Kingdom of Cambodia

Nation Religion King

Ministry of Health

National Guidelines for the Use of Pediatric Antiretroviral Therapy

November 2007

National Center for HIV/AIDS, Dermatology and STD control

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PREFACE

These guidelines are an important part of the National Center for HIV/AIDS, Dermatology and STD (NCHADS) strategy to increase access to care, especially Antiretroviral Therapy (ART) for all Cambodians in need. The Care Package of the revised NCHADS Strategic Plan for HIV/AIDS and STI Prevention and Care 2004-2007 identifies the continuous development and revision of policies and guidelines as a key strategy for achieving the objective of "improving and maintaining the quality and accessibility of care for PLHA through extension of health facility based care services nationwide"

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 revision of the 2004 guidelines was important as pediatric AIDS care services in Cambodia have increased and improved very rapidly (from 1 site in 2004 to 22 sites in 2007). At the technical working group meeting, staff from the National Center for HIV/AIDS Dermatology and STDs, the National Pediatric Hospital, Angkor Hospital for Children, and other NGO partners reviewed and revised the 2004 guidelines. Their comments, as well as clinical experience from pediatric AIDS care sites in Cambodia and elsewhere in the region, were incorporated in the revised edition of the guidelines. In addition, the WHO and US-CDC recommendations for HIV/AIDS care and treatment for children were referenced during the revision process to ensure that the guidelines are appropriate and up-to-date.

The Ministry of Health Cambodia has officially approved the National Guidelines for the Use of Pediatric Antiretroviral Therapy and encourage pediatricians to reference the guidelines when providing antiretroviral therapy to HIV-infected children.

Phnom Penh, November , 2007

Secretary of State for Health

Dr. Mam Bun Heng

ACKNOWLEDGEMENTS

The National Center for HIV/AIDS, Dermatology, and STD control would like to acknowledge the dedication of the members of 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 is represented a great achievement of HIV/AIDS care and treatment for HIV infected children in Cambodia, as September 30th, 2007, there are 2 372 children on Highly Active Antiretroviral Therapy (which is equal to 83% of eligible children to ART).

I would like to take this special occasion to thank the staff of the National Center for HIV/AIDS Dermatology and STD control (Dr. Oum Sokhom and Dr. Suos Premprey) for coordinating the revision of these guidelines. I also want to express my gratitude to the pediatricians from the National Pediatric Hospital (Prof. Chhour Y Meng, Dr. Kdan Yuvatha, Dr. Ung Vibol, and Dr. Sam Sophan), Angkor Hospital for Children (Dr. Soeung Seitaboth), French Red Cross (Dr. Olivier Marcy), Clinton Foundation and Brown University, USA (Mr. Lee Gilman and Dr. David Pugatch), who have actively participated in revising of these guidelines. Lastly, I would like thank to all partners, civil societies and CPN+ who have provided care, treatment and support to HIV-infected children in Cambodia.

Phnom Penh, November , 2007

Director of the National Centre for
HIV/AIDS, Dermatology and STI Control

Dr. Mean Chhi Vun

ABBREVIATIONS

3TC	*Lamivudine*
ABC	*Abacavir*
AIDS	*Aquired Immunodeficiency Syndrome*
ALT	*Alanine Transaminase*
AST	*Aspartate Transaminase*
ART	*Antiretroviral Therapy*
ARV	*Antiretroviral drug(s)*
AZT	*Zidovudine*
CBC	*Complete Blood Count*
CD4	*T-CD4+ Lymphocyte*
CMV	*Cytomegalovirus*
CNS	*Central Nervous System*
CK	*Creatine Kinase*
CrCl	*Creatinine Clearance*
d4T	*Stavudine*
ddI	*Didanosine*
DOT	*Directly Observed Therapy*
EC	*Enteric Coated*
EFV	*Efavirenz*
EPTB	*Extra-pulmonary Tuberculosis*
ESRF	*End Stage Renal Failure (Dialysis dependent)*
FDC	*Fixed Dose Combination*
HAART	*Highly Active Antiretroviral Therapy*
HGC	*Hard Gelatin Capsules*
HIV	*Human Immunodeficiency Virus*
HSS	*HIV Sentinel Survey*
HSV	*Herpes SimplexVirus*
IDV	*Indinavir*
IPT	*Isoniazid Preventive Therapy*
LDH	*Lactate Dehydrogenase*
LDL	*Low-Density Lipoprotein*
LIP	*Lymphoid interstitial pneumonitis*

LPV	*Lopinavir*
LPV/RTV	*Lopinavir/Ritonavir*
MAC	*Mycobacterium avium complex*
MTCT	*Mother to Child Transmission*
NCHADS	*National Center for HIV/AIDS, Dermatology and STD*
NFV	*Nelfinavir*
NNRTI	*Non-Nucleoside Reverse Transcriptase Inhibitor*
NRTI	*Nucleoside Reverse Transcriptase Inhibitor*
NtRTI	*Nucleotide Reverse Transcriptase Inhibitor*
NVP	*Nevirapine*
OHL	*Oral Hairy Leukoplakia*
OI	*HIV related Opportunistic Infection*
PCP	*Pneumocystis carinii pneumonia*
PCR	*Polymerase (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*
SGC	*Soft Gelatin Capsules*
STI	*Sexually Transmitted Infection*
SQV	*Saquinavir*
TB	*Tuberculosis*
TDF	*Tenofovir*
TST	*Tuberculin Skin Test*
VCT	*HIV voluntary counseling and testing*
VDRL	*Venereal Diseases Reference Laboratory (refers to a test for syphilis)*
WHO	*World Health Organization*

1. BACKGROUND AND INTRODUCTION:

Cambodia is a country in Asia that has a high HIV prevalence. According to the result of the 2006 HIV Sentinel Survey (HSS) from NCHADS, HIV prevalence HIV/AIDS infections among adults aged 15-49 has declined from 2.0% in 2003 to 0.9% in 2006. The estimate also showed that in 2006 the number of adults (aged 15-49) living with HIV/AIDS was 67,200, and the number of children (aged 0-14) living with HIV/AIDS was 3,870. Despite diminishing prevalence rates, the need for HIV/AIDS treatment and care will be considerable over the next decade, especially as previously infected people progress to advanced and symptomatic stages of the disease. NCHADS also estimated that in 2007 the number of adult patients (aged 15-49) in need of antiretroviral therapy (ART) is 29,200, and these numbers are expected to increase during the next five years. There are approximately 3,000 children also in need of ART.

To respond to the need of care and treatment…Since 2003, the NCHADS has been implementing a Continuum of Care (CoC) framework, which is a comprehensive care, treatment, and support for people living with HIV/AIDS, throughout the country in order to respond to the need of people living with HIV/AIDS. As a result of successful CoC implementation, …. As of September 30, 2007, NCHADS had expanded the HIV/AIDS care and treatment services (including antiretroviral therapy services) to 46 sites for adults and 22 sites for children in 20 provinces. At these sites, there are 22,981 adults and 2,372 children on HAART.

The National Guidelines for the Use of Pediatric Antiretroviral Therapy 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. Update our care and treatment to stay updated with scientific data, studies, etc… main reason the Technical Working Group decided to revise the guidelines). NCHADS with all partners decided to take this opportunity to revise the National Guidelines for the Use of Pediatric Antiretroviral Therapy, which was approved by the Ministry of Health in October 2004.

The 2007 revision of the National Guidelines for the Use of Pediatric Antiretroviral Therapy is a co-product of the NCHADS, the National Pediatric Hospital, Komar Angkor Hospital, and other partners who have been providing treatment, care and support to the children that are living with HIV/AIDS in Cambodia.

These guidelines must be used as a reference document at all of the pediatric AIDS care sites in Cambodia and used as a tool to assist clinical judgment for pediatricians to provide high quality and standardized treatment to HIV-infected children.

2. DIAGNOSIS OF HIV INFECTION IN CHILDREN

This section summarizes the diagnosis of HIV infection in infants and children. The definitive diagnosis of HIV infection in an infant at any age requires diagnostic testing that confirms the presence of the human immunodeficiency virus in the blood of the child. There are two types of tests used to identify HIV infection in children: antibody tests and virologic tests.

A. HIV Antibody Tests

Infants born to HIV-infected mothers carry maternal HIV antibodies transmitted passively during pregnancy. These antibodies can persist for as long as 18 months after birth. Thus, the interpretation of a positive HIV antibody test in children below 18 months of age is difficult. Children under 18 months of age who have positive antibody tests include those who are truly HIV infected as well as those who merely have persistent maternal antibodies but are uninfected.

In resource-limited settings, 74% of HIV uninfected children will test negative at age 9 months, and 96% of HIV uninfected children will test negative at 12 months. One hundred percent of uninfected children will have lost maternal HIV antibodies by 18 months of age. Therefore, in Cambodia, at 12 months most uninfected children will test negative for the HIV antibody.

When an asymptomatic, non-breastfeeding, HIV-exposed infant's HIV antibody test turns from positive to negative before 18 months of age, that infant is considered to be uninfected. However, children who are breastfed by HIV positive mothers have an ongoing risk of acquiring the virus. Infants who have completely stopped breastfeeding for at least 6 weeks and have a negative HIV antibody test are also defined as not infected. Because most HIV uninfected infants will have lost their HIV antibodies by the age of 12 months, positive antibody testing at this age usually indicates an infected child. However, confirmatory testing at 18 months is still recommended.

The HIV antibody test can be used for children aged 18 months or older to determine HIV infection status. A positive HIV antibody test result in a child 18 months or older indicates HIV infection. A negative HIV antibody test result in a child 18 months or older who has never been breastfed or has stopped breastfeeding for more than 6 weeks indicates that the child is **not** HIV infected.

B. HIV Virologic Tests

HIV virologic tests (e.g. Polymerase Chain Reaction or p24 antigen) can detect the HIV virus or its components in the blood of infants. Therefore, these tests can determine HIV status before 18 months of age.

Virologic tests that can be used in children include:

- assays to detect HIV DNA by PCR,
- assays to detect HIV RNA by PCR,
- assays to detect HIV p24 antigen.

HIV-DNA PCR testing can be used as early as 6 weeks of age for accurate infant diagnosis. **In Cambodia, PCR testing is recommended for all known HIV-exposed infants at 6 weeks of age** (See "Schedule of Follow-Up Visits for the HIV-Exposed Infant"—Annex A). A positive PCR test in an infant means that the child is HIV infected. However, a second PCR test to confirm HIV infection should be performed as soon as possible. Infants 6 weeks of age or older who have never breastfed, and who have a negative HIV PCR test, are presumed to be **not** HIV infected.

HIV antibody testing remains the "gold standard" for confirming that a child is truly HIV infected or uninfected. Therefore, HIV antibody testing is recommended at 12-18 months of age to confirm the child's HIV infection status, regardless of earlier PCR results (See Annex A and Child Testing Algorithms 1-4 below).

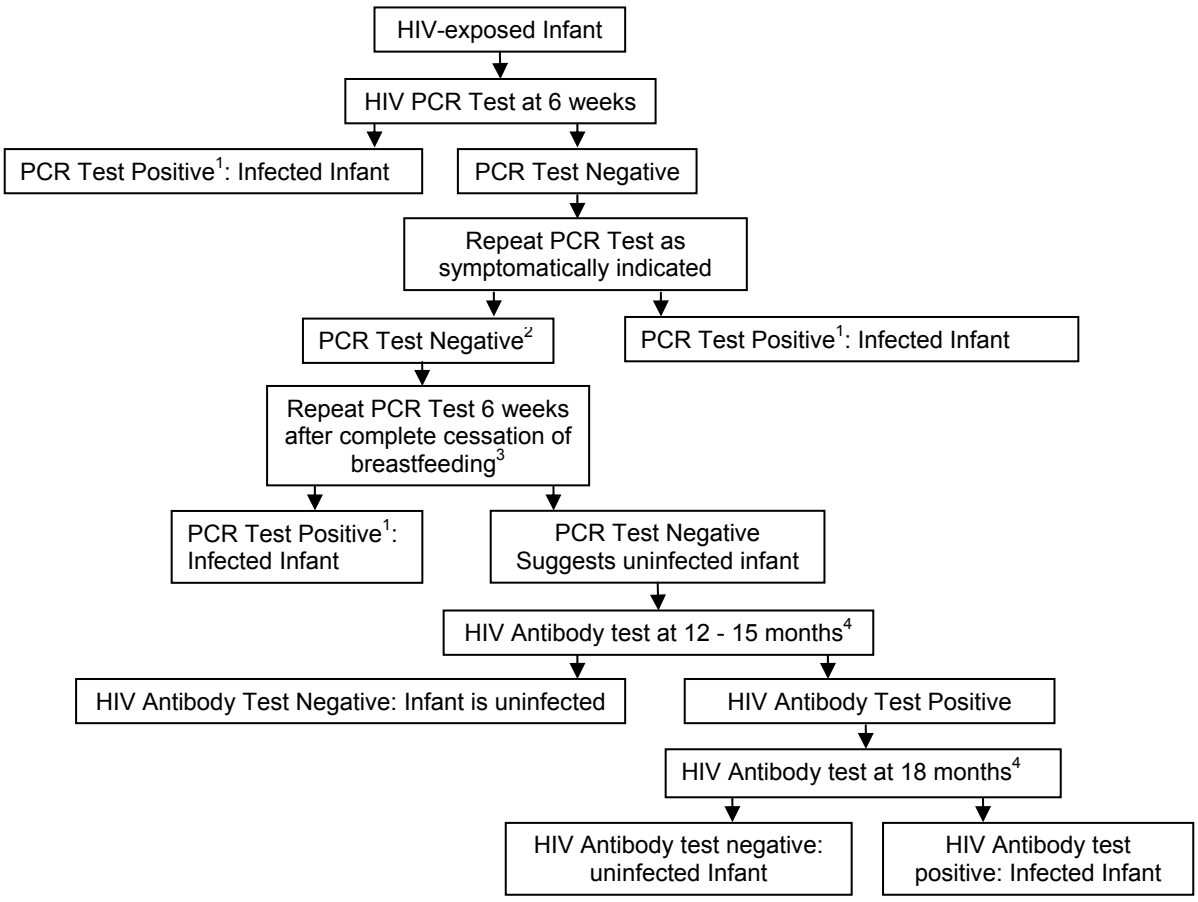
Infants who are breastfed have an ongoing risk of acquiring HIV infection. For infants who are currently being breastfed, a negative PCR test does not rule out HIV infection. Infants who have completely stopped breastfeeding for at least 6 weeks and have a negative PCR test are presumed to be **not** HIV infected. In this situation, HIV antibody testing is recommended at 12-18 months of age to confirm that the child is uninfected (See Annex A and Child Testing Algorithm 1 below).

C. Approach to the Diagnosis of HIV Infection of the HIV-Exposed Infant who is Breastfed (See Child Testing Algorithm 1 below)**:**

In Cambodia, where the majority of infants are breastfed, national policy encourages exclusive breastfeeding until the infant reaches the age of 6 months, followed by rapid weaning from breast milk to age appropriate foods. The availability of PCR testing allows for the possibility of making an early diagnosis of HIV infection at 6 weeks of age in both breastfed and non-breastfed infants. Because breastfed infants have ongoing exposure to the HIV virus through breast milk, a negative PCR test 6 or more weeks after the complete cessation of breastfeeding is required in order to reasonably exclude HIV infection in the breastfed infant. Because HIV antibody testing is considered as the "gold standard" test to confirm the HIV infection status of the infant, HIV antibody testing is still recommended as a confirmation of PCR testing beginning at 12 months of age.

The following child testing algorithm describes the approach to the diagnosis of HIV infection in the HIV-exposed, breastfed infant whose mother's HIV status is known to be positive and who is referred for evaluation:

Child Testing Algorithm 1: Diagnosis of HIV Infection in HIV-exposed Infants who are Breastfed

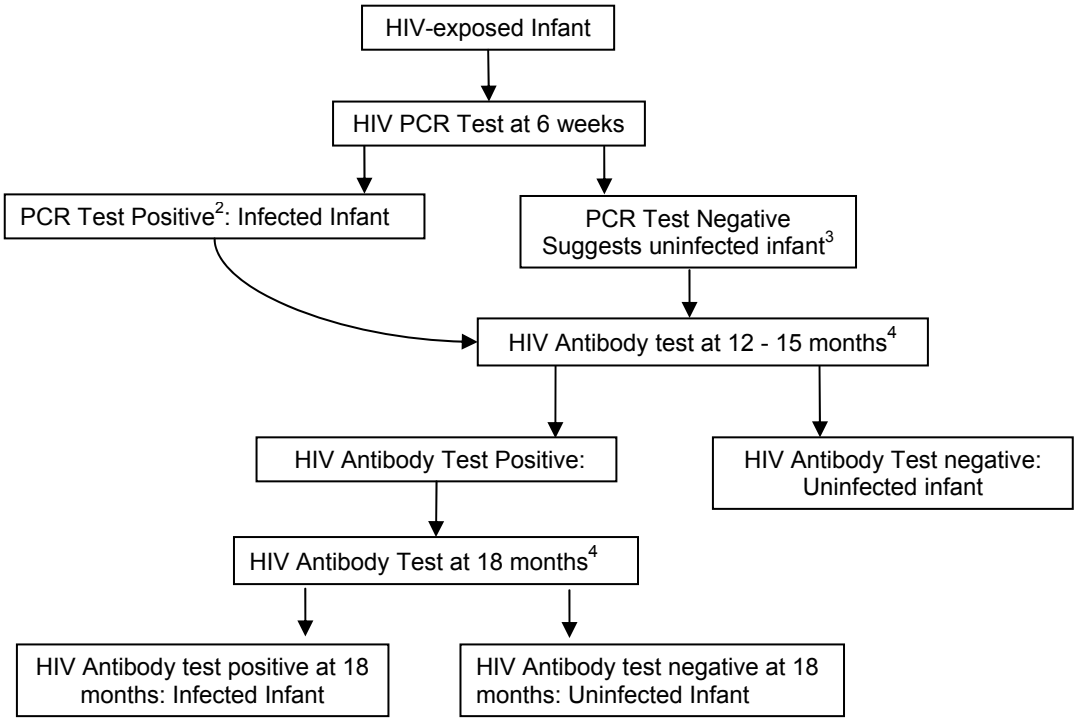


1. Positive HIV PCR result will be confirmed by a second PCR test on a new blood sample as soon as possible. Also confirm HIV status at 18 months with an Antibody test.
2. If breastfed continually past the age of 16.5 months, do not perform a PCR test. Perform HIV Antibody test at 18 months.
3. For HIV-exposed infants, abrupt weaning at 6 months is recommended.
4. For an HIV Antibody test, follow the national guidelines' algorithm for HIV Antibody testing.

D. Approach to the Diagnosis of HIV Infection of the *Non-Breastfed* HIV-Exposed Infant:

It is recognized that in selected cases, formula may be given to the infant when it is acceptable, feasible, affordable, sustainable and safe (esp. considering the availability of clean water). The following Child Testing Algorithm describes the approach to the diagnosis of HIV infection in the HIV-exposed infant whose mother is known to be infected, who has never received breast milk, and who has exclusively been fed formula milk:

Child Testing Algorithm 2: Diagnosis of HIV Infection in non breastfed, HIV-exposed Infants[1]

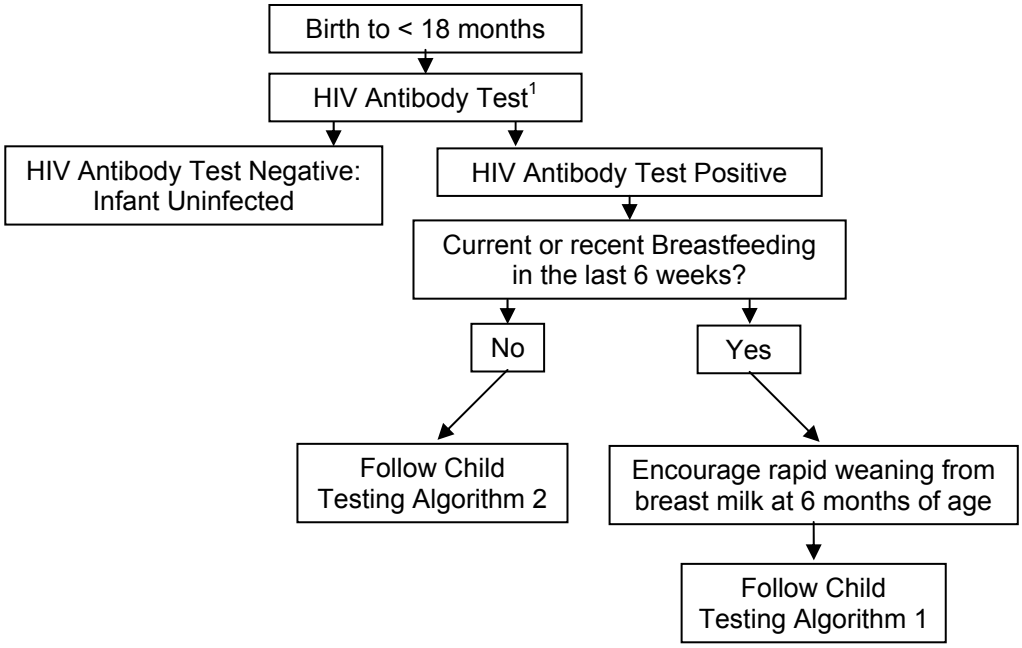


1. If the infant has received any breast milk whatsoever from the mother, the infant is considered as breastfed. Refer to Child Testing Algorithm1.
2. Positive HIV PCR result will be confirmed by a second PCR test from a new blood sample as soon as possible. Also confirm HIV status at 18 months with an Antibody test.
3. Negative HIV PCR test suggests uninfected infant. Further PCR testing should be performed if infant receives any breast milk or if infant develops signs/symptoms of AIDS.
4. For an HIV antibody test, follow the national guidelines' algorithm for HIV Antibody testing

E. Approach to the Diagnosis of HIV Infection in the Child < 18 Months of Age whose Mother's HIV Status is Unknown

Children < 18 months of age whose mother's HIV status is unknown may be identified through clinical signs and symptoms of HIV/AIDS or through other risk factors. The process of HIV testing of such children begins with an HIV antibody test. If the antibody test is negative, then the child is not HIV exposed or infected. If the antibody test is positive, then PCR testing will be the next step, followed by further testing depending upon the breastfeeding status and age of the child.

Child Testing Algorithm 3: HIV Testing of Infants whose mother's HIV status is unknown

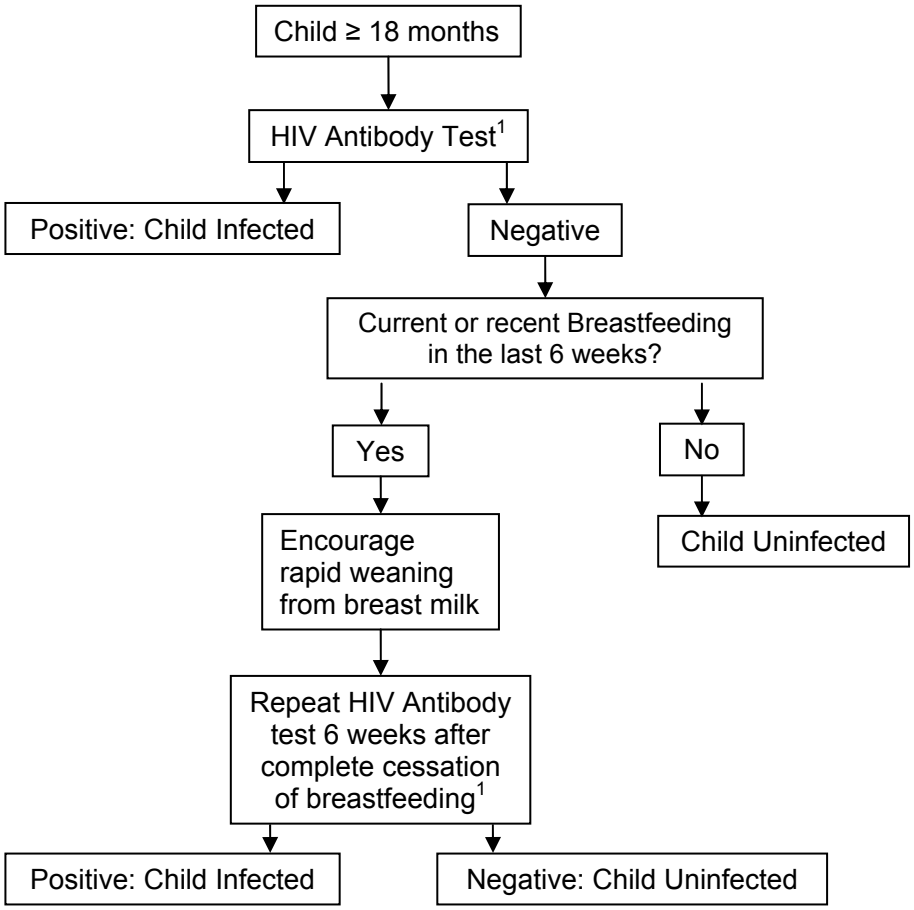


1. For an HIV Antibody test, follow the national guidelines' algorithm for HIV Antibody testing.
2. Positive HIV PCR result will be confirmed by a second PCR test from a new blood sample. Also confirm HIV status at 18 months with an Antibody test.

F. Approach to the Diagnosis of HIV Infection in the Child > 18 Months of Age whose Mother's HIV Status is Unknown and who is referred for Evaluation

Children who are > 18 months of age may be referred for evaluation of their HIV status either through clinical signs and symptoms of HIV/AIDS or because of the presence of other risk factors, such as a parent who has died of AIDS. The HIV infection status for such children may be determined by HIV antibody testing, as described by the diagram below.

Child Testing Algorithm 4: HIV Testing for Children ≥ 18 months who are referred for evaluation



1. For an HIV Antibody test, follow national guidelines' algorithm for HIV Antibody testing

3. WHEN TO START ANTIRETROVIRAL TREATMENT IN INFANTS AND CHILDREN

The decision to start ARV treatment depends on the child's HIV diagnosis, clinical status, immunological status and social parameters.

HIV diagnosis (See Chapter 1--Diagnosis of HIV Infection):
Children younger than 18 months, who have a proven diagnosis of HIV infection by PCR and children older than 18 months who have a proven HIV infection by positive antibody testing, can be considered for starting ARV treatment, depending on the clinical stage of the disease and CD4 count and percentage. In addition, when PCR is not available, very ill HIV-exposed infants who have a presumptive diagnosis of severe HIV should begin ART (see Box 1 below).

Clinical status (See Table 1 below and Annex B regarding WHO clinical staging):
The risk of mortality is increased if the child is in WHO clinical stage 3 or 4. Therefore, it is generally recommended that any child presenting with WHO stage 3 or 4 should start ART. Because children < 12 months of age have the highest risk of HIV disease progression and death, all children < 12 months of age in stage 3 should begin ART. In children >12 months who are in stage 3 with pulmonary or lymph node tuberculosis (TB), oral hairy leukoplakia, or lymphocytic interstitial pneumonia, the CD4 percentage or count should be used to determine the need and timing to start ART. Children of any age in stages 1 and 2 can be monitored regularly for the correct time to start ART, according to their CD4 percentage or count.

Immunological status (see Table 1 below and Annex C for WHO Immunologic staging):
The CD4 threshold to start ARV varies according to age. CD4% is preferred for all children. However, absolute CD4 count should also be considered.

In children with clinical stage 1 or 2, two CD4 tests below threshold should, if possible, be obtained before the initiation of ART.

In brief, **any child with the following criteria should be started on ART**:

Confirmed diagnosis of HIV (or presumptive severe HIV disease in the case of infants without access to PCR testing) and:

1. WHO Pediatric Clinical **Stage 4** (irrespective of CD4)
2. WHO Pediatric Clinical **Stage 3** (irrespective of CD4)
   ARV initiation may be delayed in children older than 12 months if CD4 are above threshold in the following cases:
   a) Pulmonary or lymph node TB
   b) Lymphocytic interstitial pneumonia
   c) Oral hairy leucoplakia
   d) thrombocytopaenia
3. WHO Pediatric Clinical Stage 1 or 2 and CD4 below threshold

Table 1: CRITERIA TO START ARV

WHO Pediatric stage	**≤ 11 months**	**12 to 35 months**	**36 to 59 months**	**≥ 5 years**
1	< 25 % (<1500 cells/mm^3)	< 20% (< 750 cells/mm^3)	<15% (< 350 cells/mm^3)	< 15% (< 250 cells/mm^3)
2				
3	Treat ALL	TREAT all except Pulmonary and Lymph Node TB, LIP, oral hairy leukoplakia or thrombocytopenia with CD4 above the threshold (see CD4 criteria)		
4	Treat ALL			

Box 1. Starting ART in Children Less Than 18 Months without a Confirmed Diagnosis of HIV Infection

If HIV PCR testing is not 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 HIV positive 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

Other factors that support the diagnosis of severe disease in an HIV seropositive infant include:

- Recent HIV-related maternal death or advanced HIV disease in the mother;
- CD4 < 20%.

Social considerations relevant to starting ARVs in children: In order to begin ART, the child needs to have a clearly defined caregiver who understands the child's needs for HIV medical care, understands the importance of medication adherence, and demonstrates a readiness to participate as the child's caregiver regarding adherence to the child's clinic appointments and medications.

4. CHOOSING A FIRST-LINE REGIMEN

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. The child's first ARV regimen offers the best chance to achieve durable viral suppression. Therefore, it is crucial to maximize the durability and efficacy of any first-line regimen by incorporating approaches to support adherence. The choice of ARV regimen should balance efficacy, toxicity, palatability and cost-effectiveness.

First-Line Regimen:
When choosing a first-line regimen for infants and children, the preferred option is two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI).

Recommended First-Line Regimens

Children < 3 years or < 10kg

Zidovudine (AZT) + Lamivudine (3TC) + Nevirapine (NVP)
or
Stavudine (d4T) + Lamivudine (3TC) + Nevirapine (NVP)

Children ≥ 3years or ≥ 10kg

Zidovudine (AZT) + Lamivudine (3TC) + Nevirapine (NVP) or Efavirenz (EFV)
or
Stavudine (d4T) + Lamivudine (3TC) + Nevirapine (NVP) or Efavirenz (EFV)

When selecting an initial pediatric regimen, there are several special issues to consider:

Choice of NRTIs:

- Lamivudine (3TC) is a potent NRTI with an excellent record of efficacy, safety and tolerability in HIV-infected children and is a core component of the dual NRTI backbone of treatment.
- Stavudine (d4T) is initially better tolerated than Zidovudine (AZT) and does not require baseline and regular hemoglobin monitoring. The use d4T is complicated by the absence of an ideal formulation for small children. While liquid Stavudine is available, it requires refrigeration and a secure cold chain, often unavailable in rural settings. An option with d4T capsules is to open the capsules and dissolve the powder in a small volume of water before administering the medication. Despite its lack of short-term toxicities, d4T is associated with a greater risk of long-term toxicities than other NRTIs, due to its effects on mitochondria, especially lipoatrophy, lactic acidosis, and peripheral neuropathy. While these toxicities have been described mainly in adult patients receiving d4T, they may limit the long-term use of d4T in children.

- Zidovudine (AZT) is generally well-tolerated in children but should not be used in cases of severe anemia (Hemoglobin (Hb) < 7.5g/dL). AZT requires close monitoring of Hb and absolute neutrophil count (ANC).

Choice of NNRTIs:

- Efavirenz (EFV) is not currently recommended for use in infants and children under 3 years of age. Therefore, Nevirapine (NVP) liquid should be used for these young children. EFV capsules can be opened and the granules can be combined with something sweet to mask the bitter taste. The decision to start EFV in a young girl entering her child-bearing years requires careful consideration. EFV has been associated with birth defects and is contraindicated during the first trimester of pregnancy.
- Nevirapine (NVP) is currently the only NNRTI syrup available for infants in Cambodia. It also exists as part of a three-drug fixed dose combination (FDC)—see Annex E. NVP may be the preferred choice for adolescent girls because of the potential for pregnancy.
- Special considerations on dosing and administration for NVP:
    - *Induction dose*: once daily for the first 14 days (to minimize the frequency of skin rash). The induction dose is half of the daily maintenance dose of NVP and is given once daily, except where the maintenance dose is divided unequally between a.m. and p.m. If the patient experiences a rash during the course of this induction dose, the dose should not be escalated to maintenance dose until the rash has subsided. If a severe rash occurs (especially if accompanied by fever, blistering or mucosal ulcerations), NVP should be permanently discontinued.
    - *Maintenance dose*: target dose is 160-200 mg/m^2/dose given twice daily and adjusted for more aggressive dosing in younger children (see Annex E).
- The use of NVP-based ARV therapy in infants who have previously received NVP as a single dose to prevent mother-to-child transmission raises concerns about resistance. Several studies have shown that both women and children who receive single-dose NVP (SD-NVP)—*ALONE and without other ARVs*—are at risk for developing NNRTI resistance mutations. In this situation, NNRTI regimens are contraindicated and a Protease Inhibitor (PI) instead of an NNRTI is recommended.
- For children enrolled in the new National Prevention of Mother-to-Child Transmission (PMTCT) Programme (i.e., received SD NVP + AZT twice a day for 1 week or 4 weeks), NNRTI–based therapy is not contraindicated and remains the recommended first-line regimen.

Choice of PIs:

- Lopinavir/Ritonavir (LPV/r) is the preferred PI for use in children. The LPV/r liquid formulation (80mg/20mg) requires a secure cold chain until the medication is delivered to the patient, at which point it can be maintained at 25^{o}C for up to 30 days. A heat-stable LPV/r tablet (200mg/50mg) is now available for use in older children.
- Nelfinavir (NFV), though not the preferred PI, can be considered in settings where temperature control is not feasible. Tablets can be split or crushed and suspended in a small volume of water for administration. Troublesome side effects of diarrhea and loose stools limit its usefulness.

Recommended First-Line Regimen
When NNRTI-Based Treatment is Contraindicated

Zidovudine (AZT) or Stavudine (d4T) + Lamivudine (3TC) +Lopinavir/ritonavir (LPV/r)

The use of a triple NRTI regimen **(AZT or d4T + 3TC + ABC)** can be considered as an option in young children < 3 years of age receiving TB treatment including Rifampicin (see Chapter 10—TB Co-infection).

5. ARV DRUG TOXICITY AND ALTERNATIVE FIRST-LINE REGIMENS DUE TO TOXICITY

ARV drug toxicities, also known as adverse events or adverse drug reactions to ARVs, are sometimes difficult to differentiate from adverse events from other drugs (e.g. INH-induced hepatitis, cotrimoxazole-induced rash), complications of HIV infection or progression of other diseases (e.g. hepatitis or malaria).

ARV toxicities in children are similar to those observed in adults but occur at different frequencies (e.g. fewer NVP-related hepatotoxicity, more EFV-related rash). Some are also specific in children, such as TDF-related loss of bone density.

ARV toxicities can occur within the first days or weeks of treatment or can be delayed. Their severity ranges from mild and moderate to severe or life threatening (Cf. Annex Severity Grading of Selected Clinical and Laboratory Toxicities). They can be classified in several types of distinct toxicities, detailed in the table below.

Table 1: Types of Distinct Drug Toxicities Observed with ARVs.

Type of drug toxicity	Details	Drugs usually involved
Hematological toxicity (drug-induced bone marrow suppression)	Anemia, neutropenia and, more rarely thrombocytopenia	AZT
Mitochondrial dysfunction	Peripheral neuropathy, lactic acidosis, hepatic toxicity, pancreatitis	d4T (all NRTIs drugs)
Lipodystrophy and metabolic abnormalities	Fat maldistribution and body habitus changes, hyperlipidaemia, hyperglycaemia, insulin resistance, diabetes mellitus, osteopenia, osteoporosis and osteonecrosis	Primarily seen with d4T and the PI class, and to a lesser degree with certain other NRTI drugs
Allergic reactions	Skin rashes and hypersensitivity reactions	More common with the NNRTI drugs but also seen with certain NRTI drugs, such as ABC

Mild or moderate toxicities most often occur shortly after beginning treatment and spontaneously resolve themselves within a few weeks of starting the medication: for instance, central nervous system (CNS) symptoms with EFV (dizziness, insomnia, abnormal dreams, and personality change), gastrointestinal (GI) intolerance with AZT. The child and caregiver must be informed about these possible distressing side effects in order to cope with them without a negative impact on adherence. The caregiver should know that if symptoms become severe, he/she should bring the child to the clinic or hospital.

Some toxicities 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 (Cf. table 2 and 3).

Other toxicities occur after months or years of antiretroviral treatment. These include lipoatrophy, neuropathy, hyperlactatemia and mitochondrial cytopathy. These toxicities can be life threatening (lactic acidosis), disabling (neuropathy), or impact adherence (lipoatrophy in adolescents).

Table 2: Summary of the major toxicities of antiretroviral drugs

Name of drug	More common side effect	Less common (more severe)	Rare
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)			
Zidovudine (ZDV, AZT)	Anemia, neutropenia Headache, nausea.	Myopathy, myositis and liver toxicity.	Lactic acidosis
Stavudine (d4T)		Lipoatrophy Peripheral neuropathy Lactic acidosis Hepatic toxicity	Increased liver enzymes
Lamivudine (3TC)			Pancreatitis (children w/ advanced HIV stage and other medications) Mitochondrial toxicity(a)
Abacavir (ABC)		Hypersensitivity reaction	Mitochondrial toxicity(a)
Didanosine (ddI)		Pancreatitis Lactic acidosis Hepatic toxicity	
Tenofovir (TDF)	Renal toxicity Fanconi's syndrome	Gastrointestinal effects Bone toxicity	
Non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs)			
Nevirapine	Skin rash Asymptomatic transaminases elevation	Hepatitis Hypersensitivity reactions	
EFV	CNS symptoms (somnolence, insomnia, confusion, abnormal dreams, abnormal thinking…) in first weeks of treatment Skin rash		Teratogenicity
Protease inhibitors (PIs)			
Lopinavir/ritonavir (LPV/r)	Diarrhea, nausea, vomiting	Lipodystrophy	Pancreatitis, hyperglycemia, ketoacidosis, diabetes and hepatitis
Nelfinavir	Diarrhea	Abdominal pain Lipodystrophy	Hyperglycemia, ketoacidosis and diabetes
Indinavir	Nausea, abdominal pain, headache, metallic taste, asymptomatic hyperbilirubinaemia and Dry skin and lips	Kidney stones/nephritis Exacerbation of chronic liver disease Lipodystrophy	Hyperglycemia, ketoacidosis, diabetes and hemolytic anemia
Ritonavir	Nausea, vomiting, diarrhea, headache, abdominal pain and anorexia	Circumoral paresthesia Increases in liver enzymes Lipodystrophy	Pancreatitis, hyperglycemia, ketoacidosis, diabetes and hepatitis.
Saquinavir	Diarrhea, abdominal discomfort, headache, nausea, paresthesia, skin rash	Lipodystrophy	Hyperglycemia, ketoacidosis and diabetes

Adapted from: PENTA guidelines for the use of antiretroviral therapy, 2004. M Sharland, S Blanche, G Castelli, J Ramos and DM Gibb on behalf of the PENTA Steering Committee.

(a): mitochondrial toxicity: lactic acidosis, hepatic toxicity, Pancreatitis. Some cases reported have been fatal.

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 specific ARV combination regimen used.

Mild toxicities do not require discontinuation of therapy or drug substitution, and symptomatic treatment may be given.

Moderate and severe toxicities may require the substitution of an ARV drug associated with toxicity by a drug in the same ARV class but with a different toxicity profile (e.g. peripheral neuropathy), or by a drug in a different class, but do not require discontinuation of all ART.

Severe life-threatening toxicities requires discontinuation of all ARV drugs and the initiation of appropriate supportive therapy, depending on the toxicity, with substitution of another drug for the one associated with the toxicity once the patient is stabilized and the toxicity is resolved (see Annex F). NNRTI drugs have a much longer half-life than NRTIs, leading to a concern that stopping all drugs simultaneously results in exposure to drugs from the NNRTI class only. However, in cases of life-threatening toxicity, all ARVs should be stopped simultaneously until the patient is stabilized.

Table 3: Management of ARV Toxicity of First-Line Drugs and Recommendations for ARV Drug Substitution

First-line ARV drug	Most frequent significant toxicity for the ARV drug	Details	Suggested first-line ARV drug substitution
Zidovudine AZT	Severe anemia(a) or neutropenia	If Hb drops by 25% or more from the baseline OR Hb <7.5 g/dl. If neutrophil count <500/mm3.	Stop AZT, switch to d4T (or ABC in d4T intolerance)
	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
	Myalgia, myopathy	CPK >10; weakness	d4T (or ABC in d4T intolerance)
	Severe gastrointestinal intolerance	Persistent nausea and vomiting that prevents ingestion of ARV. Minor degrees are common, but almost always improve during the first month of ART	d4T (or ABC in d4T intolerance)
Stavudine d4T	Peripheral neuropathy	Numbness or paresthesia of fingers, toes	Switch to AZT if no severe anemia, give vitamin B complex + analgesics
	Lipoatrophy/metabolic syndrome		AZT or ABC (in case of severe lipoatrophy)
	Lactic acidosis	Cf. above	Stop all ARVs until symptoms disappear, switch to ABC
Nevirapine NVP	Severe potentially life threatening acute	ALT>10N	Stop all ARVs, restart when ALT 2 N, replace NVP by

	symptomatic hepatitis		LPV/r
	Dry rash (mild or moderate rash Annex F Grading)	Dry rash: macules, papules, dry desquamation	Continue NVP same dose (½ dose if lead in period). Give anti-histamine drug. Switch to EFV if rash lasts more than 1 month(b)
	Wet rash (severe rash Annex F Grading)	Wet rash: vesicles, ulcers, limited moist desquamation, limited mucous membranes involvement	Stop NVP and continue NRTI, start with EFV when symptoms resolve (b) If systemic signs and/or ALT>5N, stop all ART and restart with LPV/r.
	Life-threatening rash (Stevens-Johnson syndrome or Lyell)	Extended moist desquamation, mucous membranes involvement Systemic signs, e.g. fever	Stop all ARVs, restart LPV/r based HAART when symptoms resolve.
	Hypersensitivity reaction	Systemic symptoms of fever, myalgia, arthralgia, hepatitis, and eosinophilia with or without rash	Stop all ARV until symptom resolves and switch NVP to LPV/r (EFV should be avoided)
Efavirenz EFV	Persistent and severe central nervous system toxicity	Persistent hallucinations or psychosis	Switch to NVP
	Potential teratogenicity	Adolescent girl in first trimester of pregnancy, or of childbearing potential and not receiving adequate contraception	Switch to NVP
	Dry rash		Stop all ARVs, restart with EFV when symptoms resolve.
	Wet rash or life-threatening rash (Stevens-Johnson syndrome or Lyell)		Stop all ARVs, restart with LPV/r when symptoms resolve.
Didanosine ddI	Pancreatitis	Severe nausea and vomiting Severe abdominal pain Elevated amylase Elevated lipase	Stop ddI. Replace by 3TC if second-line treatment.
Abacavir ABC	Hypersensitivity reaction	Fever, rash (often maculopapullar and mild), nausea, vomiting, diarrhea, fatigue, flank or abdominal pain, respiratory symptoms, myalgia, and arthralgia (1st 6 wks of ART, 4% of patients)	Stop immediately ABC, switch to AZT if used in first-line or 3TC if second-line **Never reintroduce ABC**

Note: 3TC-associated pancreatitis has been described in adults but is considered very rare in children. Cases of mitochondrial toxicities have also been reported.

Exclude malaria in areas of endemic malaria.

(b) EFV is not currently recommended for children <3 years of age, and should not be given to postpubertal adolescent girls who are either in the first trimester of pregnancy or are sexually active and not using adequate contraception.

6. TREATMENT FAILURE

The chronology of treatment failure is virological failure, then immunological failure, and then clinical failure. It is recommended to switch to second-line drugs before clinical failure occurs. When there is extended access to virological assessment of ART, then virological failure will become the criterion to switch to second line.

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
    - Not appropriate time
    - Not appropriate dose (misunderstanding, sharing drugs)
- Inadequate drug levels:
    - Under-dosing
    - Poor absorption (diarrhea)
    - Varying pharmacokinetics
    - Metabolic changes in a growing child
    - Drug-Drug interactions (See Annex I)
    - Prior existing drug resistance
    - Inadequate potency of the drugs chosen

It should not be concluded, on the basis of clinical criteria, that an ARV regimen is failing until the child in question has had a reasonable trial on the therapy (i.e. the child should have received the regimen for at least 6 months), adherence to therapy should have been assessed and considered to be optimal, and any intercurrent opportunistic infections should have been treated and resolved, and immune reconstitution inflammatory syndrome (IRIS) excluded. Additionally, before considering a change in treatment because of growth failure it should be ensured that the child is receiving adequate nutrition.

CLINICAL FAILURE

Clinical failure is the development of new or recurrent stage 3 or 4 events at least 6 months after starting therapy with a first-line regimen (except pulmonary or lymph node TB).

- Occurrence of new opportunistic infections or malignancies, or recurrence of infections, such as oral candidiasis that is refractory to treatment, or oesophageal candidiasis (WHO pediatric stage 3 or 4)
- Lack of or decline in growth rate in children who showed an initial response to treatment (WHO pediatric stage 3 or 4, moderate or severe unexplained malnutrition not adequately responding to standard therapy despite adequate nutritional support and without other explanation)
- Loss of neurodevelopmental milestones or development of encephalopathy (WHO pediatric stage 4)

IMMUNOLOGICAL FAILURE (after 6 months of treatment)

- Age-related severe immunodeficiency (new or after initial immune recovery or persistent despite adequate therapy), specially if <15% (12-35 months of age), <10% (36-59 months), <100 cells/mm^3 (≥ 5 years).
- Rapid rate of decline of absolute CD4 (>30%) or CD4 percentage (in children with <15% CD4 a decrease of 5 percentiles).

VIROLOGICAL FAILURE

The definition of virological failure in children is more complex. The overall aim of treatment is to reduce viral load (VL) to levels below the lowest detection threshold (50 to 400 copies/mL) as rapidly as possible and to maintain undetectable levels for as long as possible. However, in children, VL can remain detectable between 1000 and 50000 copies for a long time with excellent immunological and clinical response. The presence of continued viral replication is nonetheless associated with increasing cumulative risk of the acquisition of resistance mutations, which may eventually drive to immunological and clinical failure as well as compromise subsequent ART combinations, due to the cross-resistance induced by many resistance mutations.

Viral load is not yet a routine test in Cambodia and the issue of preserving future therapeutic options needs to be considered. If VL is available it can be used to closely monitor adherence and treatment failure by having a baseline and regular VL follow-up. If limited availability, it can be used to rule out virological success in patients with suspected clinical or immunological failure.

However, a VL consistently higher than 100,000 copies/ml (5.0 Log) alone should lead to switch to second line.

In the context of immunological +/- clinical failure, a switch to second-line is necessary even if the VL is lower than 100,000 copies/ml.

(When immunological failure +/- clinical failure is present, any VL higher than 10,000 copies (4 Log) is considered as confirming the diagnosis of failure. If VL is lower than 10.000 copies (4 Log), patient should be assessed for undercurrent OI such as Mycobacterium Avium Complex infection or Tuberculosis.)

Table 2: Correlation between Number of Copies and Log for Viral Load Testing

Copies/ml	Log
400	2,6
1,000	3,0
10,000	4,0
20,000	4,3
30,000	4,5
50,000	4,7
100,000	5,0

A significant change between two VL measurements from the same patient is defined as a 3 fold difference (+/-0.5 Log)

SUMMARY BOX: CONDITIONS TO CONSIDER TREATMENT FAILURE

- The child has received the ARV treatment for at least 6 months
- Adherence to therapy has been assessed and considered to be optimal
- Opportunistic infections have been treated and resolved
- IRIS has been excluded
- Immunological failure +/- clinical failure, virological failure

7. CHOICES FOR SECOND-LINE TREATMENT

In cases of treatment failure, the entire regimen should be changed from a first-line to a second-line regimen. The second-line regimen should preferably include 3 new drugs—2 new NRTIs and a change of drug class for the third drug. With a standard NNRTI-based first-line, the second-line regimen should be based on a Ritanovir (RTV)-boosted protease inhibitor:

Preferred second-line regimen

Abacavir (ABC) + Didanosine (ddI) + Lopinavir/ritonavir (LPV/r)

For children treated with PI in their first-line regimen, EFV can be used in the second-line regimen:

- **Abacavir (ABC) + Didanosine (ddI) + Efavirenz (EFV)**

In cases of ABC hypersensitivity in second-line treatment, ABC should be replaced by 3TC. TDF can be used in children older than 10 years of age but should not be used with ddI.

Alternative second-line regimens:

- ddI + 3TC + LPV/r (In case of ABC hypersensitivity or unavailability of ABC)
- AZT + ddI + LPV/r (If 1st line regimen contains ABC)
- TDF + 3TC + LPV/r (In children older than 10 years of age)

The following second-line regimens should be avoided:

- TDF + ddI Triple Combinations (lacks potency)
- ddI + d4T Triple Combinations (liver toxicity)

IMPORTANT
In the context of switching to second-line treatment:
Never change EFV to NVP or NVP to EFV as they are cross-resistant.
Never change D4T to AZT or AZT to D4T as they are cross-resistant.
(*These switches remain possible when switching from first-line to alternative first-line for toxicity*).

8. CLINICAL AND LABORATORY MONITORING

Clinical and laboratory assessments are required for all HIV infected children who are registered into pediatric AIDS care services. Assessments are performed at the first and subsequent visits. At the first visit, medical and psycho-social history should be obtained and recorded in the child's medical chart. Other assessments, such as counseling support, disclosure and prevention issues, as well as particular needs for home- and community-based services (HCBC), should be obtained and addressed.

A. Baseline Clinical and Laboratory Assessment
(Tables 1 and 2)

All HIV infected children who are diagnosed with HIV should undergo baseline clinical and laboratory assessment to determine the clinical stage of the HIV infection, and they should receive CD4 testing to determine eligibility for ART. Routine and ongoing clinical and laboratory monitoring should be performed to provide the clinician with baseline information. Monitoring should also be performed during follow-up HIV care for children who are either eligible or not eligible to receive ART.

A.1- ***Clinical assessment***

The clinical assessment at **baseline** should include:

- Clinical staging of HIV infection (Annex B)
- Identification of concomitant medical conditions (TB, other OIs, pregnancy)
- Detailing of concomitant medications such as cotrimoxazole and others drugs for OI prevention or treatment
- Traditional or herbal therapy
- Weight, height, head circumference, and measures of growth (Annex J)
- Development status
- Nutritional status
- Assessment of children and parents or caregivers for preparedness for ART

A.2 – ***Laboratory assessment***

The laboratory assessment at **baseline** should include:

- Measurement of CD4 (CD4 cell count and % for all children) (see Annex C)
- White Blood Cell (WBC)
- Hemoglobin
- Viral load (VL)
- Screening for TB and other HIV co–infections, treatable diseases, and HIV-related opportunistic infections (OI)
- Liver function testing (LFT) at baseline and if clinically indicated
- Fasting cholesterol, triglycerides and glucose every 12 months (adolescents only)

B. Routine Monitoring of Children *not yet* eligible for ART
(Table 1)

For children who are not eligible for ART, clinical evaluation should be performed every month for the first three months, at six months, and every six months thereafter. Because the risk of rapid disease progression is greater for infants and young children, clinical and laboratory monitoring should occur more frequently. **CD4% and count should be taken every 3 months in children <12 months of age.** The pediatric clinical and immunological stage should be evaluated at each visit.

Table 1: Schedule of Routine Clinical and Laboratory Monitoring for the HIV-Infected Child *Not on* ART

Items	Baseline	Month 1	Month 2	Month 3	Month 6	Every 6 months	Symptom Directed
Clinical							
Clinical Evaluation (a)	X	X	X	X	X	X	X
Weight, Height and Growth Charts	X	X	X	X	X	X	
Nutritional Status and Feeding	X	X	X	X	X	X	
Cotrimoxazole Need and Adherence	X	X	X	X	X	X	
Counseling for Prevention of STIs and Pregnancy (b)	X				X	X	
OI Prevention and Treatment Needs, especially TB (c)	X	X	X	X	X	X	X
Laboratory							
WBC and Hb	X				X	X	X
Liver Transaminase: ALT, ASAT (d)	X						X
CD4 % and CD4 count (e)	X				X	X	X

(a) Includes history-taking, physical examination and assessment of neurodevelopment. Children <12 months of age have higher risk of HIV disease progression and should be followed more frequently than older children.
(b) In adolescent girls 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) Exposure to TB should be assessed.
(d) Children who have elevated liver enzymes should be tested for hepatitis B and hepatitis C using serology testing.
(e) CD4% and count should be taken every 3 months in children <12 months of age.

C. Routine Monitoring of Children *on* ART
(Table 2)

Once the child is initiated on antiretroviral therapy (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.

C.1-*Clinical assessment:*

Important elements of clinical monitoring should include:

- Clinical evaluation, including neurological and developmental assessment
- Weight, height and growth assessment
- Nutritional status and feeding
- Assessment of ARV dosing, side effects, toxicities and drug interactions
- Assessment of frequency of infections such as bacterial, fungal and opportunistic infections
- Adherence to ART
- Counseling for Prevention of STIs and Pregnancy

C.2- *Laboratory assessment:*

- WBC every three months or more frequently, if clinically indicated
- Hemoglobin testing during the first few months at weeks 4, 8, 12, and then every 6 months if child is on an AZT regimen
- Liver function testing at weeks 4, 8, 12, and every 6 months or more frequently if clinically indicated
- CD4 count/percentage every 6 months, or if symptom directed
- Viral load testing every 6 to 12 months (if available)
- Fasting cholesterol, triglycerides and glucose every 12 months (adolescents only)

Some routine laboratory monitoring should be performed in accordance with the use of specific drugs and with the occurrence of certain clinical signs or symptoms during therapy.

Table 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 4	Month 5	Month 6	Every 2-3 mo	Every 6 mo	Every 12 mo	Symptom Directed
Clinical												
Clinical evaluation	X	X	X	X	X	X	X	X	X			X
Weight, Height, and Growth Charts	X	X	X	X	X	X	X	X	X			
Nutritional Status and Feeding	X	X	X	X	X	X	X	X	X			
ARV Dosing, Side Effects, Toxicities, Drug Interactions	X	X	X	X	X	X	X	X	X			
Need for OI Medications and Doses	X	X	X	X	X	X	X	X	X			
Adherence to ART		X	X	X	X	X	X	X	X			
Counseling for Prevention of STIs and Pregnancy (a)	X										X	X
Laboratory												
WBC and Hb (b)	X		(X if AZT)		X			X		X		X
Liver Transaminase: ALT, ASAT (c)	X		X		X			X				X
CD4 % and CD4 count (d)	X							X		X		X
Viral Load	X							X		X		
Fasting cholesterol, triglycerides and glucose (e)	X										X	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, especially for those on EFV regimens.
(b) WBC and Hb should be considered if on AZT at month 1 and month 3.
(c) Children who have elevated liver enzymes should be tested for hepatitis B and hepatitis C using serology testing.
(d) CD4% and count should be taken every 3 months in children <12 months of age.
(e) In adolescents, fasting tests for cholesterol, triglycerides and glucose should be performed at baseline, every 12 months, and as symptom direc

9. ADHERENCE TO ART IN CHILDREN

Greater than 95% adherence to the child's ARV drug regimen will ensure a good virological response and prevent the likelihood of viral resistance. For a child taking medication twice daily, omitting more than 1 dose in 10 days (3 in one month) implies <95% adherence, which is suboptimal.

- Adherence in children is a special challenge because of factors relating to children, caregivers, communities, medications and the interrelationships of these factors.

- For older children and adolescents, HIV status should be disclosed in order for them to take part in their treatment and have good adherence.

- The commitment of a responsible caregiver is necessary before starting ARVs. If a sick mother or father is responsible, it is preferable that a secondary (back-up), informed caregiver be involved in the care of an HIV-infected child.

- A good relationship between the healthcare providers (i.e., counselors, nurses, and doctors), the child and the caregiver helps to optimize adherence. The Home Based Care Team (HBC) plays an important role in encouraging caregivers and children to go to regular appointments and have high adherence. Regular education and support during each clinic visit is necessary to enhance and maintain good adherence.

- At least 3 educational visits with the caregiver and child are suggested prior to starting ART to make sure that the child (if old enough) and caregiver understands HIV and its natural history, the benefits and side effects of ARVs, how the medications should be taken, and the importance of not missing any doses. These visits will also be useful to identify barriers to adherence and to help the family solve potential problems.

- When choosing a regimen, it is best to minimize the number of pills, the volumes of liquids, the frequency of dosing, and/or food restrictions. FDCs (fixed dose combinations), blister packs or other facilitating presentations of drugs should be used where available.

- Techniques to improve adherence with young children include: tasting of medications, practicing the measurement of liquids, and training in pill swallowing. Adherence can be improved by using pill boxes, calendars with stickers, drawings or pictures of the drugs, labeled syringes, glasses for elderly caregivers with ocular impairments, alarm watches, 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. When possible and appropriate, it may help to match drug regimens for children and adults in the same family. Adherence can further be improved by preparing children and caregivers for common, non-severe adverse effects.

- The provider may monitor adherence using self-report methods such as diary cards, medication checks, counting of remaining pills and other measures.

- To ensure the best outcomes of children who start ART, the interruption of the first- line regimen by the family or the health facility should be avoided. Treatment must never be interrupted without a valid medical reason.

- The assessment of adherence should be a concern of every healthcare provider participating in the care of children. An assessment should be performed whenever there is a visit to a health centre in order to identify children in need of the greatest support for adherence.

10. TB AND HEPATITIS CO-INFECTION

Considerations for infants and children co-infected with tuberculosis and HIV

Tuberculosis (TB) is a major cause of illness and death for PLHA. HIV infection increases susceptibility to infection with *Mycobacterium Tuberculosis* and the risk of rapid progression to TB disease.

A. Considerations for the diagnosis of TB

In many cases, particularly in young children, diagnosis is presumptive and is based on a consultation of clinical signs and symptoms, known contact with a household member with TB disease, and the child's response to anti-TB treatment. Diagnosis for TB should be made according to the Cambodian National Guidelines for TB Treatment in Children.

B. When to start ART in children receiving TB treatment

The decision of when to start ART after starting TB therapy involves a balance between the child's age, the pill burden, potential drug interactions, overlapping toxicities and possible immune reconstitution syndrome versus the risk of further progression of immune suppression. Careful evaluation is necessary for judging when to start ART. For patients with Pulmonary TB or Lymph Node TB (WHO clinical stage 3), the results of CD4 measurements are important in making decisions about the urgency of initiating ART.

In the cases below, ART should begin between 2 and 8 weeks after the start of TB treatment, when the child has stabilized on TB therapy *(See "Table 1: Criteria to Start ARV" in Chapter 3)*:

- Extra-pulmonary TB or disseminated TB (WHO clinical stage 4), except Lymph Node TB (WHO clinical stage 3)
- Pulmonary TB or Lymph Node TB (WHO clinical stage 3) when child is <12 months of age
- Pulmonary TB or Lymph Node TB (WHO clinical stage 3) when child is >12 months of age with a CD4 test under the eligibility threshold for starting ART

For children diagnosed with Pulmonary TB or Lymph Node TB (WHO clinical stage 3) **and** CD4 >15% in children aged ≥ 36 months or CD4 >20% in children aged 12-35 months, ART should be deferred.

C. ARV regimen in children receiving TB treatment

There are many interactions between ARVs and other drugs, particularly TB drugs. The interactions between TB treatment containing Rifampicin and the NNRTI and PI classes are complex. Rifampicin stimulates the activity of the cytochrome P450 liver enzyme system, which metabolizes PIs and NNRTIs. This can lead to decreased blood

levels of PIs and NNRTIs. PIs and NNRTIs can also enhance or inhibit this same enzyme system and lead to altered blood levels of rifampin. The potential drug interactions may result in ineffectiveness of ARV drugs, ineffectiveness of TB treatment or an increased risk of drug toxicity.

- In children over 3 years of age, a standard first-line regimen of two NRTIs + EFV (i.e. AZT or d4T + 3TC + EFV) is suggested.[1]
- In children under 3 years of age, the use of standard first-line regimen of two NRTIs + NVP (i.e. AZT or d4T + 3TC + NVP) is recommended.[2, 3]
- Alternatively, in cases where the NNRTI-based treatment is contraindicated, the triple NRTI regimen (i.e. AZT or d4T + 3TC + ABC) is recommended.

D. For children on ARV regimens diagnosed with TB

ART should continue in children already on a first-line ARV regimen who are subsequently diagnosed with TB. Because of overlapping toxicities and drug-drug interactions, children who are given rifampicin and NVP should be followed up more frequently and laboratory parameters should be checked.

For children on second-line ARV regimens who are diagnosed with TB, it is necessary to seek expert advice.

E. Immune reconstitution inflammatory syndrome (IRIS) in treating TB and ART together

IRIS has been observed in patients receiving anti-TB therapy and who have been initiated on ART. This occurs as a result of the simultaneous administration of ARV and anti-TB drugs. This syndrome is characterized by a worsening of the disease after initial clinical improvement. Symptoms and signs may include high fever, dyspnea, cough, lymphadenopathy, 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 2-3 weeks. ART should generally be continued through the episode 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. However, a thorough evaluation is necessary to exclude other causes, particularly TB treatment failure, before diagnosing IRIS.

[1] Some clinicians prefer to switch back from EFV to NVP at the end of TB treatment due to factors of convenience (lower pill burden) and cost. When this occurs, NVP should be given at full dose right away.
[2] Children receiving NVP together with rifampicin are at risk of developing hepatic toxicity. Liver enzymes should be monitored monthly or more frequently according to symptoms of hepatotoxicity.
[3] NVP should be dosed at the high end of the acceptable dosing range (based on weight of child).

HIV Infected Children with Hepatitis B or C virus Co-Infection

Children with HIV/Hepatitis B Co-infection

There exists little data about the natural course or the treatment of HIV infected children co-infected with the hepatitis B virus (HBV). For children, it is not clear that treatment of HBV improves the course of HIV, nor is there evidence that treatment of HIV changes the course of HBV. However, HIV infected children with HBV may have liver complications which are related to flares in HBV activity, or they may have liver toxicity if they are receiving ARV drugs. The following should be used in managing the HBV co-infected child:

- It is important for the clinician to know whether the HIV infected child has clinically-active hepatitis. HIV infected children, whether receiving ART or not, are monitored for the presence of liver inflammation. If transaminase levels are elevated, serologic testing for hepatitis B and hepatitis C is recommended *(see Clinical and Laboratory Monitoring Tables in Chapter 9)*.
- Hepatotoxicity of ARV medications is increased in children co-infected with hepatitis B or C, but symptomatic hepatitis is not common.
- The combination of d4T and ddI should be avoided in children with elevated liver transaminase because this drug combination may especially worsen liver inflammation.
- Emtricitabine (FTC), 3TC and TDF each show activity against both HIV and HBV. The discontinuation of these drugs may potentially cause liver inflammation in the co-infected patient.
- When used as monotherapy, anti-HBV drugs lead rapidly to HBV resistance. For example, when used as monotherapy 3TC resistance is 40% after 2 years.
- For HIV/HBV co-infected children, the best time to initiate HBV treatment is not known. **Therefore, the treatment of HIV should be the first priority.** If it is decided to use antiretroviral agents, which also have anti-HBV activity (i.e. 3TC, TDF or FTC), more than one drug that is active against HBV should always be used in order to avoid HBV resistance.

Children with HIV/Hepatitis C Co-infection

As with hepatitis B, there is little data on the natural course or treatment of hepatitis C (HCV) infection in children. Eventually, hepatitis C infection may lead to liver cirrhosis; however, the process of liver damage is very gradual. It is unknown whether a child with hepatitis C infection will have a more rapid progression of HIV disease, but studies from adults have shown that patients who have HCV/HIV co-infection progress 3 times more rapidly to liver cirrhosis than those patients who have HCV alone. The drugs used to treat hepatitis C infection (interferon and ribavirin) must be given for at least 6 months, have troublesome toxicities, and are not routinely available in Cambodia. **Therefore, HCV treatment is not recommended for HIV co-infected children at this time.** However, HCV co-infected children on ARVs should have liver transaminase monitored for drug toxicity.

11. CONSIDERATIONS FOR ART IN ADOLESCENTS

Adolescence is defined as the period between 10 and 18 years of age when healthy children undergo physical, psychological and sexual growth and maturation characteristic of puberty. Many perinatally HIV-infected children in Cambodia have entered into the adolescent age group. It should also be acknowledged that some adolescents will acquire HIV infection as teenagers through adult behaviors, including sexual contact and intravenous drug use. The perinatally infected adolescent who is identified at a young age will generally have a different clinical course and HIV treatment history than the adolescent who acquires infection as a teenager.

The choice of ARV regimens and dosages for adolescents should depend on his/her sexual maturity rating (i.e. Tanner staging, see Annex K). Patients who are in early to mid-adolescence (Tanner stages I, II or III) should be started on ARVs according to the pediatric dosing schedules. Patients in late adolescence (Tanners stages IV and V) should receive ARV medications according to adult dosing schedules. Because puberty may be delayed in perinatally HIV infected children, continued use of pediatric doses in puberty-delayed adolescents can result in medication doses that are higher than usual adult doses. Since data are not available to predict optimal medication doses in this group of children, factors such as toxicity, pill burden, adherence, and virological and immunologic responses should be considered in determining when to transition from pediatric to adult doses. Adolescents who have transitioned from pediatric to adult dosing should be closely monitored for medication toxicity and efficacy.

Unique considerations must be taken into account when using the NNRTI class of drugs in adolescent girls. Because EFV may be toxic to the growing fetus, it should not be used in adolescent girls who are at risk for pregnancy (i.e. sexually active and not using adequate contraception), or who are in the first trimester of pregnancy. Symptomatic NVP-associated hepatotoxicity or serious skin rash, while uncommon, are more likely to be seen in females with higher CD4 counts (> 250 cells/mm) who have never received ARV treatment. NVP should therefore be used with caution in adolescent girls with absolute CD4 counts between 250 and 350 cells/mm^3. If used in such adolescent girls, careful monitoring, including liver transaminase levels, is needed during the first 12 weeks of therapy.

Adherence to long-term therapy is particularly difficult among adolescents. Reasons for this may include an unstructured lifestyle, lack of social supports, not knowing their HIV status, being in denial of their HIV status, and stigma. Simple ARV regimens will maximize adherence. Additionally, disclosure to the adolescent of his/her HIV status, while difficult, often helps the adolescent to adhere better to ARV medications. For these reasons, it is especially important that young people:

1) are informed about their HIV status;
2) are well educated about their condition, its treatment and the importance of adhering to care and ART;
3) are confident in their ability to talk about HIV with those whom they want to know about their condition; and
4) have a strong support system so that they know where to obtain help and advice when necessary.

Positive prevention counseling provides the adolescents with the knowledge and skills to protect themselves and their sexual partner(s) from STI and HIV infection or re-infection. Pediatric counselors or pediatricians must provide positive prevention counseling to HIV infected adolescents at every visit, or more frequently as needed. The content of counseling will vary according to individual needs. In general, counselors should talk with adolescents about:

- Route of HIV transmission
- Delay of sexual activity;
- Safety/risk of different sexual practices;
- Communication and negotiation skills for safer sex including condom use;
- Issue of partner disclosure; and
- HIV and unintended pregnancies.

In Cambodia, adolescent patients with HIV who are 15-18 years of age should receive HIV medical care and treatment from pediatric AIDS care sites or from adult AIDS care sites. (???)

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ANNEX A: Schedule of Routine Follow-Up Visits for the HIV-Exposed Infant

Age of Infant	Birth	1.5 months (6 weeks)	2.5 months (10 weeks)	3.5 months (14 weeks)	7.5 months	9 months	12 months	15 months	18 months
Number of Visits	Maternity	1st Visit at pediatric service	2nd Visit at pediatric service	3rd Visit at pediatric service	4th Visit at pediatric service	5th Visit at pediatric service	6th Visit at pediatric service	7th Visit at pediatric service	8th Visit at pediatric service
Immunizations	BCG (a) HBV[1]	OPV[1], DTP[1], HBV[2]	OPV[2], DTP[2], HBV[3]	OPV[3], DTP[3], HBV[4]		Measles			
Assess Patient By*	H, P, G, D	H, P, G, D	H, P, G, D	H, P, G, D	H, P, G, D	H, P, G, D	H, P, G, D	H, P, G, D	H, P, G, D
Provide for all Families	Education on feeding; Counseling Services	Education on feeding; Counseling Services	Education on feeding; Counseling Services	Education on feeding; Counseling Services	Education on feeding; Counseling Services	Education on feeding; Counseling Services	Education on feeding; Counseling Services	Education on feeding; Counseling Services	Education on feeding; Counseling Services
Testing and Care - Breastfeeding Infants	PMTCT regimen	Begin cotrimoxazole prophylaxis -Refer to PCR test according to guideline on Child Testing Algorithm 1			Refer to PCR test according to guideline on Child Testing Algorithm 1 (b)	Refer to PCR test according to guideline on Child Testing Algorithm 1 (b)	HIV Antibody Test (c, d)	HIV Antibody Test (c, d)	Confirmatory HIV Antibody Test (c, d)
HIV Testing and Care for Non-Breastfed Infants	PMTCT regimen	Begin cotrimoxazole prophylaxis - Refer to PCR test according to guideline on Child Testing Algorithm 2					HIV Antibody Test (c, d)	HIV Antibody Test (c, d)	Confirmatory HIV Antibody Test (c, d)

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

(a) BCG should NOT be give to an HIV-exposed infant with any signs of possible infection with HIV.

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

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

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

ANNEX B

WHO Clinical Staging of HIV for Infants and Children

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

• **Clinical Stage 2:** (1)
- 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, otorrhoea, sinusitis, tongillitis)
- Fungal nail infections

. Clinical Stage 3: (1)
- Unexplained moderated malnutrition, not adequately responding to standard therapy
- Unexplained persistent diarrhea (14 days or more)
- Unexplained persistent fever (above 37.5 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 (<7.5g/dL), neutropenia (< 0.5 x 10^9 /L_3) or chronic thrombocytopenia (<50 x 10^9 /L_3)

. Clinical Stage **4:** (1, 2)
- Unexplained severe wasting stunting or severe malnutrition not responding to standard therapy
- Pneumocystis 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)
- Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
- Extrapulmonary TB / Dissiminated TB
- Kaposi sarcoma

- Central nervous system toxoplasmosis (after the neonatal period)
- HIV encephalopathy
- Cytomegalovirus (CMV)infection ,retinitis or CMV infection affecting another organs with onset at age over one month
- Extrapulmonary cryptococcisis (including meningitis)
- Cryptococcal Meningitis
- Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis)
- Chronic cryptosporidiosis (with diarrhea)
- Chronic isosporiasis
- Disseminated non-tuberculous mycobacteria infection
- Candida of trachea, bronchi or lungs
- Disseminated mycobacteriosis, other than tuberculosis
- Cerebral or B cell non-Hodgkins lymphoma
- Progressive multifocal leukoencephalopathy (PML)
- Symptomatic HIV associate cardiomyopathy or nephropathy

(1) Unexplained refers to where the condition is not explained by other causes
(2) Some additional specific conditions can be include in regional classifications
(E.g. Penicilliosis in Asia, HIV-associated rectovaginal fistula in Africa)

ANNEX B-2: HIV STAGING IN CHILDREN USING CLINICAL AND IMMUNOLOGICAL CRITERIA

Clinical criteria:

WHO classification of HIV associated clinical disease	
Classification of HIV associated clinical disease	WHO clinical stage
Asymptomatic	1
Mild	2
Advanced	3
Severe	4

ANNEX C

WHO Classification of HIV-Associated Immunodeficiency in Infants and Children

C-1- Immunological criteria:

Using CD4 count

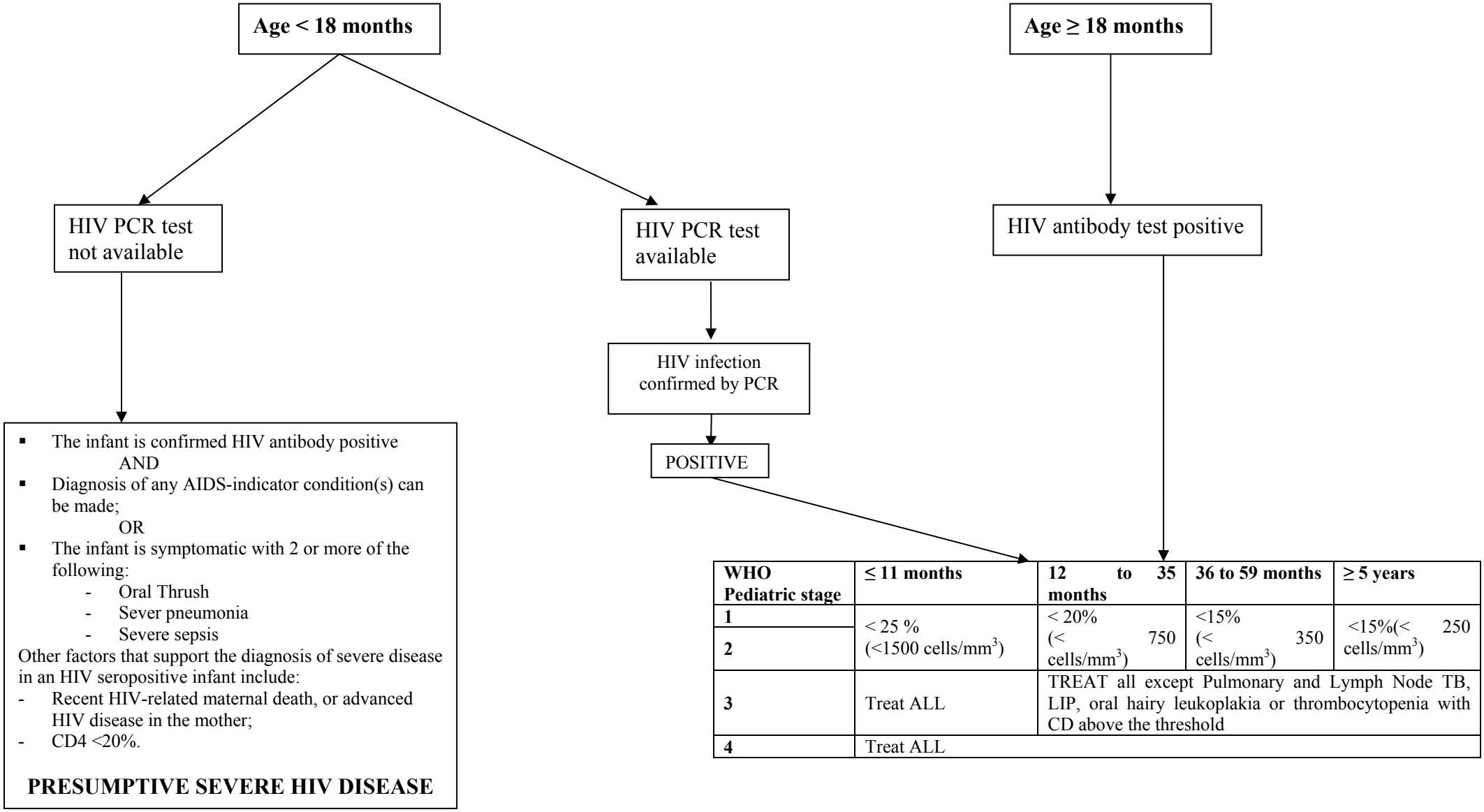
WHO Classification of HIV associated immunodeficiency using CD4 count				
Classification HIV-associated immunodeficiency	**Aged-related CD4 values**			
	≤ 11 months (%)	12-35 months (%)	36-59 months (%)	≥ 5 years (cells/mm3)
Not significant	> 35	>30	> 25	>500
Mild	30-35	25-30	20- 25	350-499
Advanced	25-29	20-24	15-19	200-349
Severe	<25	< 20	< 15	< 200 or <15%

C-2- Immunological criteria:

Using total lymphocyte count (TLC)

Diagnosing severe immunodeficiency using TLC (if CD4 is not available)				
Classification HIV-associated Immunodeficiency	Aged related TLC values (cells/mm3)			
	< 11months	12- 35 months	36-59 months	≥ 5 years
TLC	< 4000	< 3000	< 2500	< 2000
CD4 count	< 1500	< 750	< 350	< 200

ANNEX D: SUMMARY OF CRITERIA TO START ART



WHO Pediatric stage	≤ 11 months	12 to 35 months	36 to 59 months	≥ 5 years
1	< 25 % (<1500 cells/mm^3)	< 20% (< 750 cells/mm^3)	<15% (< 350 cells/mm^3)	<15%(< 250 cells/mm^3)
2				
3	Treat ALL	TREAT all except Pulmonary and Lymph Node TB, LIP, oral hairy leukoplakia or thrombocytopenia with CD above the threshold		
4	Treat ALL			

ANNEX E

Formulations and Dosages of Antiretroviral Drugs for Infants and Children

Name of drug	Formulations	Dosage	Special instructions
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)			
Abacavir **(ABC)**	-Oral solution: 20mg/mL -Tablet: 300 mg	-8 mg/kg of body weight twice daily, -Maximum dose: 300mg twice daily	-Must be cautioned about the risk *of* ***serious hypersensitivity reaction.*** -**ABC should be stopped permanently if hypersensitivity reaction.** -No food restrictions -Storage at room temperature 20-25^{o}C -Oral solution: may be refrigerated
Didanosine (ddI, dideoxynosine)	-Pediatric powder for oral solution (when reconstituted as solution containing antacid): 10mg/mL -Chewable tablets: 25mg, 50mg, 100mg, 150mg, and 200mg -Delayed-release capsules (enteric-coated beadlets): 125mg; 200mg; 250mg; 400mg.	-<3months:50mg/m^2/dose twice daily -3moths-to <13years : 90mg/m^2/dose twice daily - Maximum dose : ≥13 years or > 60kg : 200mg/dose twice daily or 400mg once daily. One-daily for chewable tablets can be given if twice-daily dosing of two tablets is not available.	-For oral suspension : must shake well and should keep refrigerated; stable for 30days. It is not easy to use and should be avoided if possible. -Food decreases absorption; take ddI on an empty stomach (1 hour before or 2 hours after meal); may be less important in children. -At least two tablets of appropriate strength must be used at any one time for adequate buffering (e.g. if the child's dose is 100mg, administer two 50mg tablets instead of one 100mg tablet. -ddI tablets should be chewed, crushed or dispersed in water or clear juice before they are taken. -Enteric-coated beadlets in capsules can be opened and sprinkled on small amount of food.
Lamivudine (3TC)	-Oral solution: 10mg/mL -Tablet: 150mg	-<30days: 2mg/kg/dose twice daily. - ≥30days: 4mg/kg/dose twice daily -Maximum dose : >50kg: 150mg twice daily.	-Well tolerated -Also active against hepatitis B -No food restrictions -For oral solution: store at room temperature (15-30^{o}C) -Tablets can be crashed and contained mixed with a small amount of water or food and immediately taken.

Stavudine (d4T)	-Oral solution: 1mg/mL -Capsules: 15mg; 20mg; 30mg; 40mg	-<30kg: 1mg/kg/dose twice daily -30 to 60kg: 30mg/dose twice daily ->60kg: 40 mg/dose twice daily	***-Do not use with ZDV:*** **(due to antagonistic effect)** -Can be administered with food - Powder for oral solution: should be protected from moisture and store in tightly closed containers at 15-30 ^{o}C. -After constitution, needs refrigeration and discard any unused portion after 30 days. -Capsules can be opened and mixed with small amount of water or food (stable in solution for 24 hours if kept refrigerated).
Zidovudine (AZT or AZV)	-Syrup: 10mg/mL -Capsules: 100mg; 250mg -Tablet: 300mg	- <4weeks: 4mg/kg/dose twice daily - 4 weeks to 13 years: 180-240mg/m^2/dose twice daily -Adult dose: 250-30mg/dose twice daily. -Maximum dose: ≥13 years: 300mg/dose twice daily **Notes:** For children with suspected nervous system involvement dose of 240mg/m^2 per dose given twice daily may be more beneficial.	***-Do not use with d4T:*** **(due to antagonistic effect)** -No food restrictions -Use with caution in children with anemia due to potential bone marrow suppression. -Syrup (oral solution): .Preferred in children<8kg since accurate dosing with capsules is not practical. . Is stable at room temperature but needs storage in glass jars and is light sensitive. -Capsules: Can be opened and dispersed in water or on to small amount of food and immediately ingested. Tablets: Can be cut in half or may be crashed and combined with a small a mount of food or water and immediately ingested.
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)			
Efavirenz **(EFV or EFZ)**	-Syrup: 30mg/mL (note: syrup has lower bioavailability and ratio of 1.3 syrup to solid formulation is suggested to achieve an equivalent dose). -Capsules: 50mg; 100mg; 200mg. -Tablets: 600mg	Target dosing: 19.5 mg/kg/day (syrup) or 15 mg/kg/day (capsule/tablet) Capsules *(liquid)* dose for > 3yrs: -10 to <15kg: 200mg *(270mg=9ml)* -15 to <20kg: 250mg *(300mg=10ml)* -20 to <25kg: 300mg *(360mg=12ml)* -25 to <33kg: 350mg *(450mg=15ml)* - 33 to <40kg: 400mg *(510mg=17ml)* -≥40kg: 600mg Administered once daily *There are insufficient data available on the appropriate dosage for children under three years.	-Storage at 15-30^{o}C -Capsules may be opened and added to liquid or food, but EFZ has peppery taste; however, can mix with sweet foods or jam to disguise the taste. -Can be taken with and without food (but avoid after high fat meals which increase absorption by 50%). -Bedtime dosing is recommended, particularly during the first two to four weeks of therapy, to improve tolerability of central nervous system side effects.

Nevirapine (NVP)	-Oral suspension: 10mg/mL -Tablet: 200mg	-Target dose for maintenance: 160-200mg mg/m^2 to maximum dose of 200mg twice daily -Induction dose: once daily for first 14 days; it is generally half the daily maintenance dose -Maintenance dose: 160-200mg/m2/dose twice daily. Adjust for more aggressive dosing in younger ages. -Dosing for PMTCT: 2mg/kg/dose within 72 hours of birth once only.	-Can be administered with food -Store suspension at room temperature; must shake well -***Must warn parents about rash.*** NVP-associated skin rash usually within the first six weeks of therapy. If mild/ moderate rash occurs during the initial 14-days lead-in period, do not increase dose until rash resolves. NVP should be discontinued immediately in patients who develop severe rash or rash accompanied by constitutional symptoms (i.e., fever, oral lesions, conjunctivitis, or blistering).
Protease Inhibitors (PIs)			
Lopinavir / ritonavir **(LPV/r)**	-Oral solution: 80mg lopinavir + 20mg ritonavir per mL. -Capsules: 133.3mg lopinavir + 33,3mg ritonavir -Tablets: 200mg lopinavir + 50mg ritonavir	Neonatal dose: No pharmacokinetic data on dosing children less than six months of age. ->6months to 13yrs: 225mg/m^2 LPV / 57.5m^2 ritonavir twice daily OR -7 to<15 kg: 12mg/kg lopinavir/3mg ritonavir/ dose twice daily -15 to 40kg: 10mg/kg LPV/ 2.5mg/kg ritonavir twice daily. ->40kg: 400mg LPV/ 100mg ritonavir (3 cap. or 5ml) twice daily.	-Should be taken with food. High fat meal increases absorption, especially of the liquid preparation. -Oral solution and capsules should be refrigerated; however, can store at room temperature up to 25°C if used within 2 months. -If co-administered with ddI, ddI should be given one hour before or two hours after LPV/r -Oral solutions: low volume but bitter taste. -Capsules: large, should not be crushed, must be swallowed whole capsule
Nelfinavir (NFV)	-Powder for oral suspension: -50mg/level scoop full of 1.25ml 200mg/level teaspoon -Tablet: 250mg, 625mg	-<10kg: 75mg/kg/dose twice daily -≥10kg: 60mg/kg/dose twice daily -≥20kg: 1250mg/dose (5 tablets) twice daily	-Take with meal or light snack to improve absorption -For oral solution: powder may be mixed with water, milk, formula, pudding, etc. (for up to six hours); do not mix with any acidic food or juice because of poor taste. -Powder and tablets can be store at room temperature. - If co-administered with ddI, NFV should be taken two hours before or one hour after ddI.
Saquinavir (SQV)	-Hard gel capsule: 200mg -Tablet: 500mg	-≥25kg: 33mg/kg three times a day	-Should not be taken as sole PI -Should be taken with food or within two hours after meal as absorption is improved. -Hard gel capsules do not need refrigeration

Meter squared body surface area calculation (m^2) = square root of (height in centimeters times weight in kilograms divided by 3600).

Fixed-dose combinations (FDC)

Fixed-dose combinations of first-line that are suitable for children are required to facilitate ART in children.

Zidovudine (AZT) + Lamivudine (3TC)

- Tablet: AZT (300mg) + 3TC (150mg)
- Oral solution: not available

Stavudine (d4T) + Lamivudine (3TC)

- Tablet: d4T (30mg) + 3TC (150mg)
- Oral solution: d4T 10mg + 3TC 40mg/5ml
- Tablet: Dual FDC 5 -- d4T (5mg) + 3TC (20mg)
- Tablet: Dual FDC 6 -- d4T (6mg) + 3TC (30mg)
- Tablet: Dual FDC 10 -- d4T (10mg) + 3TC (40mg)
- Tablet: Dual FDC 12 -- d4T (12mg) + 3TC (60mg)

Zidovudine (AZT) + Lamivudine (3TC) + Abacavir (ABC)

- Tablet: AZT (300mg) + 3TC (150mg) + ABC (300mg)
- Oral solution: not available

Stavudine (d4T) + Lamivudine (3TC) + Nevirapine (NVP)

- Tablet: d4T (30mg) + 3TC (150mg) + NVP (200mg)
- Tablet: Triple FDC 5 -- d4T (5mg) + 3TC (20mg) + NVP (35 mg)
- Tablet: Triple FDC 6 -- d4T (6mg) + 3TC (30mg) + NVP (50 mg)
- Tablet: Triple FDC 10 -- d4T (10mg) + 3TC (40mg) + NVP (70 mg)
- Tablet: Triple FDC 12 -- d4T (12mg) + 3TC (60mg) + NVP (100 mg)

ANNEX F

Weight-Band Dosing Charts for First-Line ARVs for Infants and Children

	Lamivudine (3TC)				**Stavudine(d4T)**				**Zidovudine (AZT)**					
	4mg/kg				**1mg/kg**				**180-240mg/m^2**					
Formulations	10mg/ml sol.		Tab150mg		1mg/ml sol.		Cap 15mg, 20mg, 30mg		10mg/ml sol.		Cap 100mg		Tab300mg	
Weight Range (kg)	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**
5-6.9	3ml	3ml			6ml	6ml	1/2 cap15	1/2 cap15	7ml	7ml				
7-9.9	4ml	4ml			7ml	7ml	1/2 cap20	1/2 cap20	9ml	9ml	1 cap	1 cap		
10-11.9	5ml	5ml			10ml	10ml	1/2 cap20	1/2 cap20	12ml	12ml	1 cap	1 cap		
12-14.9	6ml	6ml			12ml	12ml	1 cap15	1 cap15	14ml	14ml	1 cap	1 cap		
15-16.9	7ml	7ml	1/2 Tab	1/2 Tab	15ml	15ml	1cap15	1cap15	15ml	15ml	2 cap	2 cap	1/2 Tab	1/2 Tab
17-19.9	8ml	8ml	1/2 Tab	1/2 Tab			1 cap15	1 cap15	17ml	17ml	2 cap	2 cap	1/2 Tab	1/2 Tab
20-24.9	9ml	9ml	1/2 Tab	1/2 Tab			1 cap20	1 cap20	20ml	20ml	2 cap	2 cap	1/2 Tab	1/2 Tab
25-29.9	11ml	11ml	1Tab	1/2 Tab			1 cap20	1 cap20			2 cap	2 cap	1 Tab	1/2 Tab
30-34.9	13ml	13ml	1 Tab	1 Tab			1 cap30	1 cap30					1 Tab	1 Tab
35-40	15ml	15ml	1 Tab	1 Tab			1 cap30	1 cap30					1 Tab	1 Tab

Weight-Band Dosing Charts for First-Line ARVs for Infants and Children

	Nevirapine (NVP)						**Efavirenz (EFV)**
	160-200mg/m^2						**15mg/kg, Once Daily**
Formulations	Induction dosing, OD for 2 weeks		10mg/ml sol.		Tab.200mg		Cap 50mg, 100mg, 200mg
Weight Range (kg)	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**	**Once Daily**
5-6.9	4ml	0	6ml	6ml			
7-9.9	5ml	0	7ml	7ml			
10-11.9	6ml	0	8ml	8ml			1 cap 200
12-14.9	7ml or1/2T	0	9ml	9ml	1/2 Tab	1/2 Tab	1 cap 200
15-16.9	8ml or1/2T	0	10ml	10ml	1/2 Tab	1/2 Tab	1 Cap 200 + 1 Cap 50
17-19.9	9ml or1/2T	0	13ml	13ml	1/2 Tab	1/2 Tab	1 Cap 200 + 1 Cap 50
20-24.9	1/2 Tab	0			1 Tab	1/2 Tab	1 Cap 200 + 1 Cap 100
25-29.9	1/2Tab	0			1 Tab	1/2 Tab	1 Cap200 + 1 Cap100 + 1 Cap50
30-34.9	1Tab	0			1 Tab	1 Tab	2 cap 200
35-40	1Tab	0			1 Tab	1 Tab	2 cap 200

Weight-Band Dosing Charts for Alternative First-Line and Second –Line ARVs

	Abacavir (ABC)				**Didanosine (ddI)**			
	8mg/kg				**90-120mg/m^2**			
Formulations	20mg/ml		Tab.300mg		10mg/ml		Tab 25mg, 50mg, 100mg	
Weight Range (kg)	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**
5-6.9	2ml	2ml			4ml	4ml	2 Tab25	2 Tab25
7-9.9	3ml	3ml			5ml	5ml	2 Tab25	2 Tab25
10-11.9	4ml	4ml			6ml	6ml	2 Tab25	2 Tab25
12-14.9	5ml	5ml			7ml	7ml	1 Tab50 + 1 Tab25	1 Tab50 + 1 Tab25
15-16.9	6ml	6ml			8ml	8ml	1 Tab50 + 1 Tab25	1 Tab50 + 1 Tab25
17-19.9	7ml	7ml	1/2Tab	1/2Tab	9ml	9ml	2 Tab50	2 Tab50
20-24.9	9ml	9ml	1/2Tab	1/2 Tab	10ml	10ml	2 Tab50	2 Tab50
25-29.9	11ml	11ml	1 Tab	1/2 Tab			1 Tab100 + 1 Tab25	1 Tab100 + 1 Tab25
30-34.9	13ml	13ml	1 Tab	1 Tab			1 Tab100 + 1 Tab25	1 Tab100 + 1 Tab25
35-40	15ml	15ml	1 Tab	1 Tab			1 Tab100 + 1 Tab25	1 Tab100 + 1 Tab25

Weight-Band Dosing Charts for Alternative First-Line and Second-Line ARVs

	Lopinavir/ritonavir (LPV/r)					
	LPV: <15kg:16-12mg/kg; >15kg:10mg/kg*					
Formulations	80mgLPV + 20mg r /ml		Cap133.3 / 33.3mg LPV/r		Tab. 200/50mg LPV/r	
Weight Range (kg)	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**
5-6.9	1ml	1ml	1 cap	1 cap		
7-9.9	1.5ml	1.5ml	1 cap	1 cap		
10-11.9	2ml	2ml	1 cap	1 cap		
12-14.9	2ml	2ml	1 cap	1 cap	1 Tab	1 Tab
15-16.9	2.5ml	2.5ml	2 cap	2 cap	1 Tab	1 Tab
17-19.9	2.5ml	2.5ml	2 cap	2 cap	1 Tab	1 Tab
20-24.9	3ml	3ml	2 cap	2 cap	1 Tab	1 Tab
25-29.9	3.5ml	3.5ml	2 cap	2 cap	2 Tab	1 Tab
30-34.9	4ml	4ml	3 cap	3 cap	2 Tab	2 Tab
35-40	5ml	5ml	3 cap	3 cap	2 Tab	2 Tab

Weight-Band Dosing Charts for Pediatric Fixed Dose Combinations (FDCs)

Formulations	Triple FDC 6	Triple FDC 12	Triple FDC 5	Triple FDC 10
	d4T 6mg + 3TC 30mg + NVP 50mg	d4T 12mg + 3TC 60mg + NVP 100mg	d4T 5mg + 3TC 20mg + NVP 35mg	d4T 10mg + 3TC 40mg + NVP 70mg

Weight range (kg)	AM	PM	AM	PM	AM	PM	AM	PM
3-5.9	1	1	0.5	0.5	Not Recommended		Not Recommended	
6-9.9	1.5	1.5	1	0.5	2	2	1	1
10-10.9	2	2	1	1	2.5	2.5	1.5	1
11-11.9	2	2	1	1	2.5	2.5	1.5	1.5
12-13.9	2	2	1	1	2.5	2.5	1.5	1.5
14-16.9	2.5	2.5	1.5	1	3.5	3.5	2	2
17-19.9	2.5	2.5	1.5	1	4	4	2	2
20-24.9	3	3	1.5	1.5	4.5	4.5	2.5	2.5
25-29.9	4	4	2	2	6	6	3	3
30-40	Use d4T 30mg FDC				Use d4T 30mg FDC			

Formulations	DualFDC 6	Dual FDC 12	Dual FDC 5	Dual FDC 10
	d4T 6mg + 3TC 30mg	d4T 12mg + 3TC 60mg	d4T 5mg + 3TC 20mg	d4T 10mg + 3TC 40mg

Weight range (kg)	AM	PM	AM	PM	AM	PM	AM	PM
3-5.9	1	1	0.5	0.5	Not Recommended		Not Recommended	
6-9.9	1.5	1.5	1	0.5	2	2	1	1
10-10.9	2	2	1	1	2.5	2.5	1.5	1
11-11.9	2	2	1	1	2.5	2.5	1.5	1.5
12-13.9	2	2	1	1	2.5	2.5	1.5	1.5
14-16.9	2.5	2.5	1.5	1	3.5	3.5	2	2
17-19.9	2.5	2.5	1.5	1	4	4	2	2
20-24.9	3	3	1.5	1.5	4.5	4.5	2.5	2.5
25-29.9	4	4	2	2	6	6	3	3
30-40	Use d4T 30mg FDC				Use d4T 30mg FDC			

Weight-Band Dosing Charts for Fixed Dose Combinations (FDCs)

Formulations	AZT300mg + 3TC150mg		d4T30mg+ 3TC150mg		d4T30mg+3TC150mg NVP200mg		AZT300mg+3TC150mg + ABC300mg	
Weight range (kg)	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**
10-11.9								
12-14.9								
15-16.9			½ Tab	½ Tab	½ Tab	½ Tab	½ Tab	½ Tab
17-19.9	½ Tab	½ Tab	½ Tab	½ Tab	½ Tab	½ Tab	½ Tab	½ Tab
20-24.9	½ Tab	½ Tab	1 Tab	½ Tab	½ Tab	½ Tab + ½ NVP	½ Tab	½ Tab
25-29.9	1 Tab	1/2 Tab	1 Tab	1 Tab	½ Tab	½ Tab + ½ NVP + ½ 3TC	1 Tab	½ Tab
30-34.9	1 Tab	1 Tab	1 Tab	1 Tab	1 Tab	1 Tab	1 Tab	1 Tab
35-40	1 Tab	1 Tab	1 Tab	1 Tab	1 Tab	1 Tab	1 Tab	1 Tab

Annex G: Severity Grading of Most Common Clinical and Laboratory Toxicities from Recommended Antiretroviral Drugs for Children

	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: requires medical care and possible hospitalization	Symptoms causing inability to perform basic self-care functions:[b] requires medical or operative intervention to prevent permanent impairment, persistent disability or death
Haematology[c] ***Standard international units are listed in italics***				
Absolute neutrophil count	750–<1000/mm^3 *0.75 x 10^9–<1 x 10^9/l*	500–749/mm^3 *0.5 x 10^9–0.749 x 10^9/l*	250–500/mm^3 *0.25 x 10^9–0.5 x 10^9/l*	<250/mm^3 *<0.250 x 10^9/l*
Haemoglobin (child >60 days of age)	8.5–10.0 g/dl *1.32–1.55 mmol/l*	7.5–<8.5 g/dl *1.16–<1.32 mmol/l*	6.5–<7.5 g/dl *1.01–<1.16 mmol/l*	<6.5 g/dl *<1.01 mmol/l* Or severe clinical symptoms attributable to anaemia (e.g. cardiac failure), refractory to supportive therapy
Platelets	100 000–<125 000/mm^3 *100 x 10^9–125 x 10^9/l*	50 000–<100 000/mm^3 *50 x 10^9–<100 x 10^9/l*	25 000–<50 000/mm^3 *25 x 10^9–<50 x 10^9/l*	<25 000/mm^3 *<25 x 10^9/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 weeks 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				
Diarrhoea ≥1 year of age	Transient or intermittent episodes of unformed stools OR increase of ≤3 stools over baseline per day	Persistent episodes of unformed to watery stools OR increase of 4–6 stools over baseline per day	Grossly bloody diarrhoea OR increase of ≥7 stools per day OR intravenous fluid replacement indicated	Life-threatening consequences (e.g. hypotensive shock)
<1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR hypotensive shock
Nausea	Transient (<24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24–48 hours	Persistent nausea resulting in minimal oral intake for >48 hours OR aggressive rehydration indicated (e.g. intravenous fluids)	Persistent nausea with no or minimal oral intake resulting in dehydration with aggressive rehydration indicated
Pancreatitis	Not applicable	Symptomatic AND hospitalization not indicated (other than emergency treatment)	Symptomatic AND hospitalization not indicated (other than emergency treatment)	Life-threatening consequences (e.g. circulatory failure, haemorrhage, sepsis)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR aggressive rehydration indicated (e.g. intravenous fluids)	Life-threatening consequences (e.g. hypotensive shock)

	Grade 1	Grade 2	Grade 3	Grade 4

Parameter	Mild	Moderate	Severe	Severe and potentially life-threatening
Allergic/dermatological				
Acute systemic allergic reaction	Localized urticaria (weals) lasting a few hours	Localized urticaria with medical intervention indicated OR mild angio-oedema	Generalized urticaria OR angio-oedema with medical intervention indicated OR symptomatic mild bronchospasm	Acute anaphylaxis OR life-threatening bronchospasm or laryngeal oedema
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR superficial ulcerations of mucous membrane limited to one 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, behaviour 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	Behaviour potentially harmful to self or others OR life-threatening consequences
Altered mental status	Changes causing no or minimal interference with usual social and functional activities[b]	Mild lethargy or somnolence causing greater than minimal interference with usual social and functional activities[b]	Onset of confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social and functional activities[b]	Onset of delirium, obtundation or coma
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 alteration or paraesthesia causing inability to perform basic self-care functions[c]
Other laboratory parameters ***Standard international units are listed in italics***				
Cholesterol (fasting, paediatric <18 years old)	170–<200 mg/dl *4.40–5.15 mmol/l*	200–300 mg/dl *5.16–7.77 mmol/l*	>300 mg/dl *>7.77 mmol/l*	Not applicable
Glucose, serum, high: non-fasting	116–<161 mg/dl *6.44–<8.89 mmol/l*	161–<251 mg/dl *8.89–<13.89 mmol/l*	251–500 mg/dl *13.89–27.75 mmol/l*	>500 mg/dl *>27.75 mmol/l*
Glucose, serum, high: fasting	110–<126 mg/dl *6.11–<6.95 mmol/l*	126–<251 mg/dl *6.95–<13.89 mmol/l*	251–500 mg/dl *13.89–27.75 mmol/l*	>500 mg/dl *>27.75 mmol/l*
Lactate	<2.0 x ULN without acidosis	≥2.0 x ULN without acidosis	Increased lactate with pH <7.3 without life-threatening consequences or related condition present	Increased lactate with pH <7.3 with life-threatening consequences (e.g. neurological findings, coma) or related condition present
Triglycerides (fasting)	Not applicable	500–<751 mg/dl *5.65–<8.49 mmol/l*	751–1200 mg/dl *8.49–13.56 mmol/l*	>1200 mg/dl *>13.56 mmol/l*

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.

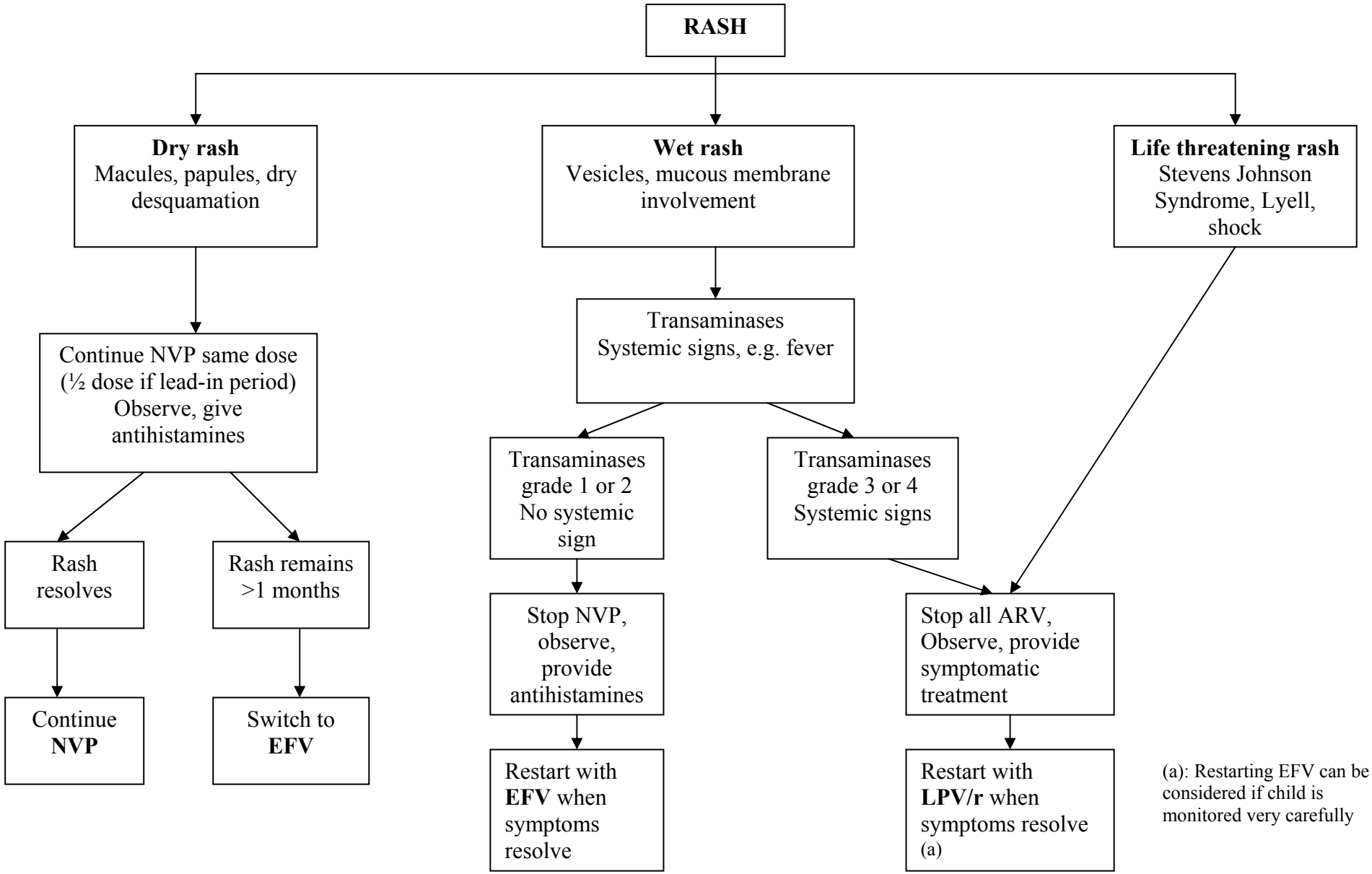
a Usual social and functional activities in young children include those that are appropriate to their age and culture (e.g. social interactions, play activities, learning tasks).

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 noted.

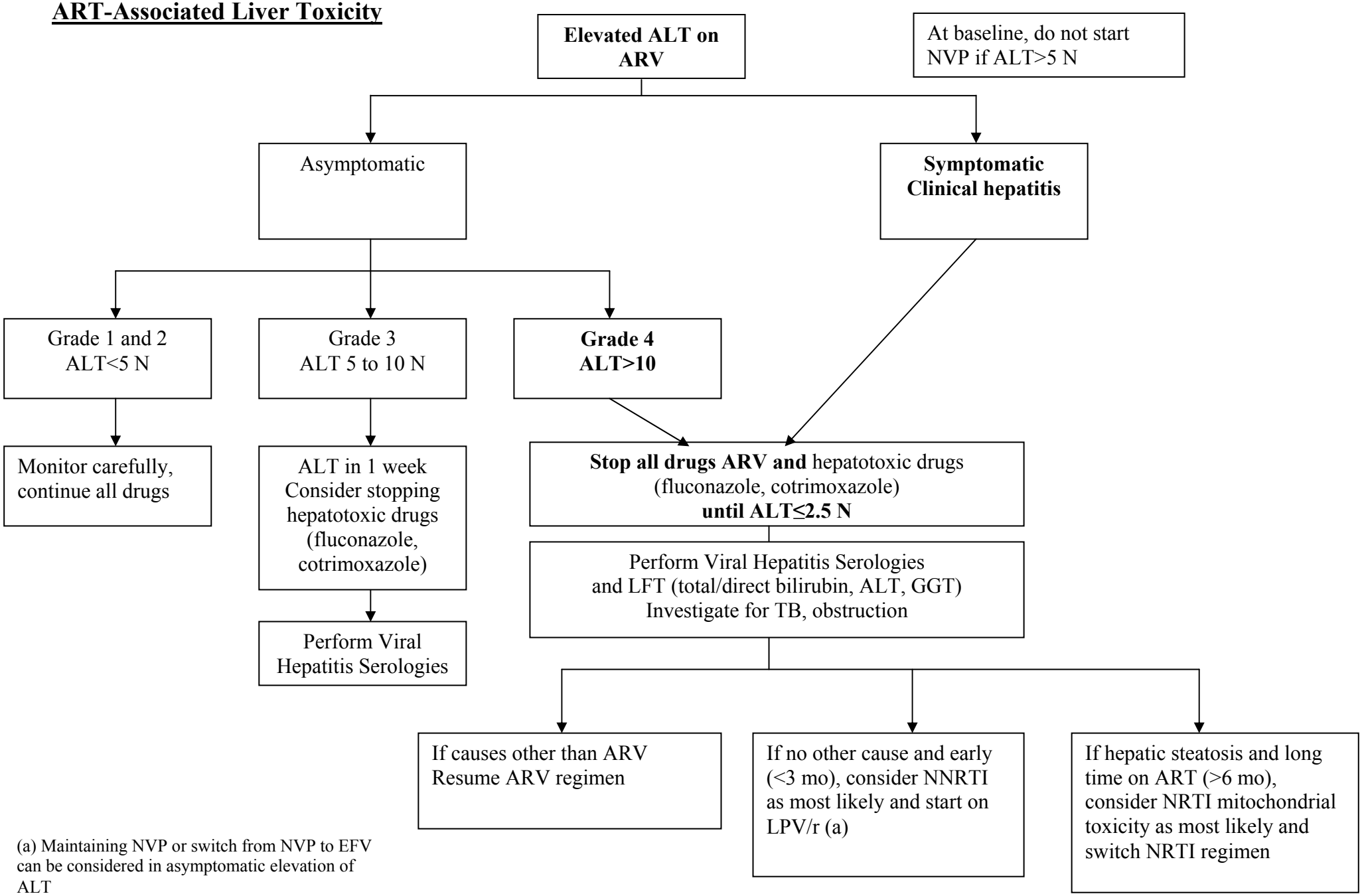
ANNEX H: Flow Diagrams for Clinical Management of ARV Toxicities

Nevirapine-Associated Rash



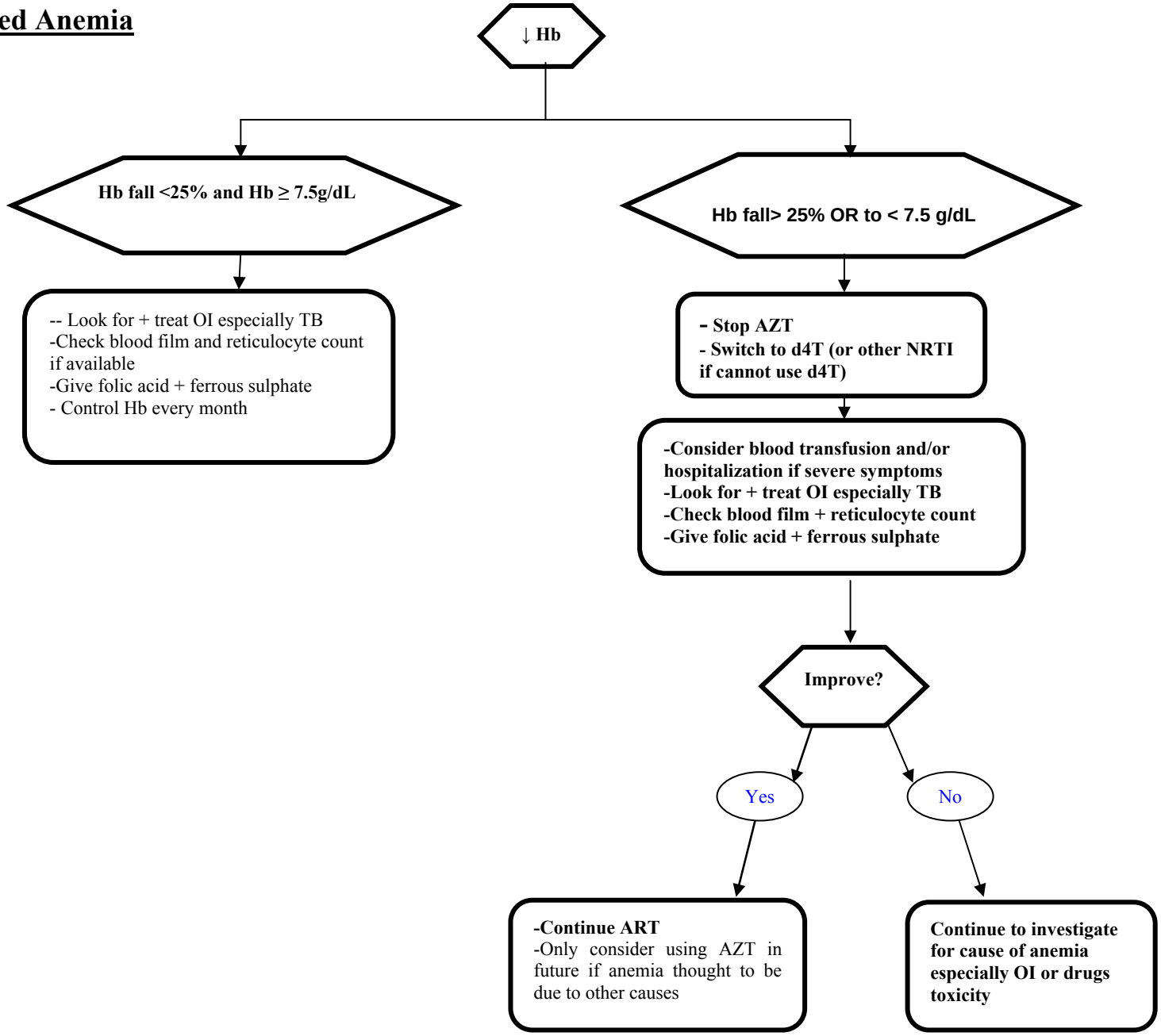
(a): Restarting EFV can be considered if child is monitored very carefully

ART-Associated Liver Toxicity

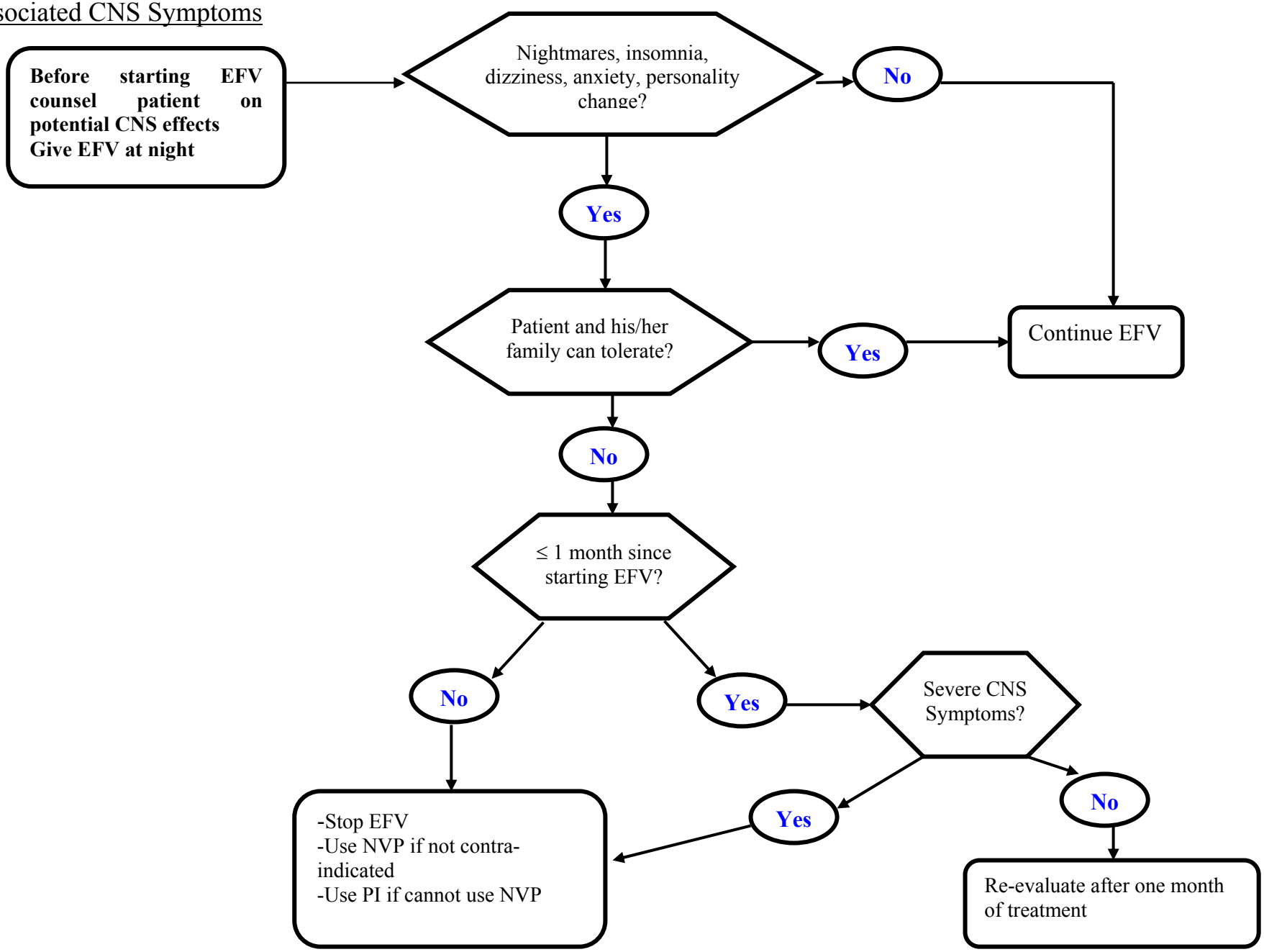


(a) Maintaining NVP or switch from NVP to EFV can be considered in asymptomatic elevation of ALT

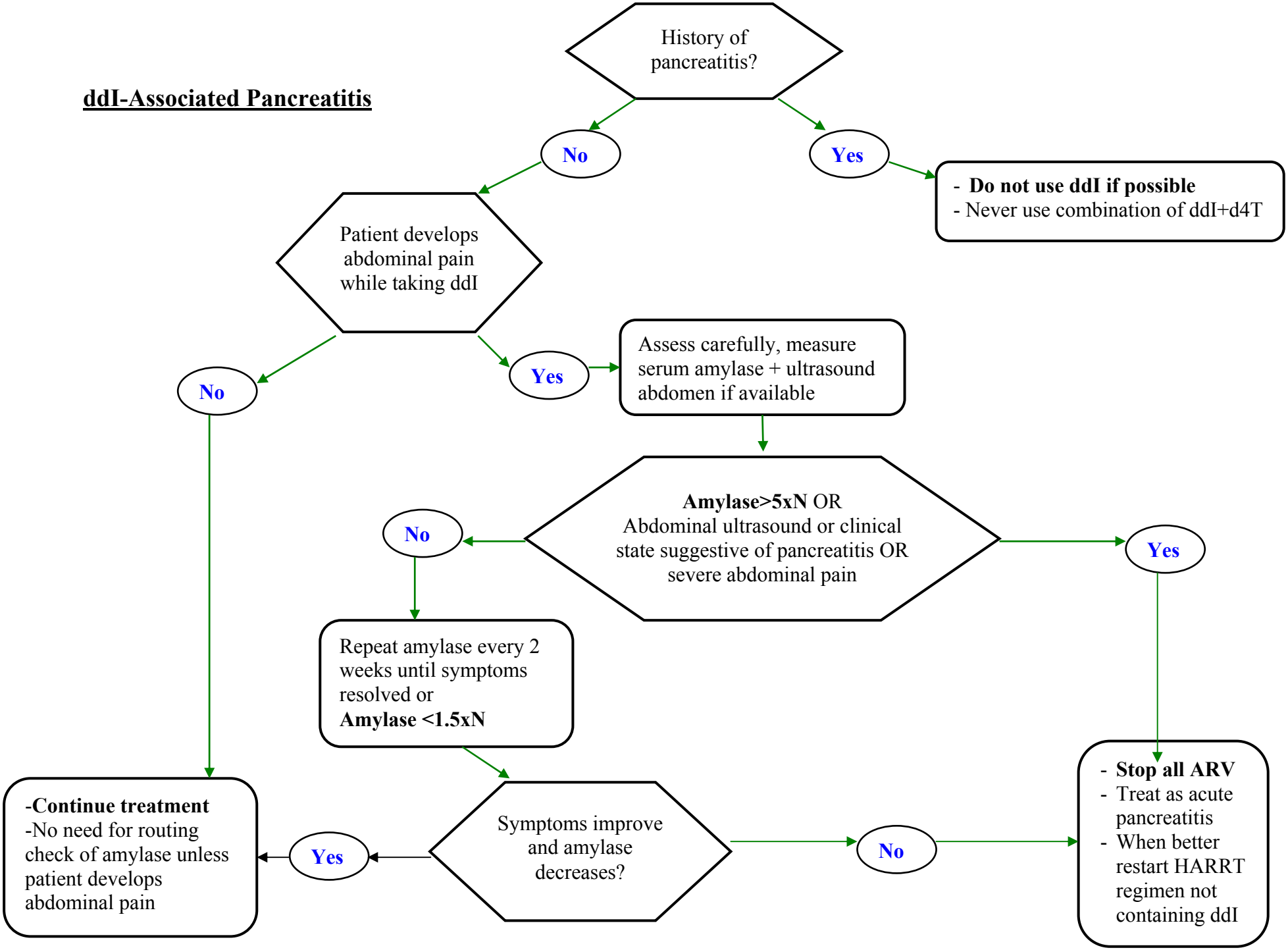
AZT-Associated Anemia



EFV-Associated CNS Symptoms



ddI-Associated Pancreatitis



ANNEX I: Important ARV Drug Interactions

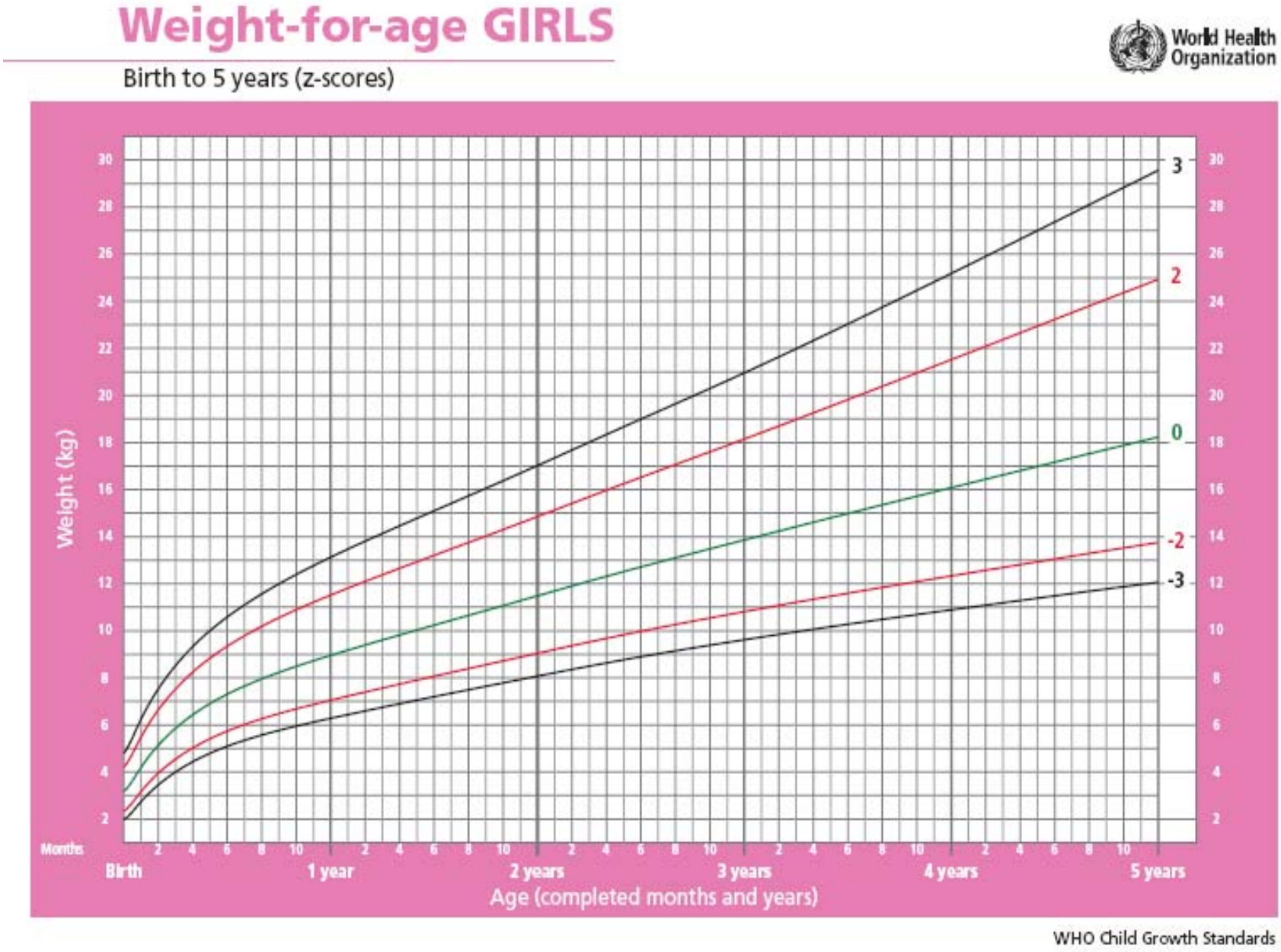
- There are many complicated interactions between ARV and with other drugs.
- The following table gives an overview of major drug interactions. There are many more interactions not listed in this table. Always check reference texts for interactions before prescribing new drugs.

Important ARV drug interactions

Interacting drug	NVP	EFV	NFV	IDV/r	LPV/r	SQV/r
Ketoconazole	X	?	OK			
Rifampicin	Use with caution	EFV 800mg/d	X	X	X	Give both drugs at full dose
Rifabutin	OK	RBT 450-600 mg/d	RBT 150mg/d NFV 1000mg tds			RBT 250mg 2-3/week
Clarithromycin	OK	X	?		?	
Oral contraceptive[1]	X	X	X	X	X	X
Methadone	Increase methadone	Increase methadone	Increase methadone	Increase methadone	Increase methadone	Increase methadone
'Statins'[2]	?	?	X		X	X
Other drugs that should not be co-administered	Garlic supplements	Astemizole Terfenadine Cisapride Midazolam Triazolam Ergotamine Dihydro-ergotamine Garlic supplements	Astemizole Terfenadine Cisapride Midazolam Triazolam Ergotamine Dihydro-ergotamine Garlic supplements	Astemizole Terfenadine Cisapride Midazolam Ergotamine Dihydro-ergotamine Garlic supplements Flecanide Pimozide	Astemizole Terfenadine Cisapride Midazolam Ergotamine Dihydro-ergotamine Garlic supplements Flecanide Pimozide	Astemizole Terfenadine Cisapride Midazolam Ergotamine Dihydro-ergotamine Garlic supplements Flecanide Pimozide
Miscellaneous	Can lower steroid levels	Monitor warfarin if co-administered				

[1]Additional or alternative methods of contraception should be used.
[2]Pravastatin can be used.

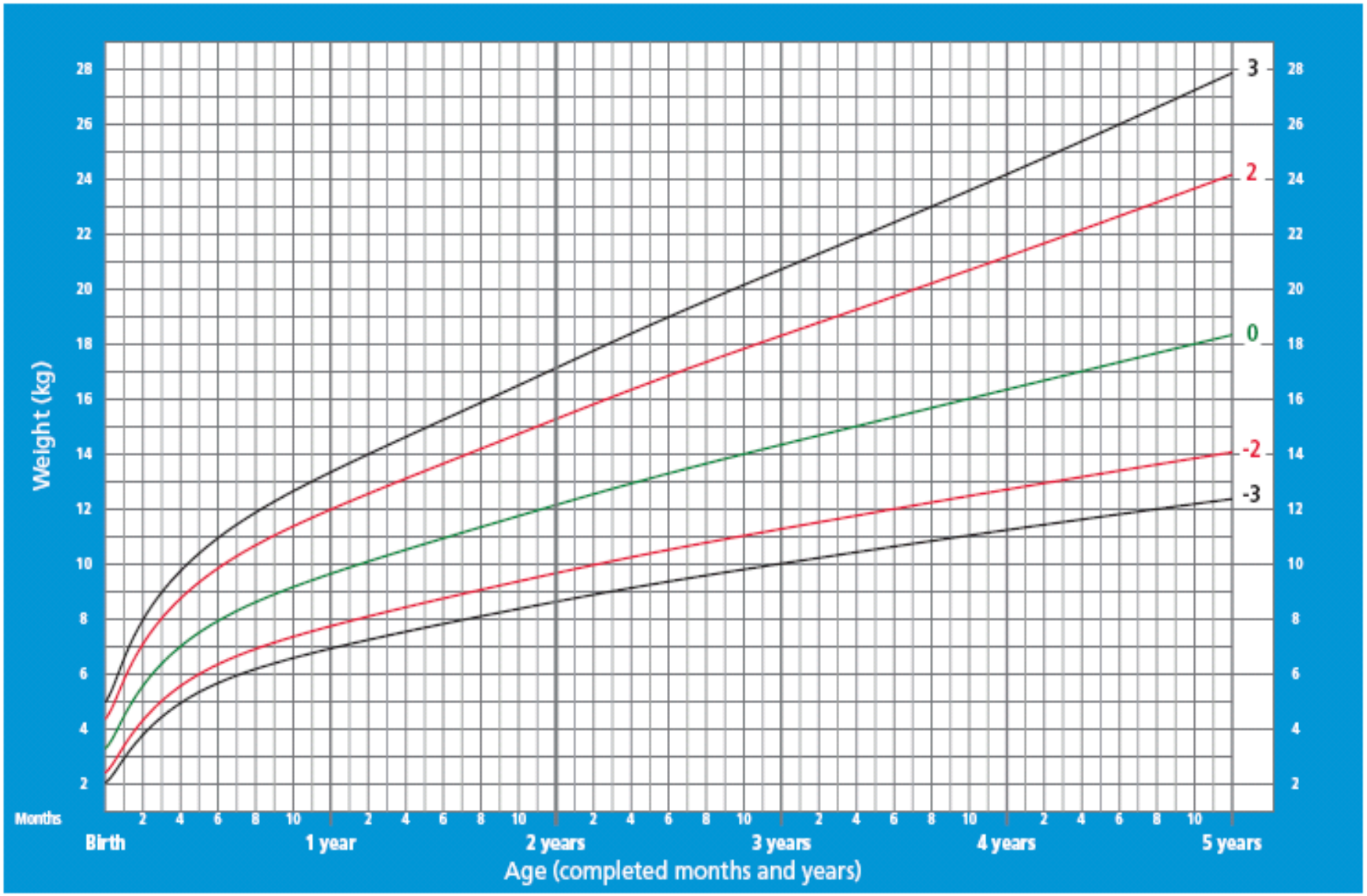
Annex J: Pediatric Weight-for-Age Growth Charts



Weight-for-age BOYS

Birth to 5 years (z-scores)

World Health Organization



WHO Child Growth Standards

ANNEX K: 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 (≤2.5 cm)	Pre-adolescent	None	Pre-adolescent
II	8–15	Breast budding (thelarche); areolar hyperplasia with small amount of breast tissue	Long downy pubic hair near the labia, often appearing with breast budding or several weeks or months later	Peak growth velocity often occurs soon after stage II	10–15	Enlargement of testes; pigmentation of scrotal sac	Minimal or no enlargement	Long downy hair, often appearing several months after testicular growth; variable pattern noted with pubarche	Not applicable
III	10–15	Further enlargement of breast tissue and areola, with no separation of their contours	Increase in amount and pigmentation of hair	Menarche occurs in 2% of girls late in stage III	10.5–16.5	Further enlargement	Significant enlargement, especially in diameter	Increase in amount; curling	Not applicable

Stage	Female				Male				
	Age range (years)	Breast growth	Pubic hair growth	Other changes	Age range (years)	Testes growth	Penis growth	Pubic hair growth	Other changes
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 occurs in 10% of girls in stage V.	13–18	Adult in size	Adult in size	Adult in distribution (medial aspects of thighs; linea alba)	Body hair continues to grow and muscles continue to increase in size for several months to years; 20% of boys reach peak growth velocity during this period

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