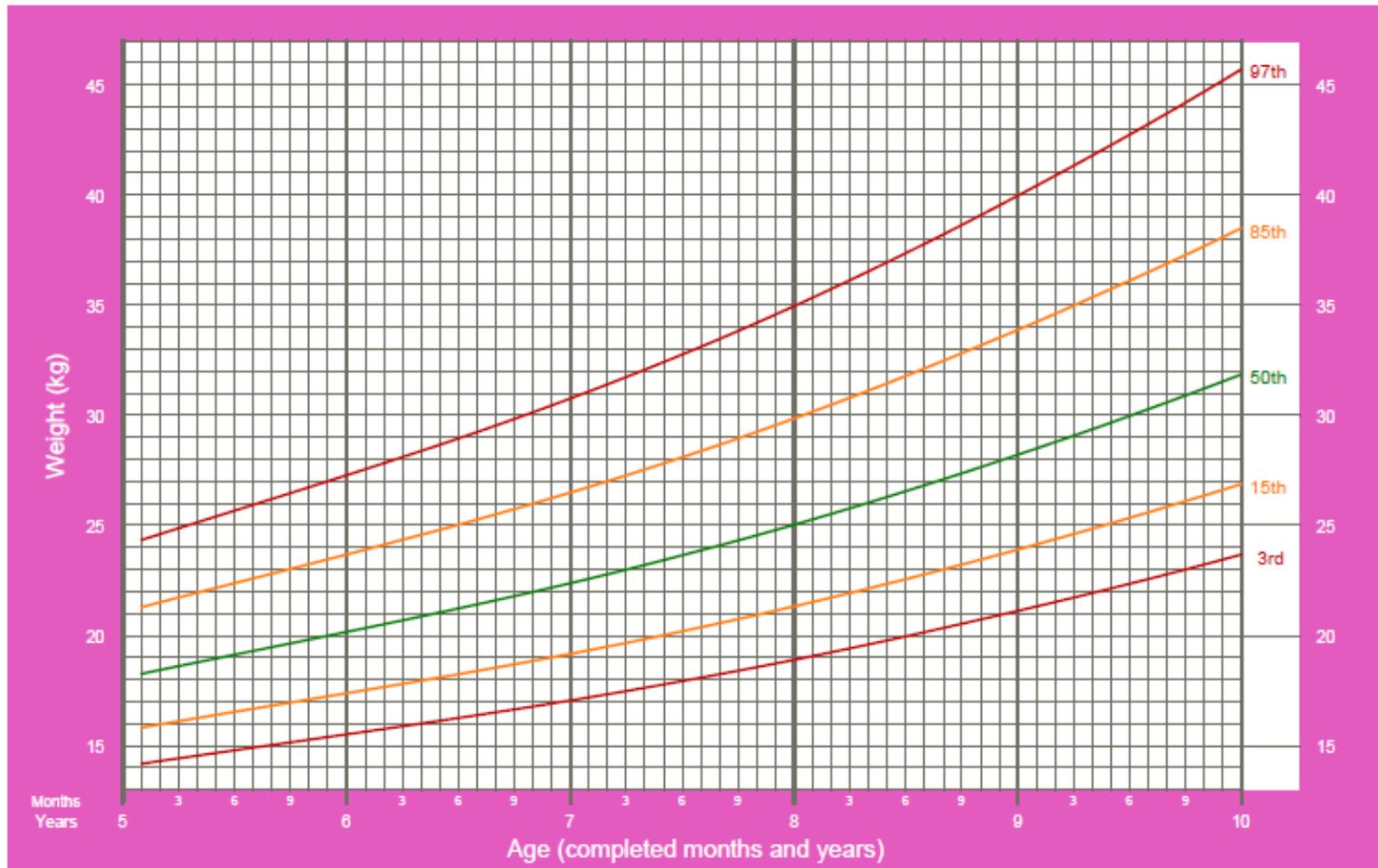
## Weight-for-age BOYS

Birth to 5 years (z-scores)



# Weight-for-age GIRLS

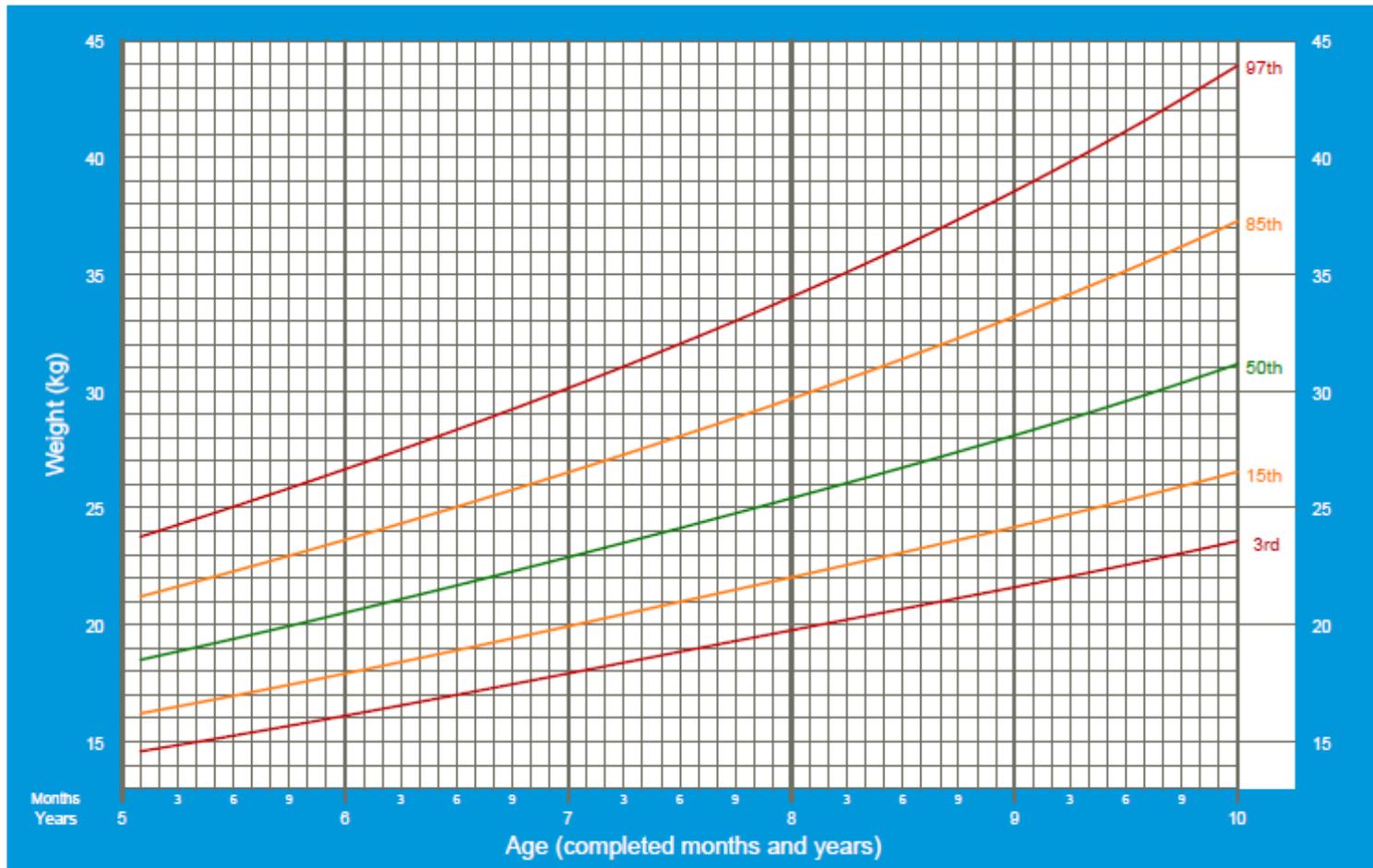
5 to 10 years (percentiles)



2007 WHO Reference

# Weight-for-age BOYS

5 to 10 years (percentiles)



2007 WHO Reference

### Annex 10: Important ARV Drug interactions

The following table gives an overview of major drug interactions. There are many more interactions not listed in this table. Always check reference texts for interactions before prescribing new drugs. <http://www.hiv-druginteractions.org> is also an excellent source of information.

Interacting drug	NVP	EFV	LPV/r	ATV/r	TDF
Ketoconazole	X	+/-		OK	Not described
Fluconazole	May cause ↑ NVP Level		OK	OK	Not described
Rifampicin	Use with caution	OK	Super boost LPV with ritonavir, to make 1:1	X	No dose adjustment necessary
Rifabutin	OK	RBT 450-600 mg/d	RBT 150mg QD no dose adjustment RBT 300mg, reduce to 150	No adjustment necessary	Not described
Clarithromycin	May decrease Clarithromycin levels	X	Dose reduction of Clarithromycin needed if renal failure	Reduce Clarithromycin by 50%	Not described
Oral contraceptive <sup>1</sup>	X	X	X	X	No dose adjustment necessary
Methadone	↑ methadone	↑ methadone	↑ methadone	OK	Not described
Statins <sup>2</sup>	+/-	+/-	X	X	Not described
SSRI Antidepressants	+/-	+/-	May cause ↑ SSRI level. Start at lowest	Not described	Not described
Anti-epileptic drugs <sup>3</sup>	X	X	X	Not described	Not described

Benzodiazepines <sup>4</sup>	X	X	X	X	Not described
Other drugs that should not be co-administered	Garlic supplements	Astemizole Terfenadine Cisapride Midazolam Triazolam Ergotamine Dihydro- ergotamine Garlic	Astemizole Terfenadine Cisapride Midazolam Ergotamine Dihydro- ergotamine Garlic Flecainide Pimozide	Astemizole Terfenadine Cisapride Midazolam Ergotamine Dihydro- ergotamine Garlic Flecainide Pimozide	
Miscellaneous	Can lower steroid levels	Monitor warfarin if co-administered			Probenecid, avoid combination

<sup>1</sup> Additional or alternative methods of contraception should be used. Medroxyprogesterone Depot generally effective but should always be used with barrier precautions.

<sup>2</sup> Pravastatin or fluvastatin can be used at the normal dose. Simvastatin must never be used.

<sup>3</sup> Levels of carbamazepine are increased, phenytoin decreased. Valproate is preferred in this situation.

<sup>4</sup> Diazepam and midazolam levels increased significantly, may cause life-threatening over-sedation. Use lorazepam if possible.

**Annex 11: Data collection form for patient required third line ART**

Data collected by: \_\_\_\_\_

Patient code: \_\_\_\_\_

Date of birth: \_\_\_\_\_

Current age: \_\_\_\_\_

Clinician phone number: \_\_\_\_\_

ART site : \_\_\_\_\_

ART site code: \_\_\_\_\_

Date: \_\_\_\_\_

<b>Patient History</b>	<b>Instructions:</b> Please fill out the following chart, using the date line on the left side of the chart to mark the time of the test, ART regimen, adherence, weight, or OI and symptoms. Every line will not be completely filled out for each date: For example: when a patient receives a CD4 test, they may not receive a VL test on the same date. Note all ART regimens and when the patient changed regimens. Please attach resistance testing results.					
Date	ART Regimen	CD4 Test Result	Viral Load Test Result	Adherence	Weight	OI and symptoms

**Annex 12: Sexual maturity rating (Tanner Staging Index) for adolescents**

Stage	Female				Male				
	Age range (years)	Breast growth	Pubic hair growth	Other changes	Age range (years)	Testes growth	Penis growth	Pubic hair growth	Other changes
<b>I</b>	0–15	Pre-adolescent	None	Pre-adolescent	0–15	Pre-adolescent testes ( $\leq 2.5$ cm)	Pre-adolescent	None	Pre-adolescent
<b>II</b>	8–15	Breast budding (thelarche); areolar hyperplasia with small amount of breast tissue	Long downy pubic hair near the labia, often appearing with breast budding or several weeks or months later	Peak growth velocity often occurs soon after stage II	10–15	Enlargement of testes; pigmentation of scrotal sac	Minimal or no enlargement	Long downy hair, often appearing several months after testicular growth; variable pattern noted with pubarche	Not applicable
<b>III</b>	10–15	Further enlargement of breast tissue and areola, with no separation of their contours	Increase in amount and pigmentation of hair	Menarche occurs in 2% of girls late in stage III	10.5–16.5	Further enlargement	Significant enlargement, especially in diameter	Increase in amount; curling	Not applicable

Stage	Female				Male				
	Age range (years)	Breast growth	Pubic hair growth	Other changes	Age range (years)	Testes growth	Penis growth	Pubic hair growth	Other changes
<b>IV</b>	10–17	Separation of contours; areola and nipple form secondary mound above breast tissue	Adult in type but not in distribution	Menarche occurs in most girls in stage IV, 1–3 years after thelarche	Variable: 12–17	Further enlargement	Further enlargement, especially in diameter	Adult in type but not in distribution	Development of axillary hair and some facial hair
<b>V</b>	12.5–18	Large breast with single contour	Adult in distribution	Menarche occurs in 10% of girls in stage V.	13–18	Adult in size	Adult in size	Adult in distribution (medial aspects of thighs; linea alba)	Body hair continues to grow and muscles continue to increase in size for several months to years; 20% of boys reach peak growth velocity during this period

Source: WHO. *Antiretroviral Therapy of HIV Infection in Infants and Children in Resource-Limited Settings: Towards Universal Access, 2006.*

### Annex 13: Child well-being assessment tool

Statement	None of the Time	Some of the Time	All of the Time
<b>Nutrition</b>			
1. I eat at least two meals a day with at least one meal including some meat and vegetables	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. I have less to eat than other members of my household	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>Education</b>			
1. I attend school regularly	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. I have the materials I need to do my class work	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. I like school	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>Financial security</b>			
1. My family has enough money to buy the things we need	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>Physical health and well-being</b>			
1. I feel strong and healthy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. I worry about my health	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. I am growing as well as other kids my age	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>Mental health and social connection</b>			
1. I am as happy as other kids my age	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. I feel optimistic about my future	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. There is an adult at home (e.g., parent/guardian) or in the community (e.g., neighbor) whom I trust and who supports me emotionally	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. I have at least one friend with whom I can share a secret and whom I trust	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>Pressure, harms, and sexual health</b>			
1. I understand the changes my body goes through during puberty (adolescence)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. I know how a girl can become pregnant and how to prevent that from happening	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. I know how to avoid getting HIV	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. I can resist pressure to do things that are harmful	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. I feel like I can make my own decisions about things that are important to me	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. My body is sometimes abused, for example I sometimes experience strong hitting or beating or bad touch.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Statement	None of the Time	Some of the Time	All of the Time
7. I do things that can put me at-risk of getting HIV or getting pregnant (girls)/or making someone pregnant (boys)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

## **Annex 14: Components of youth friendly services**

Youth-friendly services should be offered at all PAC and Adult sites where adolescents are receiving care (both pediatric and adult). Components of youth-friendly services could include (from Advocates for Youth: Serving HIV Positive Adolescents):

### **Designing Youth Friendly Facilities:**

- To assure youth's privacy, set aside a separate space for their services, or, if that is not possible, set aside some hours just for youth, in the late afternoon or evening.
- During the times set aside for youth, create a feeling that is welcoming, youthful, informal, and appropriate for the youth using the services.

### **Designing Youth Friendly Services:**

- Some sites may train youth as peer educators.
- Schedule appointments to minimize waiting time and crowding in the waiting rooms.
- Permit youth to walk-in for services without an appointment and reserve appointment spaces for youth in the evening and or after school.
- Ensure that counseling spaces are private and that others cannot overhear.
- Maintain adequate supplies and a variety of contraceptive methods.
- Whenever possible, provide contraception to young women without restrictions.
- Easy access or referral to reproductive health services or family health clinics or other facilities such as RHAC clinics, and Marie Stopes International clinics
- Allow clients' partners or friends to join if the patient wishes to be accompanied by them
- Invite adolescents to mmm groups
- Each out with education to ensure young people are aware of the importance of sexual health care.
- Inform youth about available services and assure them of confidentiality.

### **Regarding youth friendly attitudes:**

- Treat young people as respectfully as adults.
- Avoid judging young people's behavior.
- Work to develop solid, mutually trusting relationships with them.
- Provide all staff with ongoing training in adolescent development, understanding young people's needs and concerns, and treating youth confidentially and respectfully. Staff may need assistance in recognizing and changing attitudes that pose barriers to youth.
- Encourage counselors to spend as much time as necessary with each adolescent client in order to address all of her/his concerns.
- Provide adequate Time for Client and Provider Interaction

**Annex 15: Photos of oral and skin lesions in HIV-infected children**



Pruritic Papular Eruption



Molluscum Contagiosum with Giant



Cryptococcosis



Penicilliosis



Herpes Simplex Virus



Oral Human Papilloma Virus

Images courtesy of: AIDS Images Library [www.aidsimages.ch](http://www.aidsimages.ch)

**Annex 16: WHO growth monitoring tables and charts**

WHO Child Growth Standards 2006, Weight for Length (Up to 87 cm)								
GIRLS				length (cm)	BOYS			
weight (kg)	weight (kg)	weight (kg)	weight (kg)		weight (kg)	weight (kg)	weight (kg)	weight (kg)
-3SD	-2SD	-1 SD	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				Height (cm)	BOYS			
weight (kg)	weight (kg)	weight (kg)	weight (kg)		weight (kg)	weight (kg)	weight (kg)	weight (kg)
-3 SD	-2 SD	-1 SD	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

**Annex 17: Table of Opportunistic Infection Symptoms, Diagnosis, and Treatment**

Diagnosis	Symptoms	Workup	Treatment																		
<b>Mycobacterial Diseases</b>																					
Tuberculosis	<ul style="list-style-type: none"> <li>• Continuous cough of &gt;2 weeks duration</li> <li>• New loss of weight or failure to thrive</li> <li>• Persistent fever for &gt;2 weeks duration</li> <li>• Painless enlarged lymph nodes in the neck</li> </ul>	<ul style="list-style-type: none"> <li>• History of TB contact?</li> <li>• Chest x-ray, TST</li> <li>• Symptom directed:               <ul style="list-style-type: none"> <li>- Abdominal U/S</li> <li>- Lumbar puncture</li> <li>- Retina exam</li> <li>- Tissue aspirate:                   <ul style="list-style-type: none"> <li>▪ Lymph node</li> <li>▪ Bone/joint</li> <li>▪ Bone marrow</li> </ul> </li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• All forms of TB other than TB meningitis or osteoarticular TB:               <ul style="list-style-type: none"> <li>- 2 RHZE/4 RH</li> </ul> </li> <li>• TB meningitis/osteoarticular TB:               <ul style="list-style-type: none"> <li>- 2 RHZS/ 4 – 10 RH</li> <li>- Prednisolone 2 mg/kg x28d. if TB meningitis</li> </ul> </li> <li>• Consider adding azithromycin 10 mg/kg daily if CD4 below age-related MAC threshold</li> </ul> <table border="1" data-bbox="1525 730 2069 1248" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th data-bbox="1525 730 1740 906">Drug</th> <th data-bbox="1740 730 1917 906">Daily dosage in mg/kg (range)</th> <th data-bbox="1917 730 2069 906">Maximum dose/day</th> </tr> </thead> <tbody> <tr> <td data-bbox="1525 906 1740 954">Rifampicin (R)</td> <td data-bbox="1740 906 1917 954">15 (10-20)</td> <td data-bbox="1917 906 2069 954">600 mg</td> </tr> <tr> <td data-bbox="1525 954 1740 1002">Isoniazid (H)</td> <td data-bbox="1740 954 1917 1002">10 (7-15)</td> <td data-bbox="1917 954 2069 1002">300 mg</td> </tr> <tr> <td data-bbox="1525 1002 1740 1082">Pyrazinamide (Z)</td> <td data-bbox="1740 1002 1917 1082">35 (30-40)</td> <td data-bbox="1917 1002 2069 1082">2 g</td> </tr> <tr> <td data-bbox="1525 1082 1740 1161">Ethambutol (E)</td> <td data-bbox="1740 1082 1917 1161">20 (15-25)</td> <td data-bbox="1917 1082 2069 1161">1 g</td> </tr> <tr> <td data-bbox="1525 1161 1740 1248">Streptomycin (S)</td> <td data-bbox="1740 1161 1917 1248">15 (12-18)</td> <td data-bbox="1917 1161 2069 1248">1 g</td> </tr> </tbody> </table>	Drug	Daily dosage in mg/kg (range)	Maximum dose/day	Rifampicin (R)	15 (10-20)	600 mg	Isoniazid (H)	10 (7-15)	300 mg	Pyrazinamide (Z)	35 (30-40)	2 g	Ethambutol (E)	20 (15-25)	1 g	Streptomycin (S)	15 (12-18)	1 g
Drug	Daily dosage in mg/kg (range)	Maximum dose/day																			
Rifampicin (R)	15 (10-20)	600 mg																			
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Pyrazinamide (Z)	35 (30-40)	2 g																			
Ethambutol (E)	20 (15-25)	1 g																			
Streptomycin (S)	15 (12-18)	1 g																			

BCG infection	<ul style="list-style-type: none"> <li>• Abscess or ulceration at the vaccination site</li> <li>• Lymphadenitis in the axilla, supraclavicular area, or neck on same side as BCG vaccination</li> <li>• Disseminated BCG <ul style="list-style-type: none"> <li>○ Fever, weight loss</li> </ul> </li> <li>• Bone infection</li> <li>• Erythema nodosum, iritis, lupus vulgaris</li> </ul>	<ul style="list-style-type: none"> <li>• Chest x-ray</li> <li>• Lymph node aspirate</li> <li>• Retina exam</li> <li>• Culture is important to distinguish from TB</li> </ul>	<ul style="list-style-type: none"> <li>• 6 RHE <ul style="list-style-type: none"> <li>- Ensure dosed at weight-based upper limit (higher than usual for TB)</li> <li>- Consider 2 RHZE/ 4 RHE to treat BCG and TB if diagnosis uncertain and culture not available</li> </ul> </li> </ul>
<i>Mycobacterium avium</i> complex	<ul style="list-style-type: none"> <li>• Persistent or recurrent fever</li> <li>• Weight loss/Failure to thrive</li> <li>• Sweats, fatigue</li> <li>• Persistent diarrhea or recurrent abdominal pain</li> <li>• Lymphadenopathy, hepatomegaly, and splenomegaly</li> </ul>	<ul style="list-style-type: none"> <li>• CBC and LFTs <ul style="list-style-type: none"> <li>○ Pancytopenia, high alkaline phosphatase</li> </ul> </li> <li>• Lymph node aspirate for smear and culture</li> <li>• Bone marrow aspirate</li> </ul>	<ul style="list-style-type: none"> <li>• Azithromycin 10mg/kg PO daily, <i>and</i></li> <li>• Ethambutol 15 mg/kg PO daily, +/-</li> <li>• Rifampicin 15 mg/kg PO daily</li> <li>• All x 12 months, then</li> <li>• Azithromycin 5 mg/kg and ethambutol 15 mg/kg daily until CD4 above age-related cutoff on ART</li> <li>• Age-related CD4 risk for MAC: <ul style="list-style-type: none"> <li>- &lt;12 months: &lt;750 cells/mm<sup>3</sup></li> <li>- 12-24 months: &lt;500 cells/mm<sup>3</sup></li> <li>- 2 – 5 years: &lt;75 cells/mm<sup>3</sup></li> <li>- ≥6 years: &lt;50 cells/mm<sup>3</sup></li> </ul> </li> </ul>
<b>Fungal Diseases</b>			

Cryptococcal meningitis	<ul style="list-style-type: none"> <li>• Fever and headache</li> <li>• Vision change</li> <li>• Neck stiffness, cranial nerve palsy (late stages)</li> <li>• Usually age &gt;6 years and CD4 &lt;100 cells/ mm<sup>3</sup></li> </ul>	<ul style="list-style-type: none"> <li>• CBC, chemistry, LFT</li> <li>• Blood culture</li> <li>• CSF evaluation for: <ul style="list-style-type: none"> <li>- Opening pressure</li> <li>- CSF Gram stain and culture</li> <li>- India (Chinese) ink stain</li> <li>- Cryptococcal antigen</li> </ul> </li> <li>• Ophthalmologic exam</li> <li>• Chest X-Ray</li> </ul>	<ul style="list-style-type: none"> <li>• Pre-emptive fluids</li> <li>• Amphotericin B 1 mg/kg IV daily x 2 weeks, <i>then</i></li> <li>• Fluconazole 12 mg/kg PO daily x 8 weeks, <i>then</i></li> <li>• Fluconazole 6mg/kg/day (maximum 200mg) until age ≥5 years and CD4 &gt;100 cells/mm<sup>3</sup> for &gt;6 months on adherent ART</li> <li>• If opening pressure &gt;20 cm CSF: <ul style="list-style-type: none"> <li>- Remove CSF until below 20 cm or 50% of initial opening pressure</li> <li>- Repeat daily until opening pressure below 20 cm CSF</li> <li>- Do NOT use steroids or diuretics to decrease intracranial pressure</li> <li>- Consider delaying ART until after induction therapy is complete</li> </ul> </li> </ul>
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Histoplasmosis	<ul style="list-style-type: none"> <li>• Acute pulmonary histoplasmosis: <ul style="list-style-type: none"> <li>- Cough, fever, malaise, chills, myalgia, anorexia and chest pain</li> </ul> </li> <li>• Disseminated histoplasmosis: <ul style="list-style-type: none"> <li>- Prolonged fever</li> <li>- Weight loss, failure to thrive</li> <li>- Hepatosplenomegaly, lymphadenopathy</li> <li>- Large oral ulcerations</li> <li>- Discrete fungating or umbilicated skin papules or masses</li> <li>- Respiratory symptoms with cough, respiratory distress.</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Pancytopenia, elevated transaminases, and very elevated LDH</li> <li>• Chest X-Ray may show miliary pattern</li> <li>• Sometimes can see yeast on peripheral blood smear</li> <li>• Isolation of the fungus from blood, skin lesion, or bone marrow using culture is diagnostic</li> <li>• Silver staining of tissue biopsies may reveal yeast forms.</li> </ul>	<ul style="list-style-type: none"> <li>• Amphotericin B 1 mg/kg/day IV for at least 2 weeks, <i>followed by</i></li> <li>• Itraconazole 5 mg/kg PO twice daily or Fluconazole 6-8 mg/kg daily x 12 months</li> <li>• Non-hospitalized patients may be treated with itraconazole or fluconazole without amphotericin B</li> <li>• Therapy can be stopped if: <ul style="list-style-type: none"> <li>- &gt;5 years of age</li> <li>- &gt;12 months of antifungal treatment</li> <li>- CD4 &gt;15% and &gt;150 cells/mm<sup>3</sup> after 6 months of adherent ART</li> </ul> </li> <li>• Restart itraconazole or fluconazole in if the CD4 count falls below the thresholds above.</li> </ul>
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<p>Penicilliosis</p>	<ul style="list-style-type: none"> <li>• Disseminated disease with fever, anemia, weight loss, lymphadenopathy, pneumonia, and/or hepatosplenomegaly</li> <li>• Papular, umbilicated or ulcerating skin lesions are common and may be mistaken for Molluscum contagiosum or <i>Cryptococcus</i></li> <li>• CNS disease with brain abscess has been reported</li> </ul>	<ul style="list-style-type: none"> <li>• Pancytopenia, elevated liver enzymes, high alkaline phosphatase</li> <li>• Nodular or cavitory lesions on chest X-ray, may be confused with TB</li> <li>• Fungal identification from blood culture, skin lesions, lymph node, or bone marrow aspirate</li> </ul>	<ul style="list-style-type: none"> <li>• Amphotericin B 0.7 mg/kg IV daily for at least 2 weeks, <i>followed by</i></li> <li>• Itraconazole 5 mg/kg PO twice daily for 10 weeks</li> <li>• Use fluconazole 8 mg/kg PO twice daily if itraconazole is not available</li> <li>• Itraconazole 5 mg/kg PO daily should be given until immune restoration occurs.</li> <li>• Secondary prophylaxis may be discontinued if: <ul style="list-style-type: none"> <li>- &gt;5 years of age</li> <li>- &gt;12 weeks of antifungal treatment</li> <li>- Immunological restoration with CD4 &gt;150 cells/mm<sup>3</sup> after 6 months of ART</li> </ul> </li> </ul>
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<p><i>Pneumocystis jiroveci</i> pneumonia (PCP)</p>	<ul style="list-style-type: none"> <li>• Fever, tachypnea, dyspnea, and cough, usually infant 2 – 6 months</li> <li>- CD4 does not determine risk in infants</li> <li>• Abrupt or slow onset</li> <li>• Poor feeding or weight loss</li> <li>• Hypoxia often severe, room-air O<sub>2</sub> below 85% common</li> </ul>	<ul style="list-style-type: none"> <li>• CXR: bilateral hazy, ‘ground-grass’, granular, <b>or normal</b>.</li> <li>• Lung sounds often only mildly abnormal</li> <li>• LDH usually elevated</li> <li>• Sputum silver stain or DFA where available</li> </ul>	<ul style="list-style-type: none"> <li>• Cotrimoxazole 15-20/75-100 mg/kg/day, 3-4 divided doses IV for 21 days.</li> <li>- May add clindamycin 30 – 40 mg/kg/day divided q8 hours for severe disease</li> </ul> <p><u>Corticosteroids</u></p> <ul style="list-style-type: none"> <li>• Indication: <ul style="list-style-type: none"> <li>- PaO<sub>2</sub> &lt;70 mmHg, alveolar-arterial gradient &gt;35 mmHg, or O<sub>2</sub> saturation &lt;90%</li> </ul> </li> <li>• Initial doses: <ul style="list-style-type: none"> <li>- Prednisone 1mg/kg/12h (max 40mg/12h)</li> <li>- Methylprednisolone iv 1 mg/kg/6h</li> </ul> </li> </ul>
<p><b>Parasitic Diseases</b></p>			
<p>Toxoplasmosis</p>	<ul style="list-style-type: none"> <li>• Acute onset over &lt;1 week</li> <li>• Focal neurologic dysfunction, <i>and/or</i></li> <li>• New seizures, <i>plus</i></li> <li>• Fever and headache or altered level of alertness</li> </ul>	<ul style="list-style-type: none"> <li>• CT with contrast shows ring-enhancing brain lesions</li> <li>• Retina exam may show white exudates</li> <li>• Toxoplasma IgG antibody usually positive (where available)</li> <li>• Empiric treatment usually necessary</li> </ul>	<ul style="list-style-type: none"> <li>• Preferred: <ul style="list-style-type: none"> <li>- Pyrimethamine loading dose 2mg/kg/day (max 50mg) for 3 days then maintenance 1 mg/kg/d (max 25 mg), plus</li> <li>- Sulfadiazine 100 mg/kg/day divided qid, plus</li> <li>- Folinic acid 5-20 mg 3 times weekly</li> <li>- All for 6 weeks</li> </ul> </li> <li>• 2nd line therapy: <ul style="list-style-type: none"> <li>- High dose CTX (10-15/50-75 mg/kg daily) for 6 weeks</li> </ul> </li> <li>• Dexamethasone 0.6mg/kg/day for</li> </ul>

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

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