Kingdom of Cambodia
Nation Religion King

Ministry of Health

National Guidelines on Diagnosis and Antiretroviral Treatment of HIV Infection in Infants, Children and Adolescents in Cambodia

4th Edition
August 2016

National Center for HIV/AIDS, Dermatology and STD

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PREFACE

These guidelines are an important part of the National Center for HIV/AIDS, Dermatology and STD (NCHADS) strategy to eliminate mother to child transmission (MTCT) of HIV and reduce HIV-related mortality. The Strategic Plan for HIV/AIDS and STI Prevention and Control in the Health Sector for Cambodia 2015-2020 specifically highlights the need to improve case detection of HIV+ pregnant women, improve access to the full package of PMTCT services, and ensure timely access to HIV-exposed infant services, and enrolment in Pediatric AIDS Care (PAC).

The first version of the National Guidelines for the Use of Pediatric Antiretroviral Therapy was published in October 2004 to ensure high quality HIV/AIDS care and treatment for Cambodian children. The guidelines were revised in November 2007 and 2012 as PAC sites were greatly expanded. As of 2014, there are 35 PAC sites operating in 23 provinces and newly established sites have integrated pediatric care and adult AIDS care to ensure wider coverage.

During a series of technical working group meetings and at a consultative workshop, staff from NCHADS, the National Pediatric Hospital, the University of Health Science, Angkor Hospital for Children, clinical mentors, UN agencies, and other non-governmental organization (NGO) partners reviewed and revised the 2012 guidelines. Their comments, as well as clinical experience from pediatric AIDS care sites in Cambodia, were incorporated in the revised edition of the guidelines. These guidelines were updated to align with latest WHO recommendations on the use of Antiretroviral Drugs for Treating and Preventing HIV Infection.

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

Phnom Penh, 22 / August, 2016

For Minister of Health

Prof. ENG HUOT
SECRETARY OF STATE

ACKNOWLEDGEMENTS

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

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

I would like to take this special occasion to thank the staff of NCHADS (Dr. Seng Sopheap, Dr. Samreth Sovannarith, and Dr. Ngauv Bora) for coordinating the revision of these guidelines. I also want to express my gratitude to the pediatricians from the National Pediatric Hospital (Dr. Huot Chantheany and Dr. Sam Sophan), the University of Health Science (Prof. Ung Vibol), Angkor Hospital for Children (Dr. Chhraing Seng Tray), Battambang Referral Hospital (Dr. Chea Peuv), FHI360 (Dr. Laurent Ferradini and Amy Weissman), US-CDC (Dr. Perry Killam), Clinton Health Access Initiative (Ms. Kiira Gustafson, Mrs. Emily Welle, and Dr. Herb Harwell), and the United Nations Children's Fund (UNICEF, Mrs. Chin Sedtha), MAGNA (Ms. Denisa Augustinova), and Dr. Tammy Meyers who have actively participated in revising these guidelines. Lastly, I would like thank to all partners, civil societies and partners who have provided care, treatment and support to HIV-infected children in Cambodia.

Phnom Penh, 15 August, 2016
Director of the National Center for
HIV/AIDS, Dermatology and STD

Dr. Ly Penh Sun

ABBREVIATIONS AND ACRONYMS

3TC	*Lamivudine*
ABC	*Abacavir*
AIDS	*Acquired Immunodeficiency Syndrome*
ALT	*Alanine Aminotransferase*
AST	*Aspartate Aminotransferase*
ART	*Antiretroviral Therapy*
ARV	*Antiretroviral drug(s)*
AZT	*Zidovudine*
CBC	*Complete Blood Count*
CD4	*T-CD4+ Lymphocyte*
CDC	*Center for Disease Control*
CENAT	*National Centre for Tuberculosis and Leprosy Control*
CK	*Creatine Kinase*
CMV	*Cytomegalovirus*
CNS	*Central Nervous System*
CrCl	*Creatinine Clearance*
CTX	*Cotrimoxazole*
DBS	*Dried Blood Spot*
DNA	*Deoxyribonucleic acid*
DOT	*Directly Observed Therapy*
EC	*Enteric Coated*
EFV	*Efavirenz*
EIA	*Enzyme immunoassay*
ELISA	*Enzyme linked immunosorbent assay*
EPTB	*Extra-pulmonary Tuberculosis*

ESRF	*End Stage Renal Failure (Dialysis dependent)*
FDC	*Fixed Dose Combination*
FHI	*Family Health International*
FTC	*Emtricitabine*
GI	*Gastrointestinal*
HAART	*Highly Active Antiretroviral Therapy*
HBsAg	*Hepatitis B Surface Antigen*
HBV	*Hepatitis B Virus*
HCV	*Hepatitis C Virus*
HGC	*Hard Gelatin Capsules*
HIV	*Human Immunodeficiency Virus*
HLA	*Human Leukocyte Antigen*
HSS	*HIV Sentinel Survey*
HSV	*Herpes Simplex Virus*
IPT	*Isoniazid Preventive Therapy*
KBH	*Kantha Bopha Hospital*
KHANA	*Khmer HIV/AIDS NGO Alliance*
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*
LPV/R	*Lopinavir/ritonavir with extra ritonavir boosting in 1:1 ratio*
MAC	*Mycobacterium avium complex*
MTCT	*Mother to Child Transmission*
NCHADS	*National Center for HIV/AIDS, Dermatology and STD*

NMCHC	*National Maternal and Child Health Centre*
NNRTI	*Non-Nucleoside Reverse Transcriptase Inhibitor*
NRTI	*Nucleoside Reverse Transcriptase Inhibitor*
NPH	*National Pediatric Hospital*
NVP	*Nevirapine*
OI	*HIV related Opportunistic Infection*
PCP	*Pneumocystis jiroveci pneumonia*
PCR	*Polymerase chain reaction*
PLHA	*Person/people living with HIV/AIDS*
PI	*Protease Inhibitor*
PID	*Pelvic Inflammatory Disease*
PMTCT	*Prevention of Mother to Child Transmission*
PPD	*Purified Protein Derivative (skin test for tuberculosis)*
PPE	*Papular Pruritic Eruption*
PTB	*Pulmonary Tuberculosis*
R	*Ritonavir (when given in association with other PIs for boosting effect)*
RTV	*Ritonavir*
RNA	*Ribonucleic acid*
SGC	*Soft Gelatin Capsules*
STI	*Sexually Transmitted Infection*
TAMs	*Thymidine analog mutations*
TB	*Tuberculosis*
TDF	*Tenofovir disoproxil fumarate*
TST	*Tuberculin Skin Test*
VCCT	*HIV voluntary confidential counseling and testing*
UNICEF	*The United Nations Children's Fund*
VDRL	*Venereal Diseases Reference Laboratory (refers to a test for syphilis)*
VL	*Plasma HIV Viral Load*
WHO	*World Health Organization*

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 2% in 1998 to 0.7 % in 2014. In 2014, it was estimated that over 75,000 people are living with HIV/AIDS, including 28,518 women over 14 years-old who were receiving antiretroviral therapy (ART).1,2 In addition, there are an estimated 4,549 children living with HIV of whom 3,987 were receiving antiretroviral therapy (ART) at the end of 2014.3 Despite diminishing prevalence rates, the need for HIV/AIDS treatment and care will be considerable 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 5th edition of the National Guidelines for the Use of Pediatric Antiretroviral Therapy, which were originally approved by the Ministry of Health in October 2004 and revised in 2007, 2010 and 2012.

The 2015 revision of the Guidelines for Diagnosis and Antiretroviral Treatment of HIV Infection in Infants, Children and Adolescents in Cambodia is a co-product of NCHADS, National Pediatric Hospital, Angkor Hospital for Children, UNICEF, CHAI, 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 2013 WHO Consolidated Guidelines on the use of Antiretroviral Drugs for Treating and Preventing HIV Infection and the recent announcement in July 2015 of planned release of updated guidelines by WHO later in 2015.[4].[5] WHO continues to review guidelines and updated recommendations after the printing of these guidelines will be communicated to clinicians by NCHADS.

What is new in the guidelines?

- **Birth HIV virological testing for all HIV-exposed infants** and repeat testing if negative at 6 weeks or immediate confirmatory testing if first test is positive.
- **Cotrimoxazole prophylaxis for all children diagnosed with HIV continued until 15 years and/or until they transition to adult care** unless found to be HIV PCR negative or

[1] AEM modelling, 2014.
[2] NCHADS ART Facility Report, 2014.
[3] Ibid.
[4] Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach June 2013.
[5] Doherty M *New directions in the 2015 WHO Consolidated ARV Guidelines*. Eighth International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2015), Vancouver, Canada, presentation SUSA0608, 2015

cotrimoxazole toxicity suspected.

- Fluconazole prophylaxis is **no longer recommended** as primary prophylaxis to prevent cryptococcal disease.
- **All HIV-infected children <15 years-old should be started on ART regardless of CD4.**
- **All HIV-infected children <3 years and 10kg should preferably be started on a regimen containing LPV/r** regardless of prior exposure to ART for PMTCT.
- **HIV-infected children who achieve virological suppression confirmed after at least 1 year of age may be switched from LPV/r to an NNRTI-based regimen** provided a viral load will be done 3 months after the switch to assess continued virological success.
- **EFV is the preferred NNRTI option for children >3 years and >10kg.**
- **ABC is preferred as part of the NRTI backbone in first line therapy for children <10 years or ≤ 35 kg**, with AZT as an alternative.
- **TDF** is recommended as part of the NRTI backbone for **children older than 10 years and >35kg.**
- **Viral load testing is the diagnostic tool of choice for monitoring patients** on ART for treatment failure.
- A committee may be established to help guide decisions on the use of third line therapies. **Consult a mentor or the Pediatric AIDS Care Technical Working Group (PAC TWG) if a case is considered eligible for third line therapy.**
- **A comprehensive psychosocial support section has been included with emphasis on the needs of adolescents.** All healthcare workers are expected to familiarise themselves with this section and provide the necessary support to complement the work of designated counsellors.

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. Job aides and readily accessible visual tools including a pocketbook reference guide to assist with patient management have been developed to complement the guidelines. Training on the updated guidelines will also occur.

2. PATHOPYSIOLOGY 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.

HIV transmission to children

HIV is usually 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

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.[6]

[6] 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

In Cambodia, the estimated transmission rate of HIV to infants has decreased from 13.6% in 2010 to 7% in 2014. In 2014, 94% of pregnant women attended ANC in Cambodia; however, only 75% of pregnant women received HIV testing at ANC, and 78% HIV+ pregnant women received ART in 2014. There are also gaps in services for HIV-exposed infants: only 39% HIV-exposed infants receiving timely EID testing <2 months from birth in 2014; whereas 68% of HIV-exposed infants received DNA-PCR testing anytime, showing a delay in testing.

More information on the eMTCT guidelines can be found in *National Guidelines for the use of Antiretroviral Therapy in Adults and Adolescents* and in the *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*.

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 in 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 should continue infant prophylaxis with NVP alone for an additional 6 weeks (total of 12 weeks of prophylaxis)[7].
- **High-risk infants are defined as those[7]:**
    - 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 with incident HIV infection during pregnancy or breastfeeding, OR
    - identified for the first time during the postpartum period, with or without a negative HIV test prenatally.
- Table 3 Summarizes maternal and infant ARV prophylaxis for different clinical scenarios and Table 4 summarizes dosages for NVP and AZT.
- 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[8].
- Mothers living with HIV and healthcare workers can be reassured that ARV treatment is

[7] Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, Nov. 2015, Policy brief, What's new? WHO, 2015.
[8] Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, WHO, 2016

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.

Table 2. Expanded Program on Immunization (EPI) Vaccination Schedule

CAMBODIA VACCINATION SCHEDULE FOR CHILDREN

Vaccine	Route	Age					
		Birth	6 weeks	10 weeks	14 weeks	9 months	18 months
BCG	Intradermal	√					
Hepatitis B	Intramuscular	√					
Oral polio	Oral		√	√	√		
DTP-HepB-Hib (pentavalent)	Intramuscular		√	√	√		
PCV13 (pneumococcal)	Intramuscular		√	√	√		
IPV (inactivated polio vaccine)	subcutaneous				√		
Measles/Rubella MR (M9)	subcutaneous					√	
Measles (M18)	subcutaneous						√
JE (Japanese encephalitis)	subcutaneous					√	

Table 3. Nevirapine Dosing (10mg/ml):

Infant age	Weight at birth	Dosing of NVP	Dosing of AZT
From Birth to 6 weeks (Breastfeeding or non-breast feeding infants)	2000–2499g *	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 Maternal and Infant ARV Prophylaxis

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

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

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)

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 below).
- A negative antibody detection test at any age excludes HIV infection, if the child was last

breastfed ≥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 ≥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 Box 1), and where antibody testing is available. If test kits are unavailable, refer to the nearest VCCT, healthcenter, Referral Hospital, or Provincial Hospital where HIV testing can be performed.

HIV PCR TEST:

1. 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 $1mm^3$ of blood and is used for monitoring the amount of HIV in the blood in response to ART). Either HIV DNA or RNA PCR can be used for the initial detection of the HIV virus in the infant.

- 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 obtained 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.

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.

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

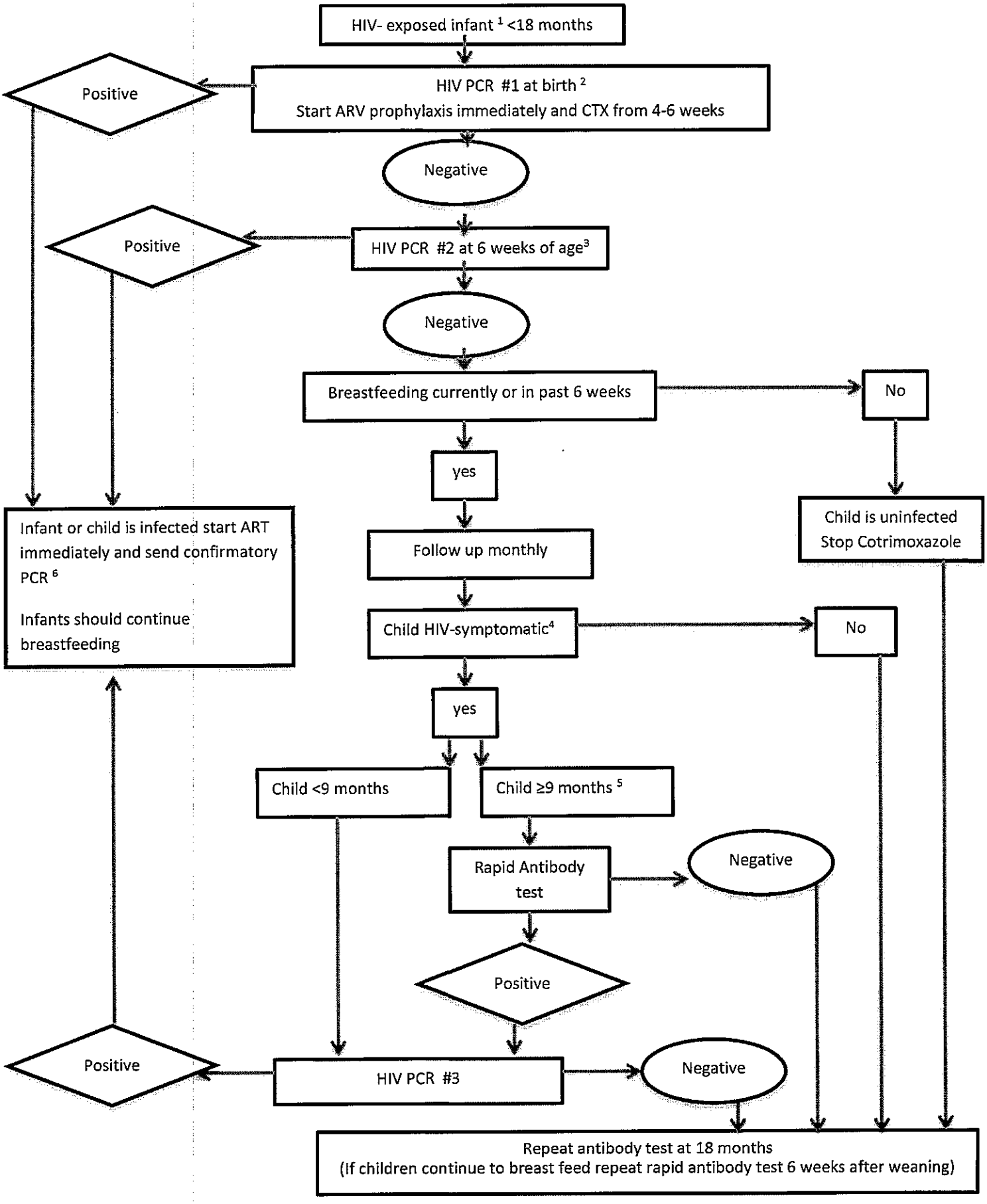
(Figure 1)

- All HIV-exposed infants require **HIV PCR testing at birth**[9] and ARV prophylaxis should be started.
- If the HIV PCR test is positive, this test should be repeated to confirm HIV-infection, and **ART should be started as quickly as possible** and ARV prophylaxis should be stopped. Do not delay ART while awaiting the result of the confirmatory test.
- **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.
- If the initial birth HIV PCR test is negative, a **further HIV PCR test should be conducted at 6 weeks of age,** or at their first contact with the healthcare system after the age of 6 weeks.
- A positive HIV PCR will require a repeat HIV PCR test for confirmation, which can be performed at the same time that ART is started. ART initiation should not be delayed while waiting for the results of this confirmatory HIV PCR test.
- 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
    - Infants ≥ 9 months can first have an antibody test. If this antibody test is positive, a HIV PCR test is indicated. If the 9 month antibody test is negative, the child is considered uninfected as long as weaning occurred ≥6 weeks prior to the test.

- Any infants <18 months who have signs and symptoms of HIV (Box 1) or are found to be exposed after birth, require HIV PCR testing at the earliest possible opportunity (if ≥9 months and not breastfeeding for ≥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 must remain on CTX until HIV infection is ruled-out with a negative HIV DNA PCR or antibody test ≥6 weeks after stopping breastfeeding.

[9] 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.

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



Footnotes for Algorithm

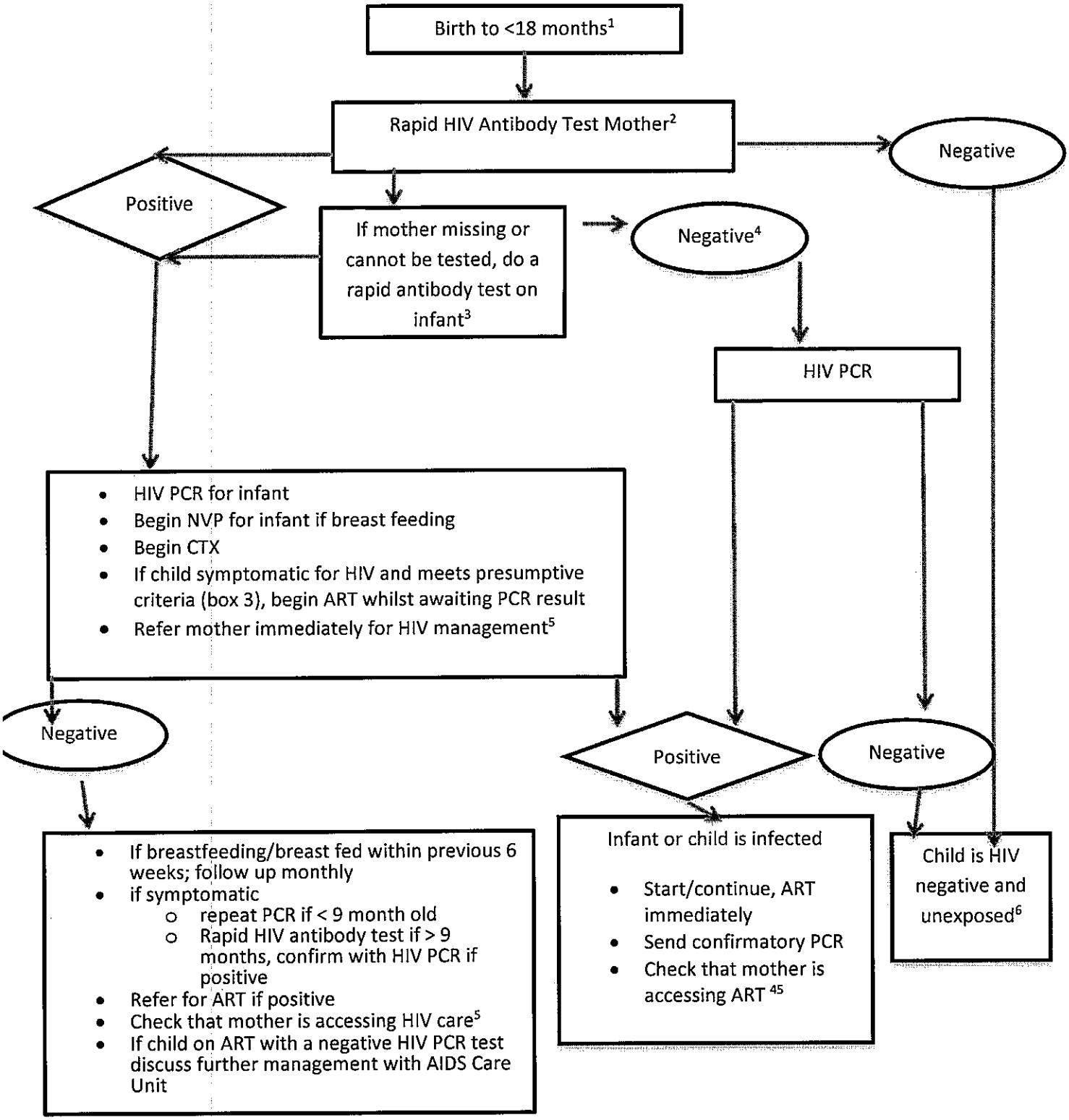
1. All women should be offered HIV testing during pregnancy or delivery. Infants of HIV seropositive mothers are considered HIV-exposed. Some women may not be identified before the baby is born. Healthcare workers should ask mothers whether they have been tested when they bring their babies for EPI visits, 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.

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

(Figure 2)

- **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 Box 1 and Box 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. (Box 3)
- 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 antibodies are 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 ≥6 weeks after the complete cessation of breastfeeding. Stop ARV prophylaxis and CTX.
    - Be sure to refer mothers for evaluation and treatment if they are found to have positive antibody tests. If a mother with HIV wishes to breastfeed she should receive 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

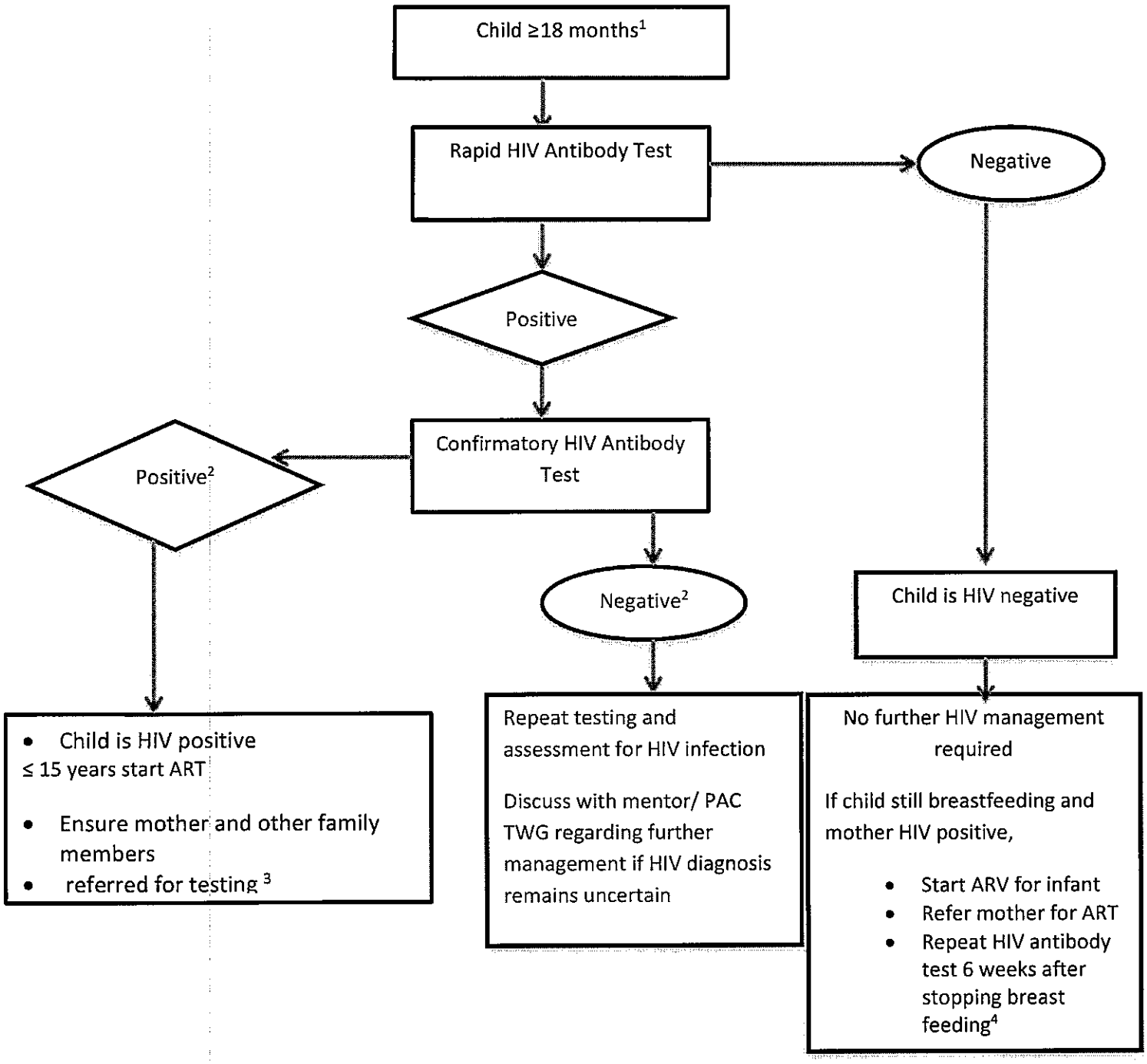
Children ≥18 months

(Figure 3)

- **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 Box 1 and Box 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 WITHIN 2 WEEKS OF DIAGNOSIS

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 the 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.

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 2nd or 3rd 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.

5. POST-EXPOSURE PROPHYLAXIS FOR CHILDREN EXPOSED TO HIV BY MEANS OTHER THAN MOTHER-TO-CHILD TRANSMISSION[10]

Children 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 breech in skin (e.g., open cuts or wounds) or direct contact with mucus 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 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 below section on adherence.)

[10] 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

Table 5. Treatment Recommendations for Post-Exposure Prophylaxis

Age	Preferred Treatment Regimen	Duration
Children <10 years <35Kg	ABC or AZT +3TC +LPV/r*	28 Days
Adolescents >10 years AND >35kg	TDF or ABC or AZT + 3TC + LPV/r or ATZ/r*	

* EFV may be used as an alternative to the protease inhibitors should there be a reason why these cannot be prescribed.

HIV testing following an exposure

Following an exposure, HIV testing should be conducted at baseline and, if negative, should be repeated at 3 months. Testing for infants, children and adolescents should receive a rapid antibody test. For infants <18 months of age, a positive HIV antibody test should be followed by an HIV PCR test. If an infant is HIV negative but with possible exposure from a maternal source, repeat testing should be completed 6 weeks or more after exposure.

Hepatitis B and C viruses (HBV/HCV) can be transmitted in similar ways to HIV and co-infection is common. All children in Cambodia should receive HBV vaccination as part of the routine vaccination schedule. Following an exposure it is important to enquire about prior HBV vaccination. HBV vaccine may be given as prophylaxis following an exposure for those who have not received this vaccine previously.

Sexually transmitted infections (STIs) such as syphilis, chlamydia, trichomoniasis, and gonococcal testing should also be conducted at family health clinics or NGO-run or private facilities such as RHAC or Marie Stopes International Clinics. Victims of sexual violence require a thorough medical examination documenting all injuries, and testing for medico legal purposes.

Pregnancy prophylaxis

Girls of child-bearing age 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.

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. See Annex 2 for guidance on how to manage children exposed to sexual violence.[11]

[11] Day, Kim and Jennifer Pierce-Weeks. 2013. The Clinical Management of Children and Adolescents Who Have Experienced

Box 1. Signs and symptoms of HIV disease in children with HIV infection

Common in HIV-infected children and uncommon in other children

- Recurrent severe pneumonia or severe bacterial infections
- Bronchiectasis
- Bilateral painless parotid swelling
- Recurrent or persistent oral candidiasis (thrush)
- Generalized lymphadenopathy or hepatosplenomegaly
- Recurrent or persistent unidentified fever
- Neurologic dysfunction of unexplained cause
- Herpes zoster
- Persistent generalized dermatitis
- Common in HIV-infected children and in HIV-uninfected children
- Anemia
- Chronic ear infections
- Recurrent or persistent diarrhea
- Severe pneumonia
- Tuberculosis
- Marasmus or failure to thrive
- 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

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

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

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

Starting ART in Children Less Than 18 Months without a Confirmed Diagnosis of HIV Infection

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

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-Based Prevention Care and Support volunteers to ensure access to maternal ART (Option B+) and follow-up of HIV-exposed infants to ensure appropriate testing and treatment.
- Infant testing as directed above and initiation of ARV prophylaxis from birth and start cotrimoxazole 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.

Recommendations for infant feeding

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.12 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 below Box 1.
  - In all cases, hygienic practices of bottle cleaning and sterilization should be taught to the mothers and caregivers of the baby.

After six months of age

- Mother should be encouraged to give complementary feeding to children from 6 months of age
- **HIV-negative mothers and women of unknown HIV status** should introduce complementary feeding and continue to breastfeed for up to 24 months or longer.
- **HIV-infected mothers whose infants are HIV-infected** (HIV-DNA PCR test positive), should introduce complementary feeding and continue to breastfeed, as recommended for the general population, up to 24 months or longer.
- **HIV-infected mothers whose infants are not HIV-infected** (HIV-DNA PCR test negative) **or are of unknown HIV status** should introduce appropriate complementary foods and continue breastfeeding for up to 24 months or longer[13] while mother continue taking ART for lifelong with fully supported for adherence[14] .
- 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 BF.
- Mothers living with HIV and healthcare workers can be reassured that shorter durations of BF less than 12 months are better than never initiating BF.

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[12] Cambodian National Interim Guidelines for the Management of Acute Malnutrition. Cambodia December 2011
[13] Breastfeeding should only stop once a nutritionally adequate and safe diet without breast milk can be provided
[14] Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, WHO, 2016

- Every effort should be made to determine the HIV status of women who have not yet been 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: 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 should be advised not to breastfed 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.

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 milk as a replacement feed to their HIV-uninfected infants or to infants who are of 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 below:

Box 4. Conditions required for safe formula feeding

Box 4: Measure for safe formula feeding: 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 diarrhoea and malnutrition, and,
- the mother or caregiver can, in the first six months, exclusively give infant formula milk, and the family is supportive of this practice, and
- the mother or caregiver can access health care that offers comprehensive child health services.

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

- 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 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 organisations.

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 (Table 6).

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).

Table 6. 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
All HIV-infected infants and children regardless of age or clinical stage of disease	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 cotrimoxazole if the child is anemic as cotrimoxazole may cause bone marrow suppression or if Grade 3/4 toxicity rash occurs (see Table 7). **Otherwise continue cotrimoxazole until children transition to adult care, regardless of ART or CD4 recovery**

Box 5. Dosage Recommendations for Cotrimoxazole Prophylaxis for HIV-exposed infants[15]

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

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

Management of cotrimoxazole-related rash is outlined in Table 7 below.

Table 7. Management of Cotrimoxazole-related Rash

Severity	Description	Management
Grade 1	Diffuse or patchy erythema May be pruritic	Continue cotrimoxazole Follow up in 3-4 days Consider antihistamines for symptom relief
Grade 2	Dry maculopapular rash May appear morbilliform Minimal exfoliation	Continue cotrimoxazole Follow up in 1-2 days Consider antihistamines for symptom relief

[15] Guidelines on post-exposure prophylaxis for HIV and the use of co-trimoxazol 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

Grade 3	Early bullae or mucosal ulceration	Discontinue cotrimoxazole immediately Hospitalize for supportive care **Never restart cotrimoxazole**
Grade 4	Toxic epidermal necrolysis or Stevens Johnson Syndrome	Discontinue cotrimoxazole immediately Hospitalize for supportive care **Never restart cotrimoxazole**

Fluconazole prophylaxis

Fluconazole prophylaxis is no longer recommended for adults or children with HIV as primary prophylaxis.[16] 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^2 (≥ 5 years of age) should be investigated for cryptococcal disease as outlined in the *National Guidelines for common and opportunistic infections in HIV infected children in Cambodia*.

Immunization, vitamin A, 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 (Table 2), vitamin A supplementations (Table 8), and deworming treatments (Table 9) 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 will be introduced shortly 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 schedule, see Table 2.

Table 8. 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

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

Table 9. Routine Deworming

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

7. NUTRITION IN HIV-INFECTED CHILDREN

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 7 Growth Charts). Consider and test for HIV infection in all infants or children with malnutrition (see Table 10 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*.[5]

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 10. Classification of Malnutrition in Children

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

Visible wasting?	No	No	Yes
Mid-upper arm circumference (age)			• <115 mm (≤60 months) • <129 mm (5 – 9 years) • <160mm (10 – 14 years)

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: 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 6).

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.

Severe Acute Malnutrition (SAM)

Children should be hospitalized if they have severe acute malnutrition (SAM), and any medical complications (see Table 11), are below 6 months of age, over 6 months with weight <4kg, bilateral pitting edema, weight loss on 3 consecutive occasions, or 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.[5]

Box 6. Energy goals for HIV-infected children with severe malnutrition

Energy goals for HIV-infected children with severe malnutrition

Stabilization phase (day 1 – 7)

- F75, goal 100 kcal/kg/day

Recovery phase

- F100 or Ready to Use Therapeutic Food (BP100)
  - 150 – 220 kcal/kg/day (age 6m – 5y)
  - 75 – 100 kcal/kg/day (age 6 – 9 years)
  - 60 – 90 kcal/kg/day (age 9 – 14 years)

Table 11. Medical Complications in Severe Acute Malnutrition Requiring Inpatient Care

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

8. TB/HIV CO-INFECTION

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, extrapulmonary 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 antituberculosis treatment
- Isoniazid preventive therapy (IPT)
- Infection control for TB

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

Isoniazid preventive therapy (IPT)

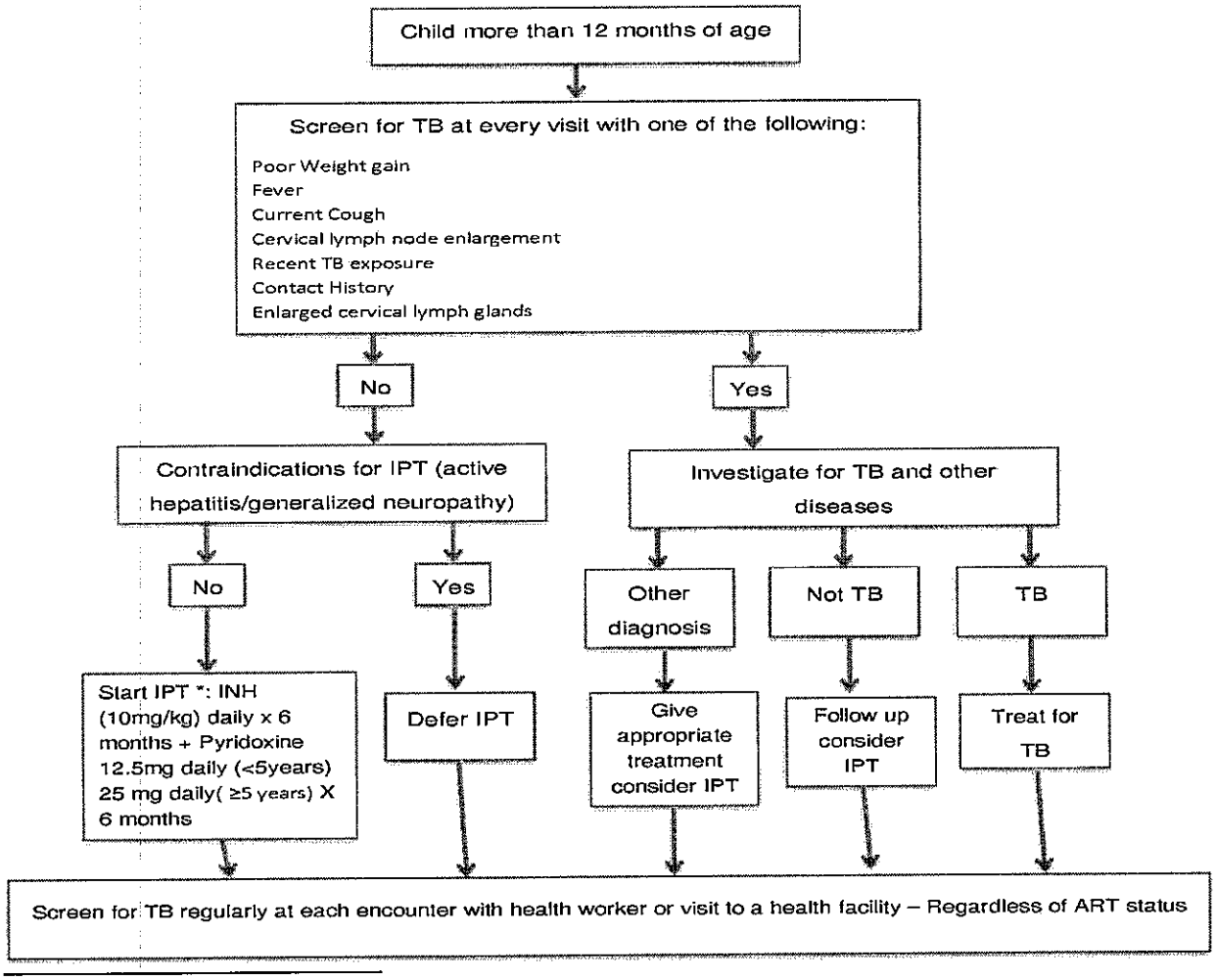
If children living with HIV have none of the above symptoms, they are considered unlikely to have active TB and those over 12 months of age are eligible for IPT (See Figure 4). In addition, children less than 12 months old with a household TB contact and all children living with HIV after a successful completion of TB disease treatment should receive IPT. IPT is only contraindicated in patients with:

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

IPT consists of administration of:
- INH: 10mg/kg (7-15mg/kg) daily for 6 months
- Pyridoxine: Age <5 years, 12.5 mg daily for 6 months
  Age ≥5 years, 25 mg daily for 6 months

In order to prevent other patients or clinic staff from being infected with TB, effective infection control measures should be in place.[17]

Figure 4. Isoniazid preventive therapy in children



[17] Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva, World Health Organization, 2011

*IPT contraindicated in the following circumstances

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

Diagnosis of active TB disease

The symptoms of active tuberculosis in young children are non-specific. Diagnosis of TB should be made according to *National Guidelines for the Diagnosis and Management of TB in Children in Cambodia*.[18]

Guidance on approach to diagnosis of TB in children

- Careful history (including history of TB contact and symptoms consistent with TB)
- Clinical examination (including growth assessment)
- Chest X-ray (if available)
- Bacteriological confirmation whenever possible (Xpert MTB/RIF is the preferred test)
- Investigations relevant for suspected pulmonary TB and suspected extrapulmonary TB

Clinical manifestations of tuberculosis in children

Children should be referred for active TB diagnosis if any one of the following is present:

- Living with patients who have active TB
- Failure to thrive
- Fever (remitting)
- Current cough (especially >2 weeks, unresponsive to standard therapy)
- Listlessness (lack of playfulness)
- Enlarged cervical lymph nodes

Other clinical manifestations of TB

- 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: Chest x-ray if available should be done. A child with TB may also have a normal chest x-ray, so normal findings cannot exclude TB disease. Usually the findings on chest x-ray in children are poorly specific for TB. Some findings that are suggestive include:

- Miliary pattern
- Hilar or mediastinal lymph node enlargement

[18] National Guidelines for the Diagnosis and Treatment of TB in Children in Cambodia, CENAT

- Airway compression by lymph nodes causing segmental hyperinflation or collapse
- Chronic parenchymal infiltrate not improving after antibiotic treatment
- Isolated unilateral pleural effusion

Bacteriological confirmation

Specimens should be obtained for TB identification whenever possible. A definitive TB diagnosis requires identification of *M. tuberculosis* from expectorated sputum, gastric fluid, lymph node fine-needle aspiration (FNA), CSF or other site. In young children gastric lavage or nasopharyngeal aspirates can be performed to collect sputum. Sputum specimen collection is more sensitive when obtained by inducing sputum by nebulizing hypertonic saline. Induced sputum can be conducted from early infancy and is even helpful in children who are older and can expectorate.

The diagnostic test of choice is XPERT MTB/RIF, which is a fully automated real-time DNA based test and can detect both TB and resistance to rifamipicin in less than 2 hours. WHO recommends XPERT MTB/RIF in addition to conventional microscopy and culture as the initial diagnostic test for TB in HIV infected children and for those suspected with MDR TB. XPERT MTB/RIF testing is becoming increasingly available in Cambodia.

TB can be difficult to diagnose in HIV-infected children because:

- Symptoms of TB might be due to other diseases, including HIV itself
- 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

In many cases, particularly in young children, diagnosis is presumptive and is based on a combination of clinical signs and symptoms, known contact with a household member with TB disease or positive TST, and findings on chest x-ray. A therapeutic trial is not recommended for TB diagnosis in HIV-infected children as symptoms may persist due to a second OI or from HIV itself. Treatment that is initiated for TB in an HIV-infected child should be completed.

Any 2 of the following criteria are highly suggestive of TB disease and treatment for TB should begin without delay, after attempting to obtain specimens for a bacterial diagnosis:

- History of TB exposure,
  and either:
- Symptoms suggestive of TB, *or*
- Abnormal chest x-ray suggestive of TB

Children who are TB suspects but who do not meet these criteria for TB should receive treatment with routine antibiotics as appropriate for a suspected bacterial infection (avoiding drugs with TB activity, such as fluoroquinolones), along with sputum AFB evaluation (with XPERT MTB/ RIF if available) and very close follow-up. Symptoms suggestive of TB that do not improve after a course of antibiotics should prompt treatment of tuberculosis in HIV-infected children unless a clear alternative diagnosis becomes apparent.

TB Treatment

All HIV-infected patients with new pulmonary TB infection should be treated with 4 drugs (including ethambutol).

TB dosing recommendations for children were amended by WHO in 2014 and are summarized in Table 10 below.

Table 12. Dosing of TB Medication for 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

**or currently available fixed dose combination (FDC) formulations and dosing recommendations for Cambodia, refer to the *National Guidelines for Diagnosis and Treatment of TB in Children*.[13]

Additional considerations for HIV-infected children

- Pyridoxine supplementation during TB treatment in patients with HIV should always be given as follows:
  - Age <5 years, 12.5 mg daily
  - Age ≥5 years, 25 mg daily

Table 13. Management of Side Effects of Anti-Tuberculosis Drugs

Side-effects	Drug(s) probably Responsible	Management
Minor side effects		*Continue anti-TB drugs*

Anorexia, nausea, abdominal pain	Rifampicin	Give tablets last thing at night or with food Investigate for drug induced hepatitis (liver function tests)
Joint pain	Pyrazinamide	Give aspirin or nonsteroidal anti-inflammatory drug
Burning sensation in feet	Isoniazid	Increase pyridoxine to 50-75 mg daily
Orange/red urine	Rifampicin	reassurance
Severe side effects		*Stop drug(s) responsible*
Jaundice	Most anti-TB drugs (isolated jaundice most common with rifampicin)	Stop all anti-TB drugs until jaundice resolves
Vomiting (consider drug-included liver failure if jaundice present)	Most anti-TB drugs	Stop all anti-TB drugs, urgent liver function tests
Confusion, seizures or psychosis	Most likely INH	Stop all anti-TB drugs, urgent liver function tests
Visual impairment	Ethambutol	Stop ethambutol
Shock, purpura, acute renal failure	Rifampicin	Stop anti TB drugs consult with TB referral center

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

Severe forms of tuberculosis requiring special treatment

For treatment of severe or complicated forms of TB including osteo-articular TB and TB meningitis as well as MDR TB, the duration of treatment may need to be extended.[11] Treatment for all forms of TB in children is the same regardless of HIV status.

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

- Another untreated infection or malignancy superimposed on TB, such as:
  - Penicilliosis
  - Histoplasmosis
  - MAC or disseminated BCG
  - Lymphoma
- Incorrect diagnosis of TB in patients with smear-negative disease

- Disseminated smear-positive MAC or BCG, since AFB smear without culture does not distinguish between the two organisms
- Immune reconstitution inflammatory syndrome (IRIS)
- Multi-drug resistant (MDR) tuberculosis

Children diagnosed with MDR TB should be referred to the specialized TB center such as at referral and provincial hospitals.

9. WHEN TO START ANTIRETROVIRAL TREATMENT IN INFANTS, CHILDREN AND ADOLESCENTS

Early treatment in HIV-infected people of all ages is increasingly associated with better morbidity and mortality outcomes. In infants in particular, dramatic reductions in mortality were demonstrated when ART was started before 3 months of age. WHO and the Ministry of Health of Cambodia therefore recommend early initiation of treatment for the majority of children. Once treatment eligibility is established ART should be initiated **within 2 weeks of diagnosis**.

Starting guidance for treatment in children

All HIV+ children <15 years of age should be initiated on ART

- Children <18 months who have an initial positive PCR test, and children ≥18 months with positive HIV antibody testing, should begin ART within 2 weeks of diagnosis (see algorithms above).
- Infants who are confirmed to be HIV-exposed by antibody testing with a presumptive diagnosis of severe HIV (Box 3) should begin ART immediately if PCR testing is not yet available (confirm HIV status as soon as possible with dried blood spot for HIV PCR)

ALL CHILDREN REGARDLESS OF CD4 AND/OR CLINICAL STAGE SHOULD START ART AS SOON AS POSSIBLE, PREFERRABLY WITHIN 2 WEEKS OF DIAGNOSIS

Following the results of the START trial, which found that patients who started treatment immediately were 53% less likely to die during the trial or develop AIDS or a serious illness than patients who waited. WHO has announced that expanded eligibility criteria for ART to include all people diagnosed with HIV will be released later in 2015.[19]

There is decreased emphasis on the need for clinical staging and CD4 to determine ART eligibility. To determine the clinical stage, a thorough history and physical examination is necessary, along with a complete blood count. Historical information is important to determine the past experience with complications, not simply those present at the time of evaluation. For example, a child who is currently asymptomatic but who has suffered from four episodes of pneumonia in the past year should be considered in clinical stage 3 even if he or she does not have pneumonia at the time of evaluation. (Please see Annexure 1 for WHO staging of disease).

[19] Doherty M *New directions in the 2015 WHO Consolidated ARV Guidelines.* Eighth International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2015), Vancouver, Canada, presentation SUSA0608, 2015

Social Considerations relevant to starting ART in Children

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. Parents or caregivers should be encouraged to find a "treatment buddy" who may help with 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 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 within 2 weeks from the time of HIV diagnosis.

10. RECOMMENDED FIRST-LINE REGIMENS

(Table 14)

- 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.

First line regimen for children <3 years of age and <10 kg

- The preferred initial ART regimen for this age group is ABC + 3TC + LPV/r regardless of exposure to NNRTI for PMTCT.
- Every effort should be made to support families to give LPV/r-based treatment:
    - LPV/r syrup requires storage in a refrigerator prior to dispensing; however, once dispensed, the drug may be stored at room temperatures, preferably at <25°C for up to 60 days. 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. (See checklist ANNEX 3)
    - LPV/r is poorly palatable. Nevertheless, there are ways to disguise the flavour by co-administering with other strong flavors such as:
        - Jam
        - Sugar
        - Peanut butter placed on the roof of the mouth just before giving medicine.
    - A solid (pellet) heat-stable formulation of LPV/r may be available in Cambodia and may be easier to use in younger children than the liquid preparation. Additional guidance on use of this formulation will be provided if it becomes available in Cambodia.

- Heat stable solid formulations of LPV/r (tablets or pellets) should **NEVER** be crushed or cut. This has been shown to reduce the absorption of LPV/r by as much as 40%.
- If after every effort has been made, LPV/r is not available, cannot be stored appropriately or tolerated, a NVP-based regimen may be used. (This is an inferior regimen and more children are likely to fail treatment if they are started on NVP-containing treatment than if they start LPV/r-based therapy).
- ABC+3TC are the recommended NRTI's for the backbone of the first-line regimen.
- AZT may be substituted if ABC hypersensitivity occurs.
- Children who achieve virological suppression (VL <1000 copies/ml confirmed on at least 2 consecutive occasions) and are over 1 year of age may switch from LPV/r to an NNRTI-based regimen. Subsequent to the switch, a **VL MUST be repeated at 3 months** to ensure continued virological success. If virological failure occurs (VL >1000 copies/ml), the original regimen with LPV/r should be resumed.
- 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**.

First line regimen for children ≥3 years - <10 years and ≥10 kg

- EFV-based regimen is preferred as it can be dosed once daily and EFV is more tolerable than NVP
- ABC + 3TC is co-formulated and can be given once daily with EFV
- Children >3 years who started on LPV/r first line may switch to the preferred EFV-based regimen if confirmed virologically suppressed on at least 2 consecutive occasions, as above for younger children
- 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. For this reason AZT is preferred for use in second line therapy rather than first line.
- EFV dosing need not be adjusted with TB therapy.
- Children >3 years old with chronic hepatitis B infection should begin a regimen that includes both TDF and 3TC along with EFV. Currently, formulations for children <35kg are not yet available in Cambodia, but may be procured for these children in the future. Consult AIDS Care Unit at NCHADS or clinical mentors for TDF dosing for younger children <35 kg who require this drug for HBV co-infection.

First line regimen for children ≥10 years AND >35kg

- From 10 years of age and **weight >35kg,** the preferred regimen is a combination of TDF + 3TC + EFV
- This harmonises with adult treatment, and a triple fixed dose combination containing EFV 600mg is available. A formulation containing EFV 400mg is being developed.
- If the FDC is poorly tolerated, the drugs may be dosed separately as individual medicines
- Creatinine clearance should be tested prior to starting TDF and should be monitored regularly (See toxicity monitoring table)

Table 14. Recommended First-line ART Regimens*

Age	Preferred regimen	Alternative	Comments
<3 years or <10kg	ABC + 3TC + LPV/r **Confirmed virological suppression after 1 year: Switch to** ABC/AZT + 3TC + NVP	ABC/ AZT + 3TC + NVP [4]	LPV/r preferred <u>regardless</u> of prior NNRTI exposure LPV/r liquid is the only available formulation. A solid pellet formulation may be available in Cambodia, and may be easier for some children and caregivers. Store liquid LPV/r in an icebox or in a cool place in the house, or in the refrigerator if available Virological suppression (VL <1000 copies/ml) confirmed on 2 consecutive occasions in children >1 year but < 3 years, consider switching LPV/r to NVP. **Repeat viral load 3 months after switching** Where LPV/r cannot be used, use 2 NRTIs and NVP, repeat viral load 6 monthly and if evidence of treatment failure switch to LPV/r based regimen AZT may be substituted for ABC if ABC hypersensitivity occurs A failing regimen containing AZT may predispose to the development of TAMS, which is why ABC is a preferred option for first line therapy
≥ 3- < 10years and ≥10kg	ABC + 3TC + EFV	ABC/AZT + 3TC + NVP	EFV is preferred over NVP since there are fewer side effects and it is dosed once daily Virological suppression (VL <1000 copies/ml) confirmed on 2 consecutive occasions in children >3 on LPV/r first line consider switching LPV/r to EFV. **Repeat viral load 3 months after switching** If ABC hypersensitivity occurs, AZT may be substituted for ABC A failing regimen containing AZT may predispose to the development of TAMS, which is why ABC is a preferred option for first line therapy
≥ 10years and >35kg	TDF + 3TC + EFV	ABC/AZT + 3TC + NVP/EFV	From the age of **10 years <u>and</u> >35kg,** TDF is recommended as part of a once daily FDC, which is the same as the recommended regimen for adults

*See Annex 4 for dosing of ART

11. ART CONSIDERATIONS IN TB AND HEPATITIS CO-INFECTION

ART and TB Treatment

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 7: 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

Selecting an ART regimen in children receiving TB treatment

(See Table 15 below)

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, 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 lopinavir concentrations in children receiving TB therapy.
- Ritonavir is poorly palatable and adherence should be monitored carefully
- For children receiving lopinavir/ritonavir solution, extra ritonavir should be added. The added ritonavir amount should be **0.75 times** the prescribed lopinavir/ritonavir **volume** so that lopinavir and ritonavir are dosed in a 1:1 ratio. (e.g. if the dose of LPV/r is 2 ml, the ritonavir liquid dose should be 1.5 ml). Older children receiving lopinavir/ritonavir tablets should also receive additional ritonavir while on rifampicin (See Table 13 and Annex 2 for dosing).
- Ritanovir 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.

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^2 per dose twice daily.
  To measure body surface area (BSA):

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

- When NVP is begun in a child already receiving rifampicin, it should be initiated at the twice-daily maintenance dosing <u>without</u> 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 describes the recommended dosing of ART and TB medication in these different scenarios. No adjustment to TB treatment is necessary.

Table 15. Recommended ART Regimens for Children Requiring TB Treatment

Age	ART after TB treatment initiated	TB develops during ART	TB Treatment when initial ART regimen failed	Comments
<3 years or <10 kg	ABC/AZT + 3TC + LPV/R (extra ritonavir should be 0.75x the prescribed LPV/r volume) OR ABC/AZT + 3TC + NVP (dosed at 200 mg/m^2)	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^2	ABC/AZT + 3TC + LPV/R (extra ritonavir should be 0.75x the prescribed LPV/r volume) OR 3rd line regimen as determined by third line committee, and discuss TB treatment options with CENAT	Use super boosted LPV/r for the duration of and 2 weeks after stopping TB treatment 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
≥3 years and <10 years and >10 kg	ABC/AZT + 3TC + EFV	If EFV-based regimen, continue EFV at the same dose If on NVP-containing regimen, NVP should be switched to EFV	AZT/ABC + 3TC + LPV/R	If on LPV/r, use super boosted LPV/R for the duration of and 2 weeks after stopping TB treatment
≥10 years – 19 years and > 35 kg	TDF + 3TC + EFV	Continue EFV-based regimen	ABC/AZT + 3TC + LPV/R	If on LPV/r, use super boosted LPV/R for the duration of and 2 weeks after stopping TB treatment

ART in Children with HIV/Hepatitis B Co-infection

(Table 16)

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.

- All HIV/HBV coinfected 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 >3 years of age with evidence of chronic HBV infection should preferably be started on an ART regimen containing TDF and 3TC which are also active against HBV. For these cases discuss dosing with clinical mentor or PAC TWG as a single formulation of TDF may need to be broken to dose appropriately
- EFV is the preferred NNRTI
- In patients with HIV and chronic HBV, the use of **two drugs with anti-HBV activity** is preferable
- Children with chronic HBV who are too young to receive TDF, the recommended 1st line regimen is the same as for children without chronic hepatitis B.

Table 16. Recommended ART Regimens for Children with Chronic Hepatitis B Infection

Age	Preferred initial regimen	Alternative Regimen
<3 years or <10 kg	ABC + 3TC + LPV/r	AZT/ABC + 3TC + NVP[1]
≥3 years and ≥10 kg	TDF + 3TC + EFV[2]	AZT/ABC + 3TC + NVP[1]

[1]Follow LFTs monthly for 2 months, then every 6 months.
[2]EFV preferred, especially if baseline ALT is elevated ≥2N.

- HIV/HBV coinfected 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 Table 10).

ART in Children with 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 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.

12. 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 17 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.

Severity Grading of Selected Clinical and Laboratory Toxicities - See ANNEX 4.

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 3 and 4). 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 17. Management of ART-Related Toxicities with First- or Second-line Regimens

First-line ARV drug	Most frequent significant toxicity	Comments	Suggested management
Abacavir ABC	Hypersensitivity reaction	Risk factor HLA-B*5701 Fever, rash (often maculopapullar and mild), nausea, vomiting, diarrhea, fatigue, flank or abdominal pain, respiratory symptoms, myalgia, and arthralgia (1st 6 wks of ART) (see BOX 7)	Stop ABC and Switch to AZT or TDF (if the child is >10 years and >35 kg) NEVER reintroduce ABC as this could result in fatal hypersensitivity
Atazanavir ATV/r	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	
Zidovudine AZT	Severe anemia[1] or neutropenia	If Hb drops by 25% or more from baseline Avoid AZT if baseline Hb <7.5 g/dl. If neutrophil count <500/mm3.	Stop AZT, switch to ABC or TDF (if the child is >10 years and >35 kg) Mild nausea can be managed with frequent small meals and antiemetics
	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)
Nevirapine NVP	Hepatotoxicity	May be associated with underlying HBV or HCV infection Mild- moderate: ALT 1.25 - <10 x normal Severe hepatotoxicity ALT>10N	Mild-moderate, 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 heptotoxicity Severe: stop all ARVs, restart when ALT 2xN, replace NVP with LPV/r
	Dry rash (mild or moderate rash – see Annex G for grading)	Dry rash: macules, papules, dry desquamation	Continue NVP same dose (continue once daily if lead in period). Give anti-histamine drug. Switch to EFV if rash lasts more than 1 week
	Wet rash or Erythema multiforme (severe rash – see Annex G for Grading)	Wet rash: vesicles, ulcers, limited moist desquamation, limited mucous membranes involvement	Stop NVP and continue NRTI for 1 week, start with EFV 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 based HAART when symptoms resolve. (EFV should be avoided)
	Hypersensitivity reaction	Systemic symptoms of fever, myalgia, arthralgia, hepatitis, and eosinophilia with or without rash	
Efavirenz EFV	Persistent and severe central nervous system toxicity Seizures	Persistent hallucinations or psychosis Pre-existing neuropsychiatric disorder or epilepsy	Switch to NVP or LPV/r
	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 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	
Tenofovir TDF	Tubular renal dysfunction (Fanconi Syndrome)	Underlying renal disease. Check creatinine clearance before starting TDF The modified Cockroft-Gault equation: Creatinine clearance = (140 - age) x ideal weight / serum creatinine (x0.85 for females)	Substitute ABC or AZT for TDF
	Decrease in Bone mineral density	This is usually detected by DEXA scan and may be not be available in Cambodia therefore only use if indicated (e.g. for HBV coinfection in children <10years and <35kg	Substitute AZT or ABC
	Flatulence, Nausea, diarrhea, abdominal discomfort	TDF contains lactose and lactose intolerant individuals may suffer these symptoms	
Lopinavir/ritonavir LPV/r	Electrocardiographic abnormality (PR and QT interval prolongations	Pre-existing conduction system disorder	If LPV/r first line treatment in children NVP or EFV can be substituted ATV/r may be substituted in children > 6 years of age and > 40 kg
	Hepatotoxicity	Worse if underlying liver disease eg HBV or HCV	
	Dyslipidaemia or lipo-hypertrophy		
	Nausea, vomiting, diarrhea		
Ritonavir (RTV)	Nausea, vomiting, diarrhea, peri-oral numbness, headache, abdominal pain and anorexia		

[1]Exclude malaria in areas of endemic malaria.

[3] If systemic signs and/or ALT>5N, stop all ART and restart with LPV/r.

Box 7. Abacavir hypersensitivity (ABC HSR)

CLINICAL FEATURES OF 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, myalgias 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.

Management of ABC Hypersensitivity

1. 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.

13. IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

- IRIS occurs as a result of a vigorous immune response to underlying or occult infections following the initiation of effective ART.
- Two forms of IRIS include:
    - "Paradoxical" IRIS, in which there is a worsening of known disease after initial improvement.
    - "Unmasking" IRIS, in which a previously unrecognized OI becomes evident shortly after the initiation of ART.
- Patients with advanced HIV disease, particularly those with a CD4 count <100 cells/μl, 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.
- IRIS has been reported in response to many different organisms although TB is the most common infection associated with IRIS.
- IRIS has been observed in up to 1/3 of adult patients receiving anti-TB therapy and who have been initiated on ART within 8 weeks of TB diagnosis.
    - Symptoms and signs of TB IRIS may include high fever, dyspnea, cough, enlarging lymph nodes, worsening of chest X-ray (CXR) findings and expanding central nervous system (CNS) lesions in patients with tuberculoma. These reactions may occur during the first 6 months of starting ART, are generally self-limiting, and last for several weeks.
- 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.
- 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
- For severe paradoxical reactions, prednisolone (1-2 mg/kg for 1-2 weeks, then gradually decreasing doses) may help, and some patients need to be hospitalized.
- IRIS is a diagnosis of exclusion, and it is important to rule out other causes of illness before deciding a child's illness is IRIS.

Box 8. BCG IRIS

BCG IRIS

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.

14. 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.

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 5-1)
- 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 9. 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 cotrimoxazole 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 I 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 dipstix and Creatinine if starting TDF

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 11 and Annex 5-2.

Box 10. 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

15. TREATMENT FAILURE

- Treatment failure initially occurs through virologic failure, then immunologic failure, and later presents as clinical failure. (Table 18)
- 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 18. Definition of Treatment Failure

Failure	Definition	Comments
Virological Failure	Plasma viral load >1000 copies /ml based on 2 consecutive measurements after 3 months with adherence support	The patient should be taking ART at least 6 months before it can be determined that the regimen has failed
Immunological Failure	Children <5 years Persistent CD4 levels < 15% or <200 cells/mm^3 Children ≥5 years Persistent CD4 levels <100 cells/mm^3	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.
Clinical Failure	New or recurrent event indicating advanced or severe immunodeficiency[1] after 6 months of effective treatment	Condition clinically distinct from immune reconstitution inflammatory syndrome (IRIS)[2]. Children with clinical failure should have a viral load performed to confirm failure.

1 WHO stage 3 or 4 condition see Annex 1 for WHO staging in children
2 See above section on immune reconstitution inflammatory syndrome (IRIS)

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

    - 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 error
- Pre-existing viral resistance (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.

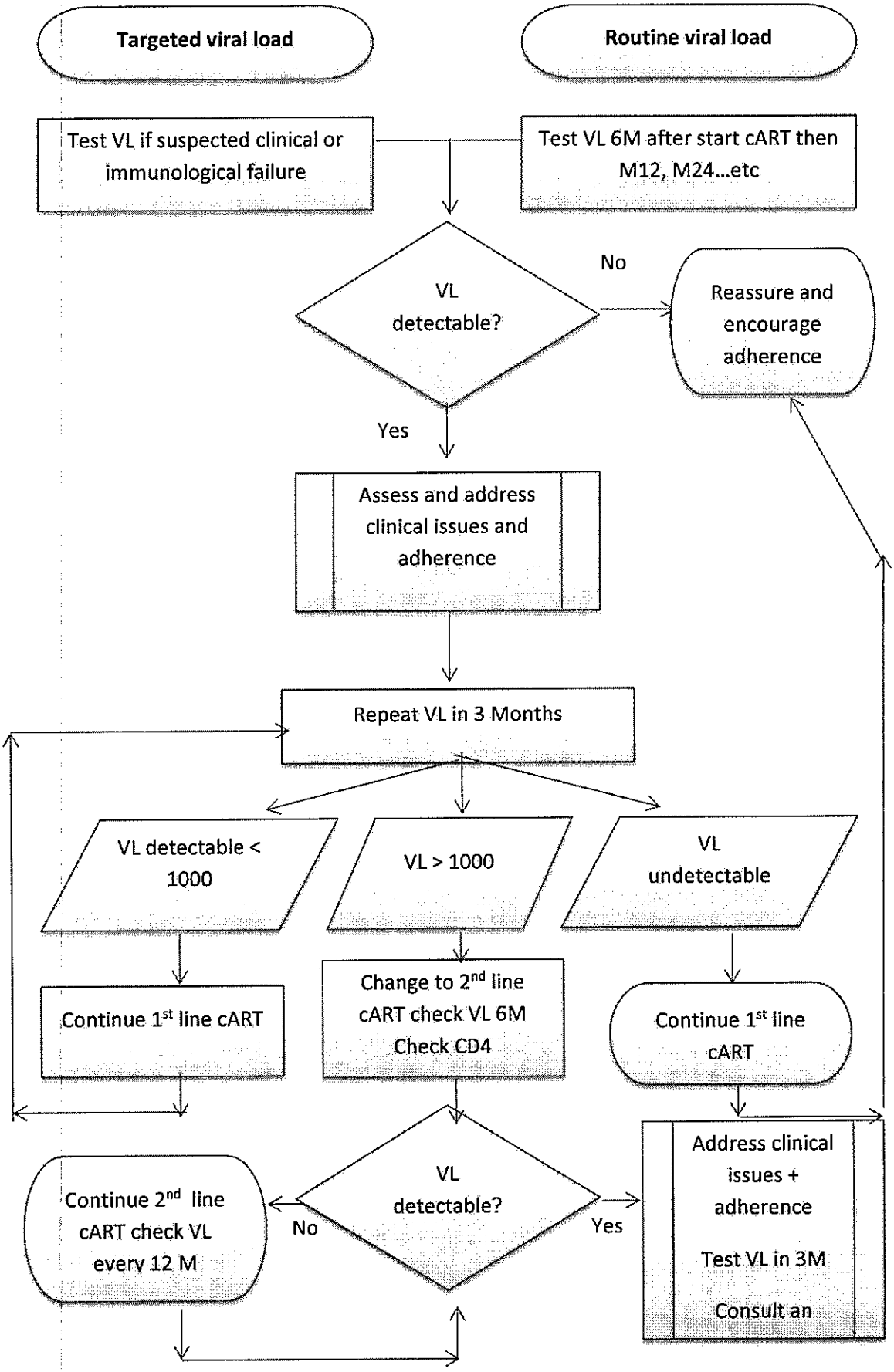
Inadequate adherence is the most common cause of virologic failure. At each visit, adherence should be confirmed by pill counts and self-report and other methods as available (visual analogue scale, pharmacy refill records or other means). Proper dosing should be confirmed and medication doses adjusted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

Viral Load Testing

(Figure 5)

- The overall aim of treatment is to reduce viral load (VL) to levels below the lowest detection threshold given by the laboratory (usually between 50 and 400 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 <1000 copies/ml but >50 this should be repeated at the next visit to ensure that the viral load is not increasing
- 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 viral load algorithm Figure 5).

Figure 5. Viral load testing strategy



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 2nd 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.

16. 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.

Second line regimen options

(Table 19)

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 intensify adherence counseling 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 intensified adherence 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 intensified adherence 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.
- Switching to an NNRTI-based regimen is unlikely to be a durable option but may be tried in older children. VL monitoring for treatment failure after 6 months should be conducted, and if VL remains elevated switch back to LPV/r and intensify adherence counseling. (See adherence section below).

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, 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.

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 or TDF (if child >10 years and >35kg).
- If AZT is used in first line, this should be switched to ABC for or TDF (if child >10 years and >35kg).
- 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*).

Treatment failure in special circumstances

- *Active tuberculosis-*
  - When 2nd line is necessary during TB treatment, additional ritonavir must be added to coformulated 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 tenofovir 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.

Table19. Recommended Second-line Regimens

	First line	Preferred regimen change	Alternative regimen change	Comments
Children	ABC/AZT+3TC+LPV/r	No change from first line regimen	AZT (or ABC) +3TC + NVP/EFV	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 intensified counseling and repeat viral load 6 monthly. 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
	ABC/AZT+3TC+EFV or NVP	AZT (or ABC) + 3TC + LPV/r *	TDF+ 3TC + LPV/r *	Use AZT if ABC used first line or ABC if AZT used in first line therapy
Adolescents (>10-19 years)	TDF/AZT+3TC+EFV	AZT + 3TC + ATV/r (if >40kg)*	AZT + 3TC + LPV/r*	Use AZT if TDF used first line or TDF if AZT used in first line therapy AND adolescent >35kg If >40kg, ATV/r is the best choice of PI, because the tablets burden can be reduced and the medication can be taken daily with TDF300mg+3TC300mg current formulation in Cambodia is a tablet of ATV/r (300mg/100mg). Because ATV was available in many formulation such as powder packets, capsule

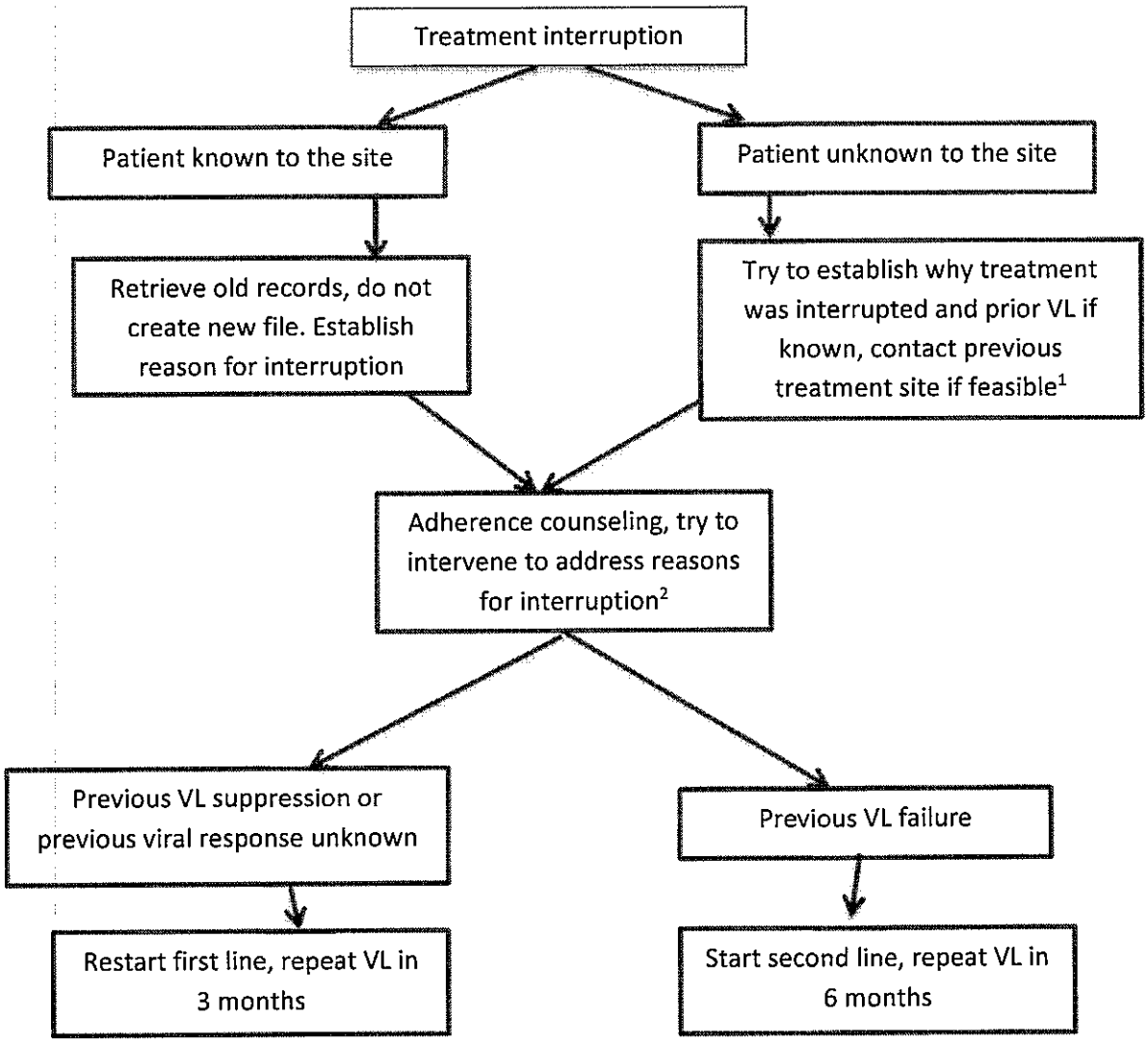
*ATV/r is licensed for use in children from 6 years of age and may be used instead of LPV/r but the current formulation is only appropriate for patients >40 kg

Management of children who have interrupted therapy

The definition of Lost to follow-up (LFU): Three months or more (90 days or more) since last missed 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 (Figure 6).

Figure 6. Approach to management of children who have interrupted treatment



[1]Where the treatment history is unknown it is advisable to start a first-line regimen and repeat VL after 3 months

[2]Reasons for interruption

- psychosocial factors, e.g., maternal illness or death
- drug supply issues
- toxicity (may need to switch individual drug if VL suppressed)
- migration

NB: If NVP is restarted after an interruption of >1 week, re-commence with the 2 week lead-in dose and check the ALT if the patient becomes symptomatic of hepatitis. If ABC is re-started, ensure there was no prior hypersensitivity reaction.

17. 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 intensive support for adherence to ensure durability of 2nd line treatment. Nevertheless some children will require 3rd line options.

New generation and new class antiretroviral drugs have been developed and combinations of highly effective drugs are now available for 3rd line options.

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)

These third line drugs are still very expensive and not routinely available in Cambodia. All patients suspected of failing second-line therapy should receive intensified adherence monitoring and viral load testing to confirm treatment failure. Poor adherence is the cause of virological failure in the majority of patients with detectable viral loads on 2nd line, and patients may not necessarily have developed drug resistance.

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 refer data collection form (ANNEX 9).

Third-line treatment will not be available and should not be prescribed outside of the public health facilities.

PSYCHOSOCIAL SUPPORT (PSS) 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).

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 behaviors (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

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 11. 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.

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).

Define roles and responsibilities for providing PSS:

- Doctors and nurses – provides 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/mmm 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.

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 (Table 20).

Table 20. 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	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. Newborn infants and babies are dependent on mothers or caregivers for all their needs. Early infancy time of rapid neurological development and when strong bonds form between infant and primary caregiver ("attachment")	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 Infants need a stable caregiver who understands HIV and ART and the need for adherence Attention must be paid to food and nutritional requirements for infants Caregivers should understand the reasons for urgent access to ART if HIV infected (for both infant and mother) Infants need appropriate neurocognitive stimulation from their caregivers Infants require a safe environment, caregivers need to be taught how to provide this	HCT should be provided for all pregnant women Provide HIV/AIDS counseling support for mother and father after learning about their diagnosis of HIV Educate parents about ART (Option B+) and its benefit for themselves and how this helps prevent HIV transmission to infants Provide infant feeding education and support (promote exclusive breast feeding, but support safe replacement feeding as necessary (see section on infant feeding) Help parents understand process of early infant diagnosis, provide support if the infant is diagnosed with HIV and the advantages of early ART. Educate parents: • How to create safe environment • About the importance of early childhood development (ECD) and how to stimulate infants and children

Infancy and pre-0school children (3-5 years)	Children are dependent on their caregivers for all requirements of daily living and medication/accessing services. This is a time of rapid neurological development.	Children need a stable caregiver who understands HIV disease and their role in ensuring adherence and retention in care. They require a safe environment. Children need stimulation to support cognitive and motor development. Children can be taught about their own bodily hygiene and safety without mentioning the word HIV (can be taught about danger of blood). Children are curious about where they come from, and the differences in genitalia between males and females.	The caregiver needs education on HIV, how medication works and importance of adherence and attending clinic appointments. Caregiver education and support is also needed on: • How to create a safe environment • Early childhood development (ECD) and how to stimulate infants and children • How to manage blood spills (universal precautions) Assessment at every visit for identifying children at risk and points of intervention. 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.
School age children (6-10 years)	Children become more independent. Children can take some responsibility e.g. can learn to remember when to take their medication.	Children need for stable caregiver who understands HIV disease and their role in ensuring adherence and retention in care. It is best that children learn their HIV status- with intensive counseling and support through the process.	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 Continue support of caregiver to promote child adherence, Assessment at every visit for identifying children at risk and points of intervention.

	Children start attending school. Still dependent on family but start making social ties	Children require a stable and safe environment. Education support if the child is developmentally delayed	Provide safe spaces at clinic, provide an accepting non-judgmental atmosphere, group support if possible for caregivers and children. Increase children's involvement in taking their medication. Provide education for children on how to keep themselves safe.
Pre/young adolescents (11-14 years)	This is usually when puberty starts. Emotional changes begin. Risk-taking behaviour may start. Adherence may decrease. Children develop stronger connections to peers.	A stable caregiver continues to be needed. Adherence support is required. Provide sexual and reproductive health information including understanding about physical changes that are occurring. Positive prevention – support and education about having safe and healthy romantic relationships; avoid sharing injection equipment. Education about risks of substance abuse (alcohol, glue sniffing, etc,). Access to family planning STI if sexually active. Preparation and support through transition.	Support HIV disclosure if this has not occurred earlier. Support adolescents in developing life and relationship skills. Counsel adolescents about how to disclose to significant others. Provide or refer for family planning or STI management. Assessment for high risk behavior and intensify counseling. Peer support and provide support groups if possible. Develop a transition plan. Familiarize adolescent with adult ART site and staff. 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. Follow up adolescents transition and assess adherence to visits and medication after transition. Intensified counseling for those who become non-adherent.
Older adolescents (15-19 years)	This is the time of transition to adults services. Adolescents develop autonomy. Sexual activity may begin. Risk-taking-behaviour may increase.		

18. 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 helps to optimize adherence.

What is adherence to treatment?

- Taking all medication including ARVs 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.

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.

Techniques to improve adherence:

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, labeled 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

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 11. 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 adolscent so that they better understnd why they need to take their medication (see below section on disclosure)

- Encourage more autonomy by teaching the child/adolescent to:

1. Incorporate dosing into daily routines and take medication at the same time each day (e.g., after brushing teeth, before a meal).
2. Keep a tally sheet of doses, mark a calendar, or use a pillbox.
3. Use visual reminders (e.g., notes on the medicine cabinet or refrigerator).
4. Use alarms from clock/watch /cellphone.
5. Children/adolescent may still respond to a reward system, eg pocket money, cell phone airtime,
6. Engage an adult family member or trusted friend to help them remember

Box 12. Tools for reinforcing 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 medicines 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).

19. 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.

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.

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.**
- **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.

Who should do the disclosure?

- Someone whom the child trusts and respects should conduct the disclosure process. Usually, this will be the caregiver. Counselors 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.
- 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.

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.

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.

Disclosing a caregiver's HIV status to the child

- School age children (from 5 years) should be told of their caregivers' HIV status.
- 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.

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 education 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

Box 13. 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.

The disclosure process

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

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, counselors should investigate the reasons for this and help to solve the issue. The time frame for disclosure depends on the child and situation, the counslor may need to exercise patience in dealing with the family.

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.

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.

20. 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 9). 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 9 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

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.

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.

I- 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.

II- 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 11.

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

III- 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.

IV- 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.

A. 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 adolescents 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.

B. 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.

C. 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 PLHA, who may be someone who has recently transitioned successfully, works with the patient to create and track progress on an individualized transition plan. PLHA 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.

VI- Evaluation before transition occurred

A-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

Checklist for Successful Transition

- The patient has accepted his or her HIV status
- The patient has learned how to negotiate appointments and has been introduced to the adult ART clinic
- The 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. And, if they don't understand the answer, to ask again
- Be sure to understand the medications that you are taking. What are their names and when do you take them

B-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

ANNEXES

ANNEX 1: WHO Clinical Staging

- **Clinical Stage 1:**
  - Asymptomatic
  - Persistent generalized lymphadenopathy (PGL)

- **Clinical Stage 2:**
  - Unexplained persistent hepatomegaly
  - Papular Pruritic Eruptions (PPE)
  - Extensive wart virus infection
  - Extensive molluscum contagiosum
  - Recurrent oral ulceration (two or more episodes in 6 months)
  - Unexplained persistent parotid enlargement
  - Linear gingival erythema (LGE)
  - Angular cheilitis
  - Herpes zoster
  - Recurrent or chronic upper respiratory tract infections (URTI) (otitis media, otorrhea, sinusitis, tonsillitis)
  - Fungal nail infections

- **Clinical Stage 3:**
  - Unexplained moderate malnutrition, not adequately responding to standard therapy
  - Unexplained persistent diarrhea (14 days or more)
  - Unexplained persistent fever (above 37.5^{0} C intermittent or constant, for longer than one month)
  - Persistent oral candidiasis (after the first 6 weeks of life)
  - Oral hairy leukoplakia
  - Acute necrotizing ulcerative gingivitis/stomatitis/periodontitis
  - Lymph node TB
  - Pulmonary TB
  - Severe recurrent bacterial pneumonia
  - Symptomatic lymphoid interstitial pneumonitis (LIP)
  - Chronic HIV associated lung disease include bronchectasis
  - Unexplained anemia (<8/dL), neutropenia (< 0.5×10^{9} /L) or chronic thrombocytopenia (<50×10^{9} /L)

- **Clinical Stage 4:**
  - Unexplained severe wasting stunting or severe malnutrition not responding to standard therapy
  - *Pneumocystis jiroveci* pneumonia
  - Recurrent severe bacterial infections (>2 episodes in 12 months, infections include empyema, pyomyositis bone or joint infection, meningitis but excluding pneumonia)
  - Chronic herpes simplex infection (orolabial or cutaneous of more than one

month's duration or visceral at any site)

- Esophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
- Extrapulmonary TB / Disseminated TB
- Kaposi sarcoma
- Central nervous system toxoplasmosis (after the neonatal period)
- HIV encephalopathy
- Cytomegalovirus (CMV) infection, retinitis or CMV infection affecting other organs with onset at age over one month
- Extrapulmonary cryptococcosis (including meningitis)
- Disseminated endemic mycosis (extrapulmonary histoplasmosis, penicilliosis)
- Chronic cryptosporidiosis (with diarrhea)
- Chronic isosporiasis
- Disseminated non-tuberculous mycobacteria infection (including MAC infection)
- Candida of trachea, bronchi or lungs
- Cerebral or B cell non-Hodgkins lymphoma
- Progressive multifocal leukoencephalopathy (PML)
- Symptomatic HIV associated cardiomyopathy or nephropathy

*Unexplained refers to where the condition is not explained by other causes

Annex 2 Principals for managing child victims of sexual assault

Principal	Action
Promote the child's best interest	1. Secure physical and emotional safety (well-being) throughout care and treatment 2. Evaluate positive and negative consequences of actions with participation of the child and caregiver (as appropriate) 3. The least harmful course of action is always preferred 4. All actions should ensure that the child's rights to safety and ongoing development are not compromised
Ensure the safety of the child	1. Ensure physical and emotional safety 2. All actions should safeguard the child's physical and emotional well-being in the short and long term
Comfort the child	1. Offer comfort, encouragement, and support 2. Assure that service providers are prepared to handle the disclosure of sexual violence and exploitation appropriately 3. Believe the child when they have chosen to disclose sexual violence and exploitation 4. Never blame the child in any way for the sexual violence and exploitation they have experienced 5. Make the child feel safe and cared for as they receive services
Ensure appropriate confidentiality	1. Information about the child's experience of sexual violence and exploitation should be collected, used, and stored in a confidential manner 2. Ensure the confidential collection of information during all aspects of care including interviews and history taking 3. 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 4. Store all case information securely 5. If mandatory reporting is required under local law, inform the child and caregiver at the time they are seen 6. If the child's health or safety is at risk, there may be limits to confidentiality to protect the child
Involve the child in decision making	1. Children have a right to participate in decisions that have implications in their lives 2. 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 3. 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 4. If a child's wishes are not able to be followed, then the reasons behind not being able to follow them should be explained
Treat every child	1. Use the principle of non-discrimination and inclusiveness for all children 2. All children should be offered the same high-quality care and treatment, regardless of their ethnicity, religion, sex,

fairly and equally	ability/disability, family situation, status of their parents or caregivers, cultural background, or financial situation, affording them the opportunity to reach their full potential 3. No child should be treated unfairly for any reason
Strengthen children's resiliencies	1. Each child has unique capacities and strengths, and possesses the capacity to heal 2. Identify and build upon the child's and family's natural strengths as a part of the recovery and healing process 3. Factors that promote the child's resilience should be identified and built upon during the episode of care 4. 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)
Health care providers should be appropriately trained and skilled in managing children who have experienced sexual violence and exploitation	All providers responsible for caring for children who have experienced sexual violence and exploitation should: 1. Undergo training and orientation to the sexual violence/post-rape care clinic and referral protocols 2. Have specialized training on the medical forensic examination 3. 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 Health care centers should: 1. Identify and train dedicated practitioners (doctors, forensic nurses, or clinic officers) to provide post-rape care and services for children
The health and welfare of the child takes precedence over the collection of evidence	2. Crisis intervention; treatment of serious injuries; and assessment, treatment, and prevention of HIV, pregnancy, and STIs are of primary importance 3. 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 4. Children should NEVER be forced to undergo the medical forensic examination against their will unless the examination is necessary for medical treatment (WHO 2003)
Reporting to police should not be a prerequisite for obtaining medical care	1. The child's decision regarding police involvement should be respected at all times 2. The child should not be pressured, coerced, or forced to report the sexual violence and exploitation as a condition of receiving their medical care 3. 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 4. Reporting is often tied to payment of fees, 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.

	5.	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
	6.	Police forms should be kept ideally at the facility for children who present to the facility first and should be available free of charge
	7.	The child should be offered all available services including emergency contraception (EC) where legal, HIVnPEP, and other needed health services even if there is no physician available to sign medicolegal forms, or if the child chooses not to report to the police
Use the person-first approaches to care	1.	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
	2.	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
	3.	Ensure that someone who is trained is available when necessary for communication alternatives (e.g., sign language) for patients who may require this approach

ANNEX 3: Checklist for Storage of liquid LPV/r

Checklist for storage of liquid LPV/r

- ☐ Refrigerator at home
- ☐ Icebox for storage of food
- ☐ Able to afford daily supply of ice
- ☐ Access to reliable refrigeration in the neighborhood
- ☐ Trust neighbor or friend to store medication

If none of the above available or caregiver unable to provide a plan to keep the LPV/r solution cold. NVP should be used

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		25–34.9 kg	
			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
EFV[a]	Tablet (scored)	200 mg	–	–	–	–	1 (once daily)		1.5 (once daily)		1.5 (once daily)		2 (once daily)	
LPV/r[b]	Tablet (heat stable)	100/25 mg	–	–	–	–	2	1	2	2	2	2	3	3
LPV/r[b]	Tablet (heat stable)	200/50 mg	–	–	–	–	–	–	–	–	–	–	2	2
LPV/r[b]	Syrup	80/20 mg/ml	1 ml	1 ml	1.5 ml	1.5 ml	2 ml	2 ml	2.5 ml	2.5 ml	3 ml	3 ml	–	–
LPV/r	Pellets	40/10 mg	2	2	3	3	4	4	5	5	6	6	–	–
NVP	Syrup	10 mg/ml	5 ml	5 ml	8 ml	8 ml	10 ml	10 ml	–	–	–	–	–	–

[a] 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 finalisation 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.

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

[c] 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		25–34.9 kg	
			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)	
ABC/3TC	Tablet (dispersible)	120/60 mg	1 (once or twice daily)		1.5 (once or twice daily)		2 (once or twice daily)		2.5 (once or twice daily)		3 (once or 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
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

Important Points to Note:

1) As suggested in the guidelines, TDF based regimens can be prescribed to children and adolscents under 35 kgs 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

ANNEX 5: ARV Toxicity Severity Grading

	Grade 1	Grade 2	Grade 3	Grade 4
Parameter	**Mild**	**Moderate**	**Severe**	**Severe and potentially life-threatening**
General guidance on estimating severity grade				
Characterization of symptoms and general guidance on management	Symptoms causing no or minimal interference with usual social and functional activities [a] 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: require medical care and possible hospitalization	Symptoms causing inability to perform basic self-care functions [b]: require medical or operative intervention to prevent permanent impairing, persistent disability or death
Haematology [c] Standard international units are listed in italics				
Absolute neutrophil count	750-<1000/mm^3 0.75x10^9 -< 1x10^9/l	500-749/mm^3 0.5x10^9-0.749x10^9/l	250-500/mm^3 0.25x10^9 -<0.5x10^9/l	250/mm^3 0.250x10^9/l
Hemoglobin (child>60day of age)	8.5-10.0g/dl 1.32-1.55mmol/l	7.5-<8.5g/dl 1.16-<1.32mmol/l	6.5-<7.5g/dl 1.01-<1.16mmol/l	<6.5g/dl <1.01mmol/l or sever clinical symptoms attributable to anaemia (e.g. cardiac failure), refractory to supportive therapy
Platelets	100000-<125000/mm^3 100x10^9-125x10^9/l	50000-<100000/mm^3 50x10^9-<100x10^9/l	25 000-<50000/mm^3 25x10^9-<50x10^9/l	<25000/mm^3 25x10^9/l or bleeding
Gastrointestinal [c]				
Laboratory				
ALT (SGPT)	1.25-2.5 x ULN	2.6-5.0 x ULN	5.1-10.0 x ULN	>10.0 x ULN
AST (SGOT)	1.25-2.5 x ULN	2.6-5.0 x ULN	5.1-10.0 x ULN	>10.0 x ULN
Bilirubin (>2 week of age)	1.1-1.5 x ULN	1.6-2.5 x ULN	2.6-5.0 x ULN	>5.0 x ULN
Lipase	1.1-1.5 x ULN	1.6-3.0 x ULN	3.1-5.0 x ULN	>5.0 x ULN
Pancreatic amylase	1.1-1.5 x ULN	1.6-2.0 x ULN	2.1-5.0 x ULN	>5.0 x ULN
Clinical				
Diarrhea ≥ 1 year of age	Transient or intermittent episodes of unformed stools OR increase of ≤ 3	Persistent episodes of unformed to watery stools OR increase of 4-6 stools over baseline per day	Grossly bloody diarrhea OR increase of ≥ 7 stools per day OR intravenous fluid	Life-threatening consequence (e.g. hypotensive shock)

< 1 year of age	stools over baseline per day Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR mild dehydration	replacement indicated Liquid stools with moderate dehydration	Liquide stools resulting in severe dehydration with aggressive rehydration indicated or hypotensive shock
Nausea	Transient (<24hours) 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 hemorrhage, Sepsis)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistence vomiting resulting in orthostatic hypotension OR aggressive rehydration indicated (e.g. intravenous fluids)	Life-threatening consequence (e.g. hypotensive shock)
Allergic/ dermatological				
Acute systemic allergic reaction	Localized urticarial (weak) Lasting a few hours	Localized urticarial with medical intervention indicated OR mild angio-oedema	Generalized urticarial OR angio-oedema with medical intervention indicated OR symptomatic mild bronchospasm	Acute anaphylaxis OR life threatening bronchospasm or laryngeal ledema
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 of bullae OR superficial ulcerations of mucous membrane limited to once site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR ulceration of mucous membrane involving two or more distinct mucosal sites OR toxic epidermal necrolysis (TEN)
Neurological				
Alteration in personality, behavior or mood[b]	Alteration causing no or minimal interference with usual social and functional activities[b]	Alteration causing greater than minimal interference with usual social and functional activities[b]	Alteration causing inability to perform usual social and functional activities[b] AND intervention indicated	Behavior potentially harmful to self or others OR life-threatening consequence
Altered mental status	Change causing no or minimal interference with usual social and	Mild lethargy or somnolence causing greater than minimal interference with usual social and	Onset of confusion, memory impairment, lethargy, or somnolence causing inability to	Onset of delirium, obtundation or coma

	functional activities[b]	functional activities[b]	perform usual social and functional activities[b]	
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[b]	Muscle weakness causing greater than minimal interference with usual social and functional activities[b]	Muscle weakness causing inability to perform usual social and functional activities[b]	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 social and functional activities	Disabling sensory alternation or paraesthesia causing inability to perform basic self-care functions[c]
Other laboratory parameters *Standard international units are listed in italics*				
Cholesterol (fasting, pediatric<18 years old)	170-<200mg/dl 4.40-5.15mmol/l	200-300mg/dl 5.16-7.77mmol/l	>300mg/dl >7.77mmol/l	Not applicable
Glucose, serum, high: non fasting	116-<161mg/dl 6.44-<8.89mmol/l	161-<251mg/dl 8.89-<13.89mmol/l	251-500mg/dl 13.89-27.75mmol/l	>500mg/dl >27.75mmol/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-<751mg/dl 5.65-<8.49mmol/l	751-1200mg/dl 8.49-13.56mmol/l	>1200mg/dl >13.56mmol/l

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.

a 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).

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

c Values are provided for children in general except where age groups are specifically not

ANNEX 6-1: Schedule of routine clinical and laboratory monitoring for the HIV-infected child not on ART

Items	Baseline	Month 1	Month 2	Month 3	Every 3 months	Every 6 months	Every 12 months	Symptom Directed
				Clini				
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
Cotrimoxazole Need and Adherence	X	X	X	X	X	X	X	X
Counseling for Prevention of STIs and Pregnancy (b)	X				X			X
OI Prevention and TB symptom screening,(c)	X	X	X	X	X	X	X	X
				Laborat				
WBC and Hb	X							X
CD4 % and CD4 count	X					X		X
Liver Transaminase: ALT, ASAT	X							X
Hepatitis B Surface Ag and Hepatitis C Ab if available	X							X
Pregnancy test (d)	X							X

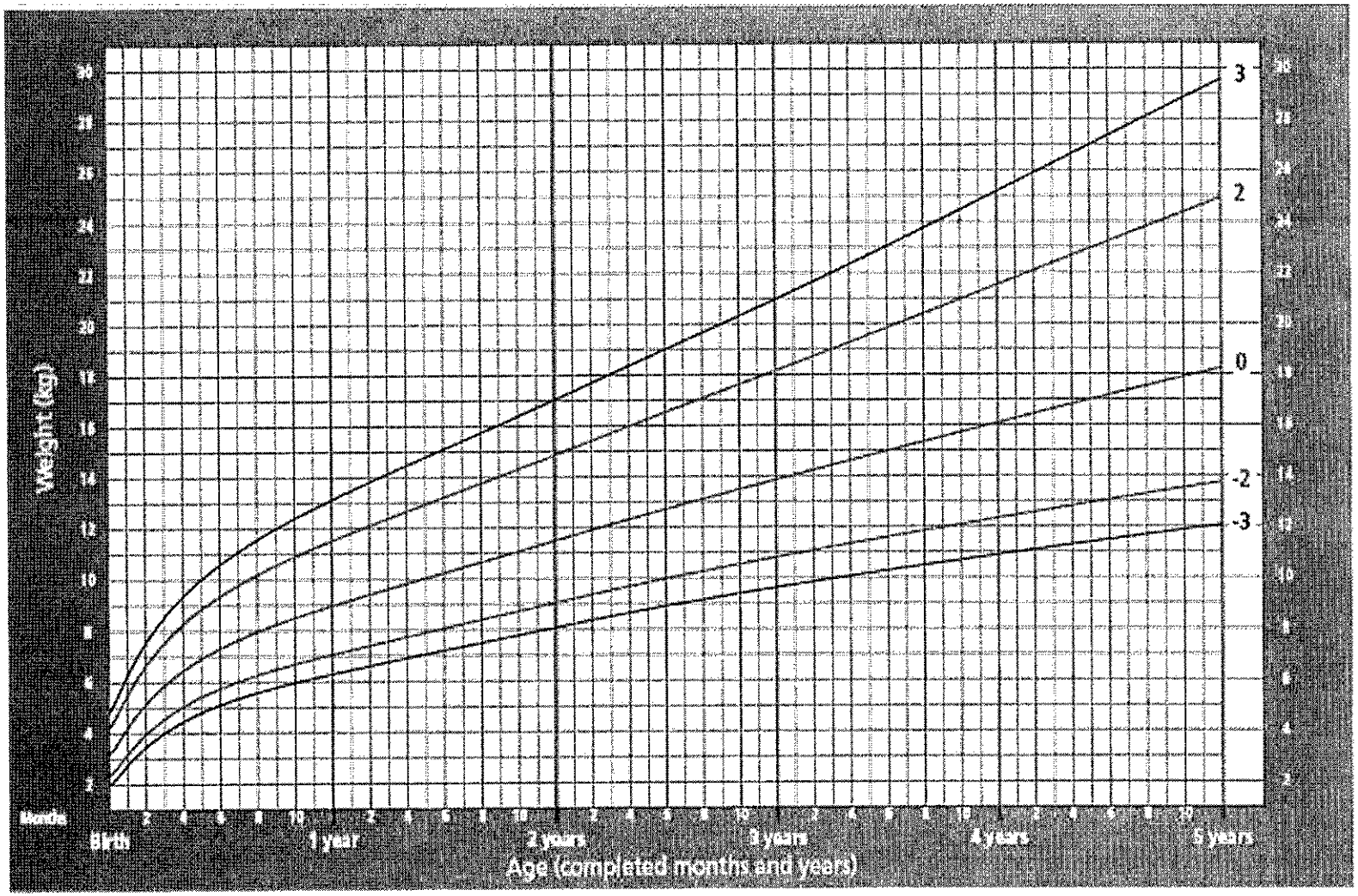
(a) Includes history-taking, physical examination and assessment of neurodevelopment.
(b) Adolescents of reproductive age, provide counseling on family planning, prevention of STIs, prevention of transmission of HIV to others, and the risk of transmitting HIV to their infants. Pregnancy test should be 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 6-2: 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
Clinical										
Clinical evaluation	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, Side Effects, Toxicities, Drug Interactions	X	X	X	X	X	X	X			
Need for OI Medications and Doses	X	X	X	X	X	X	X			
Adherence to ART		X	X	X	X	X	X			
Counseling for Prevention of STIs and Pregnancy (a)	X				X	X	X			X
Laboratory										
WBC and Hb (b)	X			X(b)						X
Liver 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 dipstix if on TDF	X				X	X	X			
Fasting cholesterol, triglycerides and glucose (d)	X(d)								X(d)	X

(a) In adolescent girls, 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 performed at baseline and as indicated from counseling.
(b) If on AZT, Hb should be measured at week 8
(c) Repeat ALT at week 4 and week 8 if elevated at baseline, if hepatitis B or C coinfection, or if on other hepatotoxic drugs (e.g. TB medications)
(d) In adolescents, fasting tests for cholesterol, triglycerides and glucose should be performed at baseline and every 12 months when receiving EFV or LPV/r

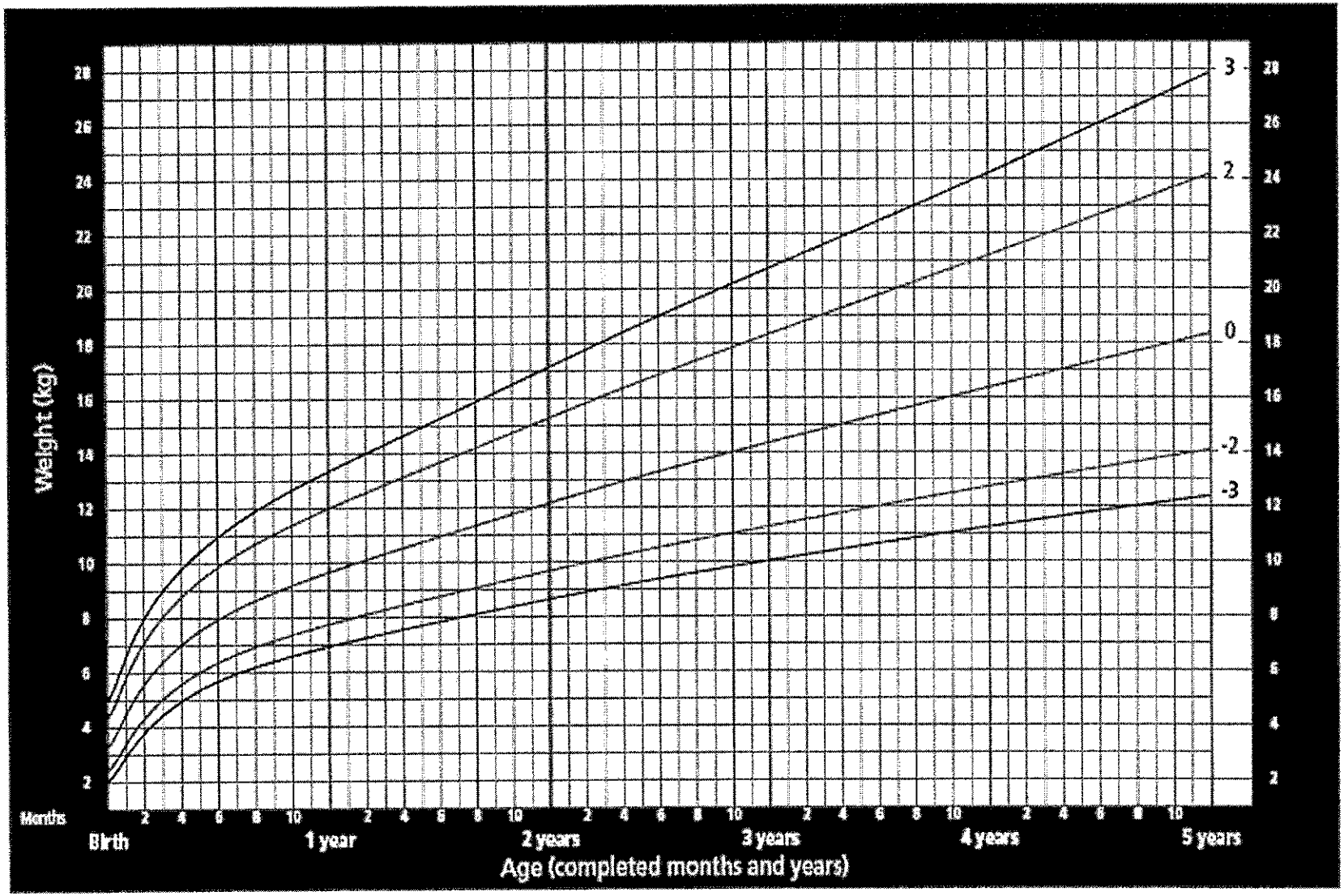
ANNEX7: Pediatric Weight-for-Age Growth Charts



Weight-for-age BOYS

World Health Organization

Birth to 5 years (z-scores)

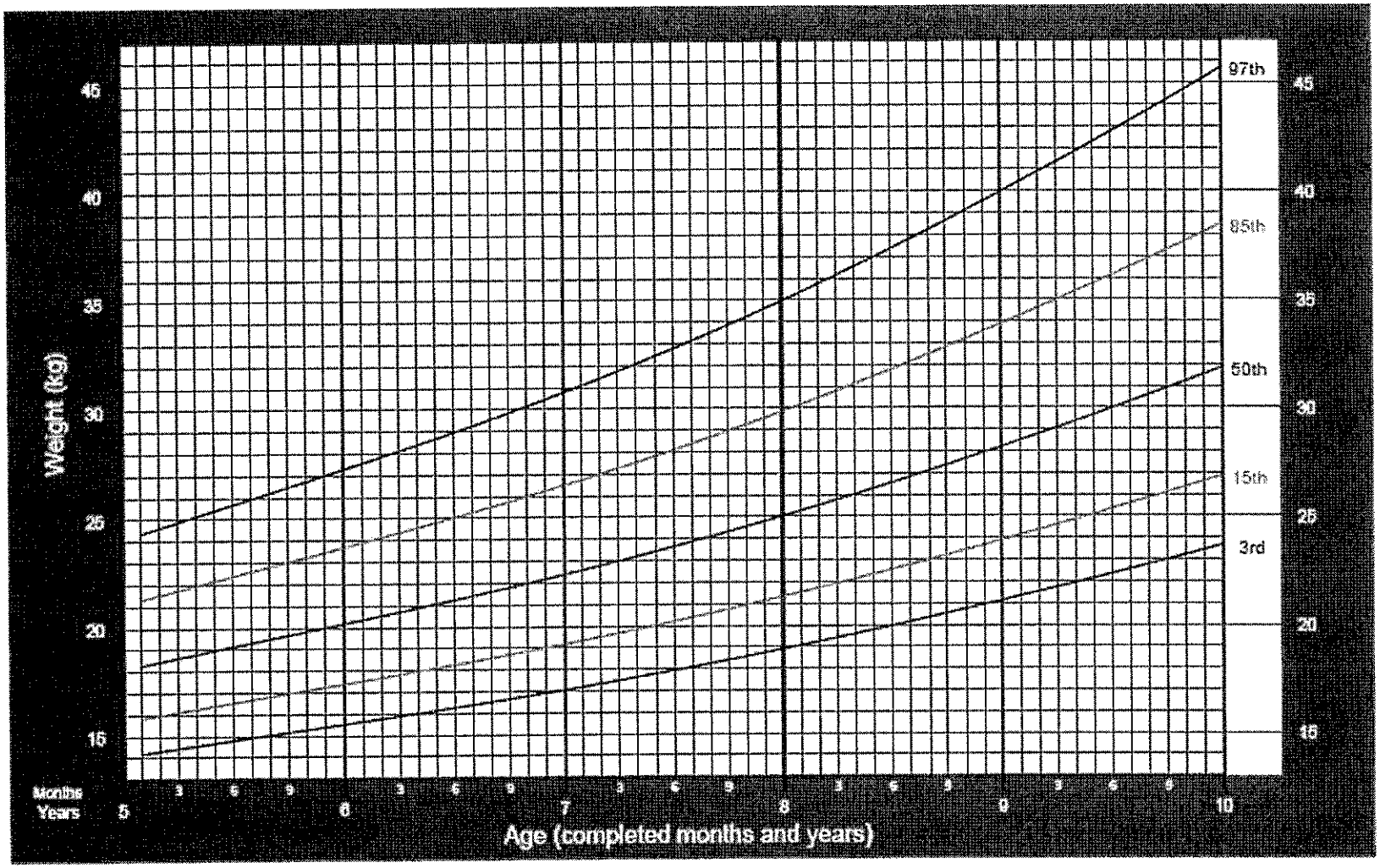


WHO Child Growth Standards

Weight-for-age GIRLS

World Health Organization

5 to 10 years (percentiles)

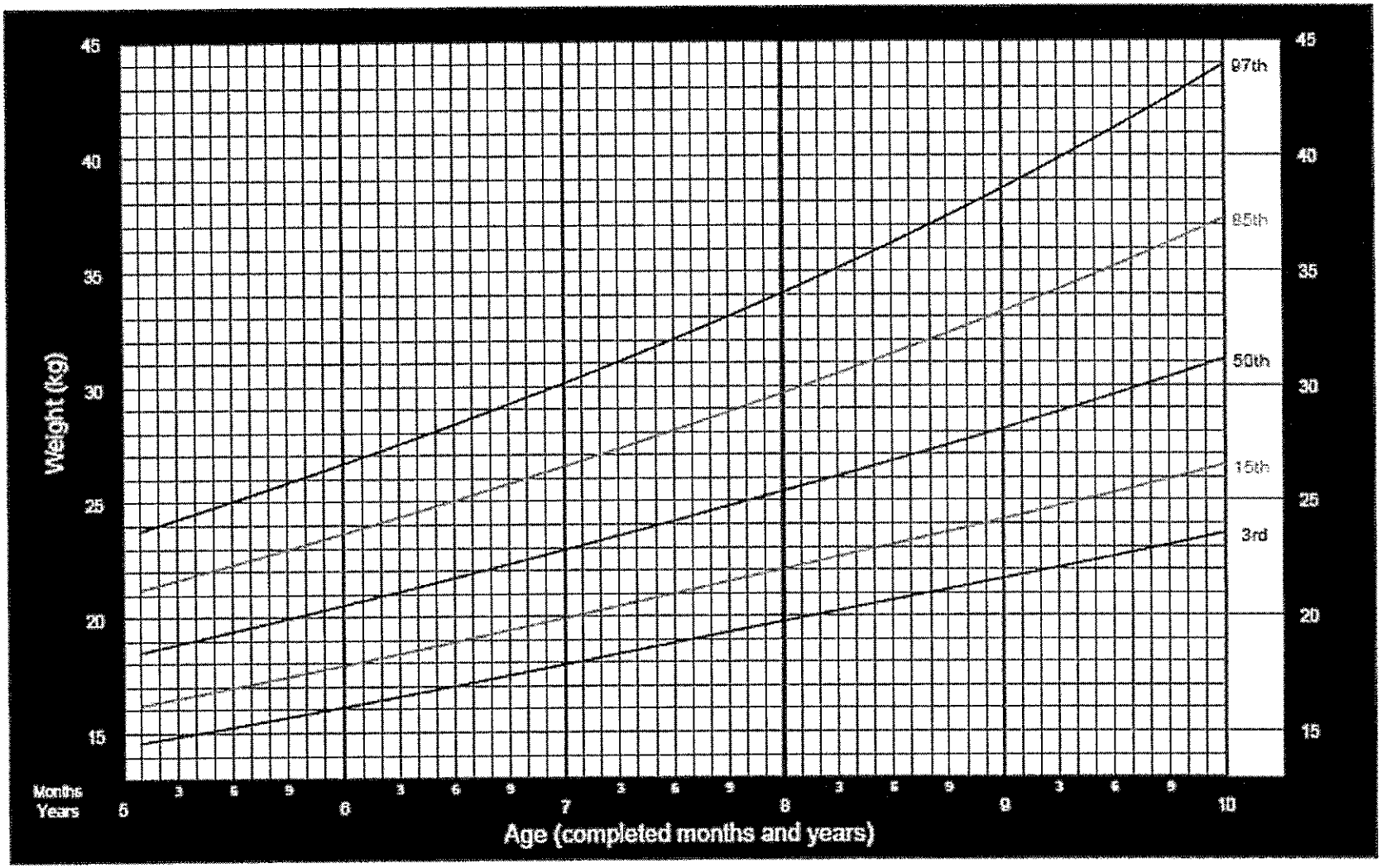


2007 WHO Reference

Weight-for-age BOYS

World Health Organization

5 to 10 years (percentiles)



2007 WHO Reference

ANNEX 8: 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 mg QD	No adjustment necessary	Not described
Clarithromycin	May decrease clarithro levels	X	Dose reduction of clarithro needed if renal failure	Reduce clarithro by 50%	Not described
Oral contraceptive[1]	X	X	X	X	No dose adjustment necessary
Methadone	Increase methadone	Increase methadone	Increase methadone	OK	Not described
'Statins'[2]	+/-	+/-	X	X	Not described
SSRI Antidepressants	+/-	+/-	May cause ↑ SSRI level. Start at lowest dose	Not described	Not described
Anti-epileptic drugs[3]	X	X	X	Not described	Not described
Benzodiazepines[4]	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 Flecanide Pimozide	Astemizole Terfenadine Cisapride Midazolam Ergotamine Dihydro- ergotamine Garlic Flecanide Pimozide	
Miscellaneous	Can lower steroid levels	Monitor warfarin if co-administered			Probenecid, avoid combination

[1]Additional or alternative methods of contraception should be used. Medroxyprogesterone Depot generally effective but should always be used with barrier precautions.
[2]Pravastatin or fluvastatin can be used at the normal dose. Simvastatin must never be used.
[3]Levels of carbamazepine are increased, phenytoin decreased. Valproate is preferred in this situation.
[4]Diazepam and midazolam levels increased significantly, may cause life-threatening over-sedation. Use lorazepam if possible.

ANNEX 9 Data Collection Form: Patient Requiring Third Line ART

Date:

Data collected by:

Patient code
Date of Birth:
Current age:
Clinician Phone number:
ART Site:
ART Site Code:

Patient History	**Instructions:** 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 10 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
I	0-15	Pre-adolescent	None	Pre-adolescent	0-15	Pre-adolescent testes(≤2.5cm)	Pre-adolescent	None	Pre-adolescent
II	8-15	Breast budding(thelarche): areolar hyperplasia with small amount of breast tissue	Long downy public hair near the labia, often appearing with breast budding or several weeks or months later	Peak growth velocity 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
III	10-15	Further enlargement of breast tissue and areola,with no	Increase in amount and pigmentation of hair	Menarche occurs in 2% of girl late in stage III	10.5-16.5	Further enlargement	Signification enlargement, especially in diameter	Increase in amount: curling	Not applicable

		separation of their contours							

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	
IV	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	
V	12.5-18	Large breast with single contour	Adult in distribution	Menarche occur 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 growth 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 11 Child Well-Being Assessment Tool

Statement	None of the Time	Some of the Time	All of the Time
Nutrition			
1. I eat at least two meals a day with at least one meal including some meat and vegetables	☐	☐	☐
2. I have less to eat than other members of my household	☐	☐	☐
Education			
3. I attend school regularly	☐	☐	☐
4. I have the materials I need to do my class work	☐	☐	☐
5. I like school	☐	☐	☐
Financial security			
6. My family has enough money to buy the things we need	☐	☐	☐
Physical health and well-being			
7. I feel strong and healthy	☐	☐	☐
8. I worry about my health	☐	☐	☐
9. I am growing as well as other kids my age	☐	☐	☐
Mental health and social connection			
10. I am as happy as other kids my age	☐	☐	☐
11. I feel optimistic about my future	☐	☐	☐
12. 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	☐	☐	☐
13. I have at least one friend with whom I can share a secret and whom I trust	☐	☐	☐
Pressure, harms, and sexual health			
14. I understand the changes my body goes through during puberty (adolescence)	☐	☐	☐
15. I know how a girl can become pregnant and how to prevent that from happening	☐	☐	☐
16. I know how to avoid getting HIV	☐	☐	☐
17. I can resist pressure to do things that are harmful	☐	☐	☐
18. I feel like I can make my own decisions about things that are important to me	☐	☐	☐

Statement	None of the Time	Some of the Time	All of the Time
19. My body is sometimes abused, for example I sometimes experience strong hitting or beating or bad touch.	□	□	□
20. I do things that can put me at-risk of getting HIV or getting pregnant (girls)/or making someone pregnant (boys)	□	□	□

ANNEX 12 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
- Reach 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 13 Membership of the Sub-Technical Working Group of Pediatric AIDS Care:

1. Dr. Ly Penh Sun	Director of NCHADS
2. Dr. Hout Chan Theany	Vice director of National Pediatric Hospital
3. Dr. Seng Sopheap	Technical Bureau, NCHADS
4. Dr. Sovannarith	AIDS Care Unit, NCHADS
5. Dr. Ngauv Bora	AIDS Care Unit, NCHADS
6. Dr. Ky Sovathana	AIDS Care Unit, NCHADS
7. Dr. Ung Vibol	Vice Dean of Faculty of Medicine
8. Dr. Kim Ratana	National Mother and Child Health Center
9. Dr. Lam Phirum	National Mother and Child Health Center
10. Dr. Khun Kim Eam	National Center for TB and Leprocy Control (CENAT)
11. Dr. Siek Meng	Khmer-Soviet Friendship Hospital
12. Dr. Chea Peuv	Battambang Reference Hosptial
13. Dr. Chhraing Seng Tray	Koma Angkor Children Hospital
14. Representative of CHAI	
15. Representative of FHI	
16. Representative of UNICEF	
17. Representative of WHO	
18. Representative of US-CDC	
19. Representative of Magna	Denisa Augustinova, Say Leakhena
20. Representative of ANRS	
21. Representative of RHAC	
22. Representative of Marie Stopes International	
23. Representative of UNESCO	

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