Kingdom of Cambodia
Nation Religion King

Ministry of Health

National Guidelines for the Use of Pediatric Antiretroviral Therapy In Cambodia

3rd Edition
June 2011

National Center for HIV/AIDS, Dermatology and STD

TABLES

BOXES

PREFACE

These guidelines are an important part of the National Center for HIV/AIDS, Dermatology and Sexual Transmitted Diseases (NCHADS) strategy to increase access to care, especially Antiretroviral Therapy (ART) for all Cambodians in need. The Care Package of NCHADS Strategic Plan for HIV/AIDS and Sexual Transmitted Infections (STI) Prevention and Care identifies the continuous development and revision of policies and guidelines as a key strategy for achieving the objective of "improving and maintaining the quality and accessibility of care for 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 guidelines were revised in November 2007 as Pediatric AIDS Care sites greatly expanded. Presently, there are 32 Pediatric AIDS care sites operating in 20 provinces and plans are in place to integrate pediatric care in selected adult AIDS care sites to ensure even wider coverage.

During a series of technical working group meetings, staff from the National Center for HIV/AIDS Dermatology and STI, the National Pediatric Hospital, Angkor Hospital for Children, and other non-governmental organization (NGO) partners reviewed and revised the 2007 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 World Health Organisation (WHO) and the United States Centers for Disease Control (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 encourages pediatricians to reference the guidelines when providing antiretroviral therapy to HIV-infected children.

Phnom Penh, 27/06/, 2011

Prof. ENG HUOT
SECRETARY OF STATE

ACKNOWLEDGMENTS

The National Center for HIV/AIDS, Dermatology, and STIs would like to acknowledge the dedication of the members of the Pediatric AIDS Care Technical Working Group (TWG) (see page 96) in the creation of the 1st Edition National Guidelines for the Prevention and Treatment of Opportunistic Infections among HIV-exposed and HIV-infected Children in Cambodia. Throughout the process, they contributed high quality suggestions, enthusiasm, and hard work.

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

I would like to take this special occasion to thank the staff of the National Center for HIV/AIDS, Dermatology and STD control (Dr. Seng Sopheap, Dr. Samreth Sovannarith, and Dr. Ngauv Bora) for coordinating the revision of these guidelines. I also want to express my gratitude to the pediatricians from the National Pediatric Hospital (Professor Chhour Y Meng, Dr. Kdan Yuvatha, Dr. Ung Vibol, and Dr. Sam Sophan), Angkor Hospital for Children (Dr. Soeung Seitaboth), Battambang Referral Hospital (Dr. Chea Peuv), FHI (Dr. Laurent Ferradini), Clinton Health Access Initiative (Ms. Magdalena Barr-Dichiara and Ms. Cabrie Kearns), and UNICEF and Brown University, USA (Ms. Penelope Campbell and Dr. Benjamin Westley), who have actively participated in revising these guidelines. Lastly, I would like to thank all partners, civil societies and PLHIV networks who have provided care, treatment and support to HIV-infected children in Cambodia.

Phnom Penh, 16 June, 2011

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ABBREVIATIONS

3TC	*Lamivudine*
ABC	*Abacavir*
AIDS	*Acquired 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*
CK	*Creatine Kinase*
CMV	*Cytomegalovirus*
CNS	*Central Nervous System*
CrCl	*Creatinine Clearance*
CTX	*Cotrimoxazole*
d4T	*Stavudine*
ddI	*Didanosine*
DBS	*Dried Blood Spot*
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*
HBsAg	*Hepatitis B Surface Antigen*

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/r	*Lopinavir/ritonavir coformulated in 4:1 dosing ratio*
LPV/R	*Lopinavir/ritonavir with extra ritonavir boosting in 1:1 ratio*
MAC	*Mycobacterium avium complex*
MTCT	*Mother to Child Transmission*
NCHADS	*National Center for HIV/AIDS, Dermatology and STD*
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 jiroveci 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*
TAMs	*Thymidine analog mutations*
TB	*Tuberculosis*
TDF	*Tenofovir disoproxil fumarate*
TST	*Tuberculin Skin Test*
VCCT	*HIV voluntary confidential counseling and testing*
VDRL	*Venereal Diseases Reference Laboratory (refers to a test for syphilis)*
VL	*Plasma HIV Viral Load*
WHO	*World Health Organization*

1. BACKGROUND AND INTRODUCTION

Through concerted efforts of all stakeholders including the government, UN agencies, development partners, civil society and the community for the last 17 years, Cambodia has been successful in bringing down the prevalence of HIV infection among the general population aged 15-49 years from 2% in 1998 to 0.7 % in 2010. It is estimated that there are 56,200 people currently living with HIV (PLHIV), and among these 3,881 are children <15 years of age who are receiving ART. 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.

Since 2003, NCHADS has been implementing a Continuum of Care (CoC) framework, which is a comprehensive care, treatment and support system for people living with HIV/AIDS. Through September 2010, NCHADS has expanded HIV/AIDS care and treatment services to 52 sites for adults and 32 sites for children in 20 provinces.

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. This revision represents the 3rd edition of the National Guidelines for the Use of Pediatric Antiretroviral Therapy, which were originally approved by the Ministry of Health in October, 2004 and revised in November, 2007.

The 2010 revision of the National Guidelines for the Use of Pediatric Antiretroviral Therapy is a co-product of NCHADS, the National Pediatric Hospital, Angkor Hospital for Children, UNICEF, and other partners who have been providing treatment, care, and support to children living with HIV/AIDS in Cambodia.

These guidelines should be used as a reference document at all pediatric AIDS care sites in Cambodia and assist clinical judgment for pediatricians in order 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 or child <18 months of 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.

2.1 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.
- 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, 96% of HIV-uninfected children will test antibody negative at 12 months and 100% will have lost maternal HIV antibodies by 18 months of age.
- Antibody tests include rapid tests, which are used to screen for HIV, and ELISA/EIA tests, which are very specific and may be used to confirm HIV

Before the age of 18 months:

- 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.
- 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 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, and immediate virologic testing is indicated to confirm infection.
- Definitive antibody testing at 18 months is also recommended in all children with positive virologic testing.

After the age of 18 months:

The HIV antibody test is 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.

2.2 HIV Virologic Tests

HIV virologic tests 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
  - In Cambodia, HIV DNA PCR is performed as a qualitative test by dried blood spot (DBS) that returns either a POSITIVE or NEGATIVE result. It is used to diagnose HIV infection in children under 18 months of age.
- Assays to detect HIV RNA by PCR
  - In Cambodia, HIV RNA PCR is performed as a quantitative test requiring blood collected by venipuncture. It is primarily used to determine the plasma HIV viral load (VL) during therapy, but may also be used to confirm HIV infection in children <18 months of age. There is a small risk of false-positive results with values of less than 10,000 copies/mL.
- Assays to detect HIV p24 antigen.
  - Not routinely used in clinical settings in Cambodia.

- In Cambodia, PCR testing is recommended for all known HIV-exposed infants at 4 - 6 weeks of age (See "Schedule of Follow-Up Visits for the HIV-Exposed Infant"—Annex A).
- Cotrimoxazole prophylaxis should also begin at 4-6 weeks of age in all HIV-exposed infants
- A positive DNA PCR test means that the child is HIV-infected, and ART should begin without delay.
- A second PCR test to confirm HIV infection should be performed as soon as possible, but ART should not be delayed while awaiting the result.
- Infants 6 weeks of age or older who have never breastfed, and who have a negative DNA PCR test, are presumed to be not HIV infected (see algorithm #2).

2.3 Infants and Children Requiring HIV-testing

- HIV-infected infants progress to clinical disease very rapidly, with 20% having severe immunosuppression at 6 weeks of age.
- Effective antiretroviral therapy (ART) dramatically reduces the risk of death in HIV-infected infants and children.
- For this reason, ***all HIV-exposed infants require HIV DNA PCR testing at 4-6 weeks of age, or at their first contact with the healthcare system after the age of 6 weeks***.
- All older children discovered to have an HIV-infected mother or sibling also require testing at the earliest possible opportunity per the appropriate Child Testing Algorithm.

However, there will continue to be children presenting for care in whom maternal HIV-status is unknown. Identifying HIV+ children early in their clinical course is challenging because many of the signs and symptoms of early HIV disease are also common in HIV-uninfected children (Box 1):

- ***Any infant or child with signs or symptoms that could indicate HIV infection should have their mother's HIV status determined***.
- ***At a minimum, certain high-risk children should be tested as summarized in Box 2.***

If the mother's status is unknown and she is not immediately available for testing, the infant should be tested as per Child Testing Algorithms #3 or #4 below.

Box 1: Signs and symptoms in children with HIV-infection

Common in HIV-infected children and uncommon in other children

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

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

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

Signs and symptoms strongly suggestive of HIV-infection

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

Adapted from:

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

Box 2: At a minimum, the following groups of children should be tested for HIV

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

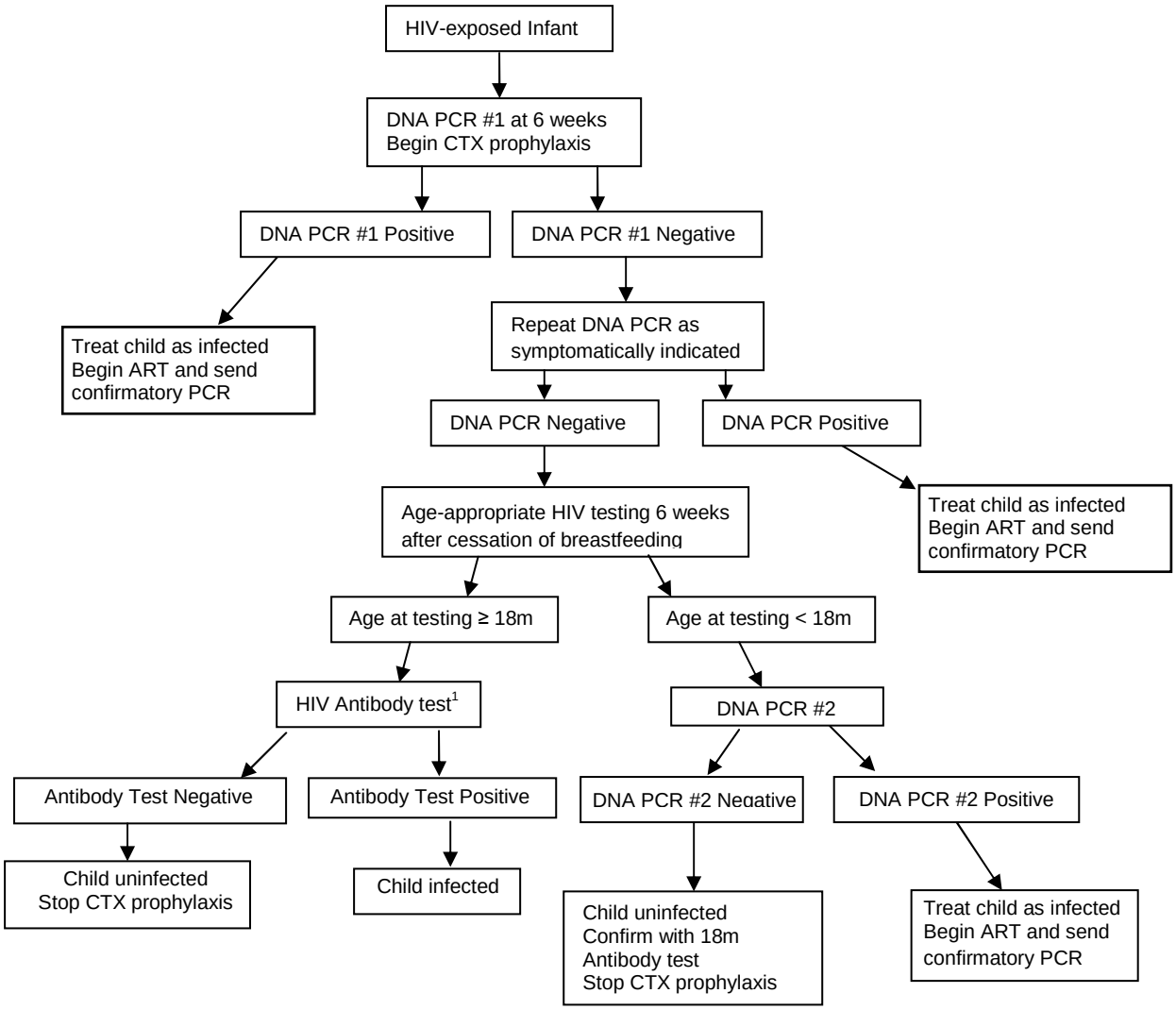
2.4 Diagnosing HIV Infection in the HIV-Exposed Infant who is Breastfed

In Cambodia, the majority of infants are breastfed and national policy encourages exclusive breastfeeding until the infant reaches the age of 6 months, followed by introduction of complementary foods and continued breastfeeding for up to 12 months.

For infants who are currently being breastfed and have an ongoing risk of acquiring HIV infection (algorithm #1):

- A positive PCR test at 6 weeks of age indicates that the infant is HIV-infected and should initiate ART without delay.
    - Mothers of HIV-infected children should continue to breastfeed for as long as the general population, up to 24 months or longer as desired
- A negative PCR test does not rule out HIV infection.
- A 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.
- Infants who have completely stopped breastfeeding for at least 6 weeks and have a negative HIV antibody or PCR test are presumed to be not HIV infected.
- HIV antibody testing is recommended at 18 months of age to confirm that the child is uninfected if negative antibody status has not been previously documented. (See Annex A and Child Testing Algorithms #1 - 4).
- Any infant or child with ongoing HIV exposure must remain on cotrimoxazole until HIV is ruled-out with a negative virologic or antibody test 6 weeks after the complete cessation of breastfeeding.

Child Testing Algorithm #1:
Diagnosis of HIV Infection in Exposed Infants who received ANY Breastmilk:



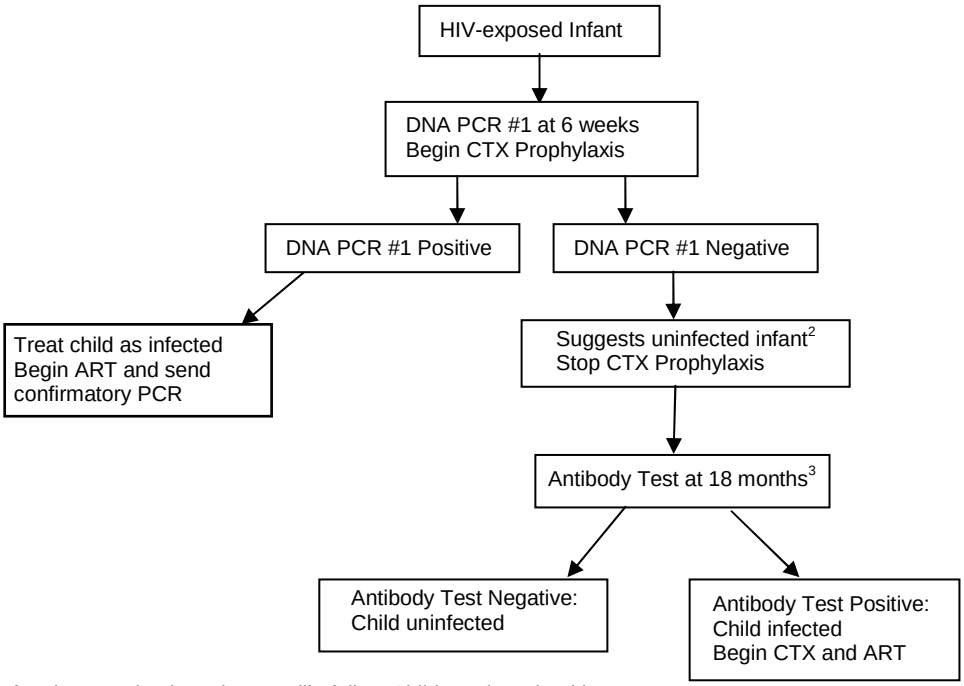
[1]Follow National Guidelines algorithm for antibody testing

2.5 Diagnosis of HIV Infection in the *Non-Breastfed* HIV-Exposed Infant

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

Child Testing Algorithm #2:

Diagnosis of HIV Infection in Exposed Infants who have Never Received Breastmilk[1]

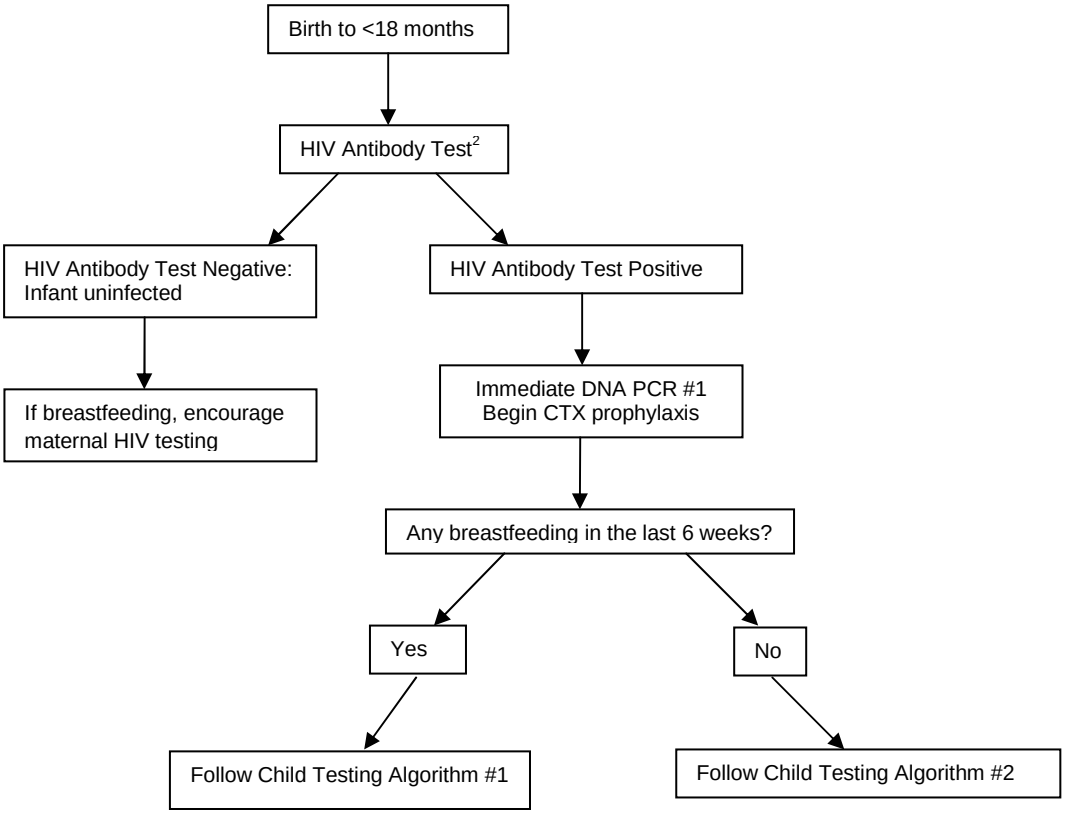


[1]If the infant has received *any* breastmilk, follow Child Testing Algorithm #1.
[2]Perform repeat PCR testing if infant develops signs/symptoms that could be related to HIV
[3]Follow National Guidelines algorithm for HIV Antibody testing

2.6 Diagnosis of HIV Infection in Children < 18 Months of Age with Unknown Exposure Status

- 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 infected, assuming that breastfeeding has ceased for >6 weeks. If available and agreeable to testing, an HIV antibody test may alternatively be performed on the biological mother. Antibody testing of infants does not reliably rule-out HIV-exposure.
- If the infant's antibody test is positive, immediate PCR testing is needed and cotrimoxazole prophylaxis should be initiated. Further testing depends 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]



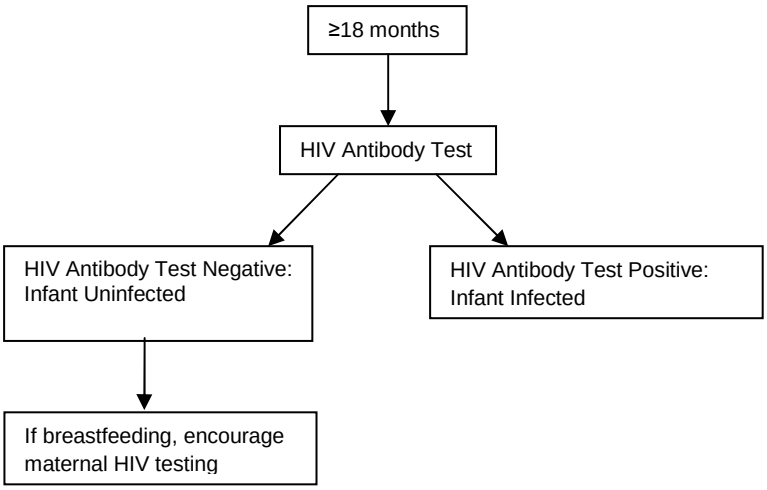
[1]If available for testing, an HIV antibody test may be performed on the biological mother. If negative, the child may be considered uninfected. If positive, follow child testing algorithm #1 or #2 as appropriate.
[2]Follow National Guidelines algorithm for HIV Antibody testing

2.7 Diagnosis of HIV in children >18 months of age

Children who are >18 months of age may be referred for evaluation of their HIV status for many reasons, including signs and symptoms that could indicate HIV infection, or because of known or suspected HIV exposure.

The HIV infection status for such children may be determined by HIV antibody testing, as outlined in Child Testing Algorithm #4.

Child Testing Algorithm #4: HIV Testing for Children ≥ 18 Months



[1]Follow National Guidelines algorithm for HIV Antibody testing

3. WHEN TO START ANTIRETROVIRAL TREATMENT IN INFANTS AND CHILDREN

The decision to start ART in a child with presumptive or confirmed HIV infection is complex, and must ensure that the benefits of treatment outweigh the risks of toxicity in the short and long term. This depends on the child's age, clinical status, immunologic status, and social parameters.

3.1 ART initiation for children < 2 years of age

- Children younger than 18 months who have an initial positive PCR test, and children older than 18 months but younger than 2 years with positive antibody testing, should begin ART without delay.
- Ideally this should occur within two weeks of HIV diagnosis.
- In addition, HIV-exposed infants who are antibody positive with a presumptive diagnosis of severe HIV should begin ART when PCR testing is not available (see Box 4 below).

3.2 ART initiation for children ≥ 24 months of age according to Clinical and Immunologic Staging

- Children ≥24 months of age with proven HIV infection should receive clinical and immunologic staging and may qualify for ART based on the criteria in Table 1.
- The risk of HIV-related mortality increases in WHO clinical stage 3 or 4. Therefore, all children ≥24 months presenting with WHO clinical stage 3 or 4 should start ART at any CD4 count.
- Children ≥24 months of age with WHO clinical stages 1 and 2, ART should be initiated according to immunologic criteria described in Table 1.
- Children ≥24 months who do not meet immunologic criteria for the initiation of ART must be monitored regularly for repeat clinical and immunologic staging. At a minimum, HIV-infected children should be evaluated with clinical staging every 3 months and CD4 determination every 6 months. See Table 1 and Annex B for WHO clinical staging.

3.3 Immunologic Staging

- The CD4 threshold for starting ART varies according to age.
- For initiation of ART, use of the CD4 percentage (%CD4+) is preferred for all children <5 years of age, with absolute CD4 cell counts used for those ≥5 years.
- Measuring CD4 percentage should be considered in children of all ages. During acute illness, it is common for the absolute CD4 cell count to fall while the %CD4+ remains in the normal range. Discordant absolute and %CD4+ values can be useful in distinguishing this event. However, for the purposes of determining ART eligibility, the *lower* of the two values should generally be used. (See Table 1 and Annex C for WHO immunologic staging).
- In children with clinical stage 1 or 2, two CD4 tests below threshold should, if

possible, be obtained before the initiation of ART. This is particularly important in cases of severe discrepancy between the absolute and %CD4+, especially with a preserved %CD4+ but low absolute CD4 cell count. If either value falls below the age-related ART threshold on initial CD4 testing, repeat values should be sent without delay and the child prepared for ART while awaiting confirmatory testing.

Box 3: Summary of criteria for starting ART

Infants and children meeting the following criteria should be started on ART

- All infants and children <24 months of age with confirmed[1] HIV infection
- Infants <18 months of age with presumptive severe HIV disease where PCR testing is not readily available (Box 4)
- Children ≥24 months of age with confirmed HIV infection and:
    1. WHO Pediatric Clinical **Stage 4**, *or*
    2. WHO Pediatric Clinical **Stage 3**, *or*
    3. Age 24 – 59 months and CD4+ <25% or <750 cells/mm^3, *or*
    4. Age ≥5 years and CD4 count <350 cells/ mm^3

[1]Infants <18 months of age with a single positive DNA PCR assay should begin ART without delay, preferably within 2 weeks of diagnosis. ART need not be delayed while awaiting results of confirmatory PCR testing

3.4 Social Considerations relevant to starting ART in Children:

In order to begin ART, children must:

- 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.

Table 1: Criteria to start ART*

<table>
<tr><th>WHO Clinical Stage</th><th>< 24 months</th><th>24 to 59 months</th><th>≥ 5 years</th></tr>
<tr><td>1</td><td rowspan="2">Treat ALL</td><td rowspan="2">< 25% or
<750 cells/mm^3</td><td rowspan="2">< 350 cells/mm^3</td></tr>
<tr><td>2</td></tr>
<tr><td>3</td><td>Treat ALL</td><td colspan="2">Treat ALL</td></tr>
<tr><td>4</td><td colspan="3">Treat ALL</td></tr>
</table>

***After appropriate counseling and preparation**

Box 4: Presumptive diagnosis of severe HIV infection

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

4. RECOMMENDED FIRST-LINE REGIMENS

- The use of three ARV medications is currently the standard treatment for HIV infection in order to achieve the best possible suppression of viral replication and to arrest the progression of HIV disease.
- 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 selecting the most potent available regimen and incorporating approaches to support adherence.
- The choice of ARV regimen should balance efficacy, toxicity, palatability and cost-effectiveness.

4.1 Choice of First-Line Regimen:

- When choosing a first-line regimen for infants and children, it is important to consider the age of the child as well as the regimen used for prevention of mother-to-child transmission (PMTCT).
- For children ≥3 years of age or >10kg, a regimen that includes two NRTIs (AZT or d4T plus 3TC) and one non-nucleoside reverse transcriptase inhibitor (NVP or EFV) is recommended. Nevirapine is the NNRTI of choice for most children.
- For children <3 years of age or <10kg, a regimen that includes two NRTIs (AZT or d4T plus 3TC) and NVP is recommended.
- Children <12 months of age who become infected with HIV after receiving 6 weeks of daily infant NVP should be started on a regimen that includes two NRTIs (AZT or d4T plus 3TC) and LPV/r.

Children receiving rifampicin-based therapy for active tuberculosis may require alterations to their ART regimens. For selection of ART regimens in children with active tuberculosis, refer to Chapter 10, Tables 11 and 12.

Adolescents with chronic hepatitis B infection who are old enough to safely receive tenofovir should begin a regimen that includes tenofovir and either 3TC or FTC along with an NNRTI. Refer to Chapter 10, Box 13.

Children who had a lapse or default during prior treatment should generally be restarted on their initial regimen, unless treatment was discontinued due to severe intolerance or there was previous evidence of treatment failure. A viral load should be checked 6 months after the re-initiation of therapy.

Box 5: 1st line ART regimens

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)

Children <12 months of age exposed to infant daily NVP for PMTCT*

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

Or

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

*Where LPV/r is not available due to lack of an adequate cold-chain infrastructure, use the standard 1st line regimen of 2 NRTIs and NVP.

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

4.2 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. Lamivudine is also active against hepatitis B virus, although resistance rapidly emerges when not used with a second hepatitis B active agent.
- Zidovudine (AZT) is generally well-tolerated in children and is the preferred NRTI to be used in combination with 3TC from a toxicity standpoint. It is available in several fixed-dose combinations allowing treatment in children of all ages, and the tablets

may be broken or crushed as needed. AZT results in significantly lower rates of lipodystrophy and peripheral neuropathy than d4T when used for extended periods of time. The most rigorous recent pediatric ART trials have all used AZT and 3TC as the NRTI backbone for treating children under 3 years of age. However, AZT should not be used in cases of severe anemia (Hemoglobin (Hb) < 7.5g/dL), in which case d4T should be substituted. AZT requires monitoring of Hb 8 weeks into treatment.

- Stavudine (d4T) is initially better tolerated than Zidovudine (AZT) and does not require 8-week hemoglobin monitoring. d4T is widely available in several FDC tablet strengths that can be broken or crushed to allow for treatment of children of a wide range of age groups. Despite its lack of short-term toxicities, d4T is associated with a greater risk of long-term toxicity than other NRTIs due to its effects on mitochondria, especially lipodystrophy, lactic acidosis, and peripheral neuropathy. These toxicities have been increasingly described in children and may limit the drug's long-term use. For this reason, AZT is preferred as a first-line NRTI for children. Children currently receiving and tolerating d4T should remain on the regimen. However, d4T should be swapped to AZT at the first sign of lipodystrophy, lactic acidosis, or peripheral neuropathy.

4.3 Choice of NNRTIs:

- Efavirenz (EFV) is not currently recommended for use in those under 3 years or under 10 kg due to the lack of clear pharmacokinetic data to guide dosing in these children. Therefore, nevirapine should be used for these young children. In older children, EFV is the NNRTI of choice when receiving rifampicin-based TB therapy. EFV capsules can be opened and the granules combined with something sweet to mask the bitter/peppery taste. EFV has been associated with birth defects and is contraindicated during the first trimester of pregnancy. The decision to start EFV in a young girl entering her child-bearing years requires careful consideration to ensure that she remains sexually inactive or compliant with two forms of contraception.
- 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 is the preferred NNRTI for children without contraindications to NVP therapy, such as ALT >5N, or ongoing TB therapy in those >3 years and >10kg in whom EFV is preferred.
- Special considerations on dosing and administration for NVP:
    - Induction dose 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. Induction dosing is necessary because NVP induces its own clearance by inducing the CYP 3A4 enzyme system in the liver. 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. Because rifampicin and efavirenz both also induce CYP 3A4,

children receiving rifampicin or efavirenz may begin NVP without induction dose but directly at the maintenance dosing.

- Maintenance dose: target dose is 160-200 mg/m^2/dose given twice daily. It is important to use the upper-end of the dosing scale in younger children and those receiving rifampicin-based TB therapy whom are unable to receive efavirenz (see Annex E).

4.4 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 60 days; at higher temperatures the drug degrades at a faster rate. The ritonavir component is ethanol-based, which gives the liquid an unpalatable flavor. However, the volume needed to effectively treat infants is very small, making administration less challenging in these youngest children. In general, persistence will allow successful administration in almost all children. A heat-stable LPV/r tablet (200mg/50mg and 100/25) is now available for use in older children, which avoids the problem of poor liquid palatability. It is important to note that the tablets may not be broken or crushed, which limits their use to children old enough to swallow large tablets.

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

- ARV drug toxicities, also known as adverse events or adverse drug reactions, 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).
- In general, ART is better tolerated in young children than adults. As children age, side-effect profiles of various drugs more closely mirror those seen in adults.
- Most notably, d4T is extremely well tolerated in young children, but with time peripheral neuropathy and lipodystrophy frequently occur as in their adult counterparts.

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 (See Annex G: Severity Grading of Selected Clinical and Laboratory Toxicities). They can be classified in several types of distinct toxicities, detailed in the table below.

Table 2: Types of drug toxicities observed with ARVs

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

- Mild or moderate toxicities most often occur shortly after beginning treatment and spontaneously resolve 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 (See Table 3 and 4)
- Other toxicities occur after months or years of antiretroviral treatment. These include lipodystrophy, peripheral neuropathy, hyperlactatemia and mitochondrial toxicity. These toxicities can be life threatening (lactic acidosis), disabling (neuropathy), or impact adherence (lipoatrophy in adolescents).

Table 3: Summary of major ARV-related toxicities

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[1]
Abacavir (ABC)		Hypersensitivity reaction	Mitochondrial toxicity[1]
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 (NVP)	Skin rash Asymptomatic transaminases elevation	Hepatitis Hypersensitivity reactions	
Efavirenz (EFV)	CNS symptoms (somnolence, insomnia, confusion, abnormal dreams, abnormal thinking) in first weeks of treatment		Teratogenicity
Protease inhibitors (PIs)			
Lopinavir/ritonavir (LPV/r)	Diarrhea, nausea, vomiting	Lipodystrophy	Pancreatitis, hyperglycemia, ketoacidosis, diabetes and hepatitis
Nelfinavir (NFV)	Diarrhea	Abdominal pain Lipodystrophy	Hyperglycemia, ketoacidosis and diabetes
Indinavir (IDV)	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 (RTV)	Nausea, vomiting, diarrhea, headache, abdominal pain and anorexia	Circumoral paresthesia Increases in liver enzymes Lipodystrophy	Pancreatitis, hyperglycemia, ketoacidosis, diabetes and hepatitis.
Saquinavir (SQV)	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.

[1] 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. **An exception is d4T related toxicity with lipodystrophy or peripheral neuropathy where a change to AZT should be made immediately.**

Moderate and severe toxicities require the substitution of an ARV drug associated with toxicity by a drug in the same ARV class with a different toxicity profile 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 H). 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 4: Drug substitutions for ARV-related toxicities

First-line ARV drug	Most frequent significant toxicity	Details	Suggested first-line ARV drug substitution
Zidovudine AZT	Severe anemia[1] 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 the case of d4T intolerence)
	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	Fat maldistribution Hyperlipidemia Diabetes	AZT or ABC (in case of severe lipoatrophy)
	Lactic acidosis	As above	Stop all ARVs until symptoms disappear, switch to ABC

Nevirapine NVP	Severe potentially life threatening acute symptomatic hepatitis	ALT>10N	Stop all ARVs, restart when ALT 2 N, replace NVP by LPV/r
	Dry rash (mild or moderate rash Annex G 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[3]
	Wet rash (severe rash Annex Grading)	Wet rash: vesicles, ulcers, limited moist desquamation, limited mucous membranes involvement	Stop NVP and continue NRTI, start with EFV when symptoms resolve[3]
	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[2]	Persistent and severe central	Persistent hallucinations or psychosis	Switch to NVP
	Potential teratogenicity	Adolescent girl in first trimester of pregnancy, or of childbearing potential and not receiving adequate	Switch to NVP
	Dry rash		Stop all ARVs, restart with EFV when symptoms resolve.
	Wet rash or life-threatening rash (Stevens-Johnson		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.
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, 1%)	Stop ABC immediately, switch to AZT if used in first-line or ddI if second-line **Never reintroduce ABC**

Note: 3TC-associated pancreatitis and mitochondrial toxicity has been described in adults but is very rare in children.

[1]Exclude malaria in areas of endemic malaria.

[2] 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.

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

6. 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.

6.1 Baseline Clinical and Laboratory Assessment

- All HIV infected children who are diagnosed with HIV should undergo baseline clinical and laboratory assessment to determine the clinical stage of HIV infection, and they should receive CD4 testing.
- Monitoring should also be performed during follow-up HIV care for children who are either eligible or not eligible to receive ART.
- The standard baseline clinical and laboratory assessment of children newly diagnosed with HIV is outlined in Box 6.

Box 6: Baseline evaluation of children with newly diagnosed HIV infection

Clinical assessment
• 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 K) • Developmental status • Nutritional status • Assessment of children and parents or caregivers for preparedness for ART
Laboratory assessment
• Measurement of CD4 and %CD4+ • White blood cell count (WBC) • Hemoglobin measurement • Hepatitis B surface Ag and Hepatitis C Ab • Liver function testing (LFT) • Pregnancy test (adolescent girls only)

- HIV-infected children have extremely high rates of malnutrition and inadequate rate of growth. Routine monitoring of nutritional status per the National Guidelines is essential in all HIV-infected children.
- When malnutrition is detected, aggressive measures are warranted and must be

performed in accordance with protocols for the treatment of malnutrition in children with HIV. See the *National Guidelines for the Prevention and Treatment of Opportunistic Infections among HIV-exposed and HIV-infected Children.*

6.2 Routine Monitoring of Children *not yet* eligible for ART

- For children who are not eligible for ART, clinical evaluation should be performed every month for the first three months, and every three months thereafter.
- The pediatric clinical and immunologic stage should be evaluated at each visit.
- The routine monitoring of children not yet eligible for ART is outlined in Table 5

6.3 Routine Monitoring of Children *on* ART

- Once the child is initiated on ART, ongoing clinical and laboratory monitoring should take place in the context of the routine clinical care of the child.
- Clinical and laboratory assessments of the child and caregivers should include assessing their understanding of ART, drug regimen and dosing, and drug side effects, as well as medication adherence and anticipated psycho-social and community support.
- The routine clinical and laboratory monitoring of children receiving ART is outlined in Box 7 and Table 6.

Box 7: Routine clinical and laboratory monitoring in children receiving ART

Clinical assessment
• WHO clinical staging • TB symptoms screen • Neurological and developmental assessment • Weight, height, weight-for-height, head circumference*, and growth assessment • Nutritional status and feeding • Evaluation of any interval illnesses • Assessment of ARV dosing, side effects, toxicities and drug interactions • Adherence to ART • Counseling for prevention of STIs and pregnancy (adolescents) • Evaluate medication dosing for interval weight gain
Laboratory assessment
• Measurement of CD4 and %CD4+ every 6 months • Hemoglobin measurement at week 8 (if on AZT) • Viral load (VL) at month 6, then every 12 months • Fasting lipid panel yearly in adolescents receiving EFV or LPV/r • Other testing as symptomatically indicated

*Under 2 years of age

Table 5: Schedule of routine clinical and laboratory monitoring for the HIV-infected child *not* on ART

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

(a) Includes history-taking, physical examination and assessment of neurodevelopment.
(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) TB symptoms screen should be performed at every visit.
(d) As indicated by history or symptoms in adolescent females

Table 6: Schedule of routine clinical and laboratory monitoring for the HIV-infected child *on* ART

Items	Baseline	Week 2	Month 1	Month 2	Month 3	Month 6	Every 3 months	Every 6 months	Every 12 months	Symptom Directed
Cl										
Clinical evaluation	X	X	X	X	X	X	X			X
Weight, Height, and Growth Charts	X	X	X	X	X	X	X			
Nutritional Status and Feeding	X	X	X	X	X	X	X			
ARV Dosing, Side Effects, Toxicities, Drug Interactions	X	X	X	X	X	X	X			
Need for OI Medications and Doses	X	X	X	X	X	X	X			
Adherence to ART		X	X	X	X	X	X			
Counseling for Prevention of STIs and Pregnancy (a)	X				X	X	X			X
Labor										
WBC and Hb (b)	X			X[(b)]						X
Liver Transaminase: ALT, ASAT (c)	X		X[(c)]	X[(c)]		X[(c)]		X[(c)]		X
CD4 % and CD4 count	X					X		X		X
Viral Load						X			X	X
Fasting cholesterol, triglycerides and glucose (d)	X[(d)]								X[(d)]	X

(a) In adolescent girls, provide counseling on family planning, prevention of STIs, prevention of transmission of HIV to others, and the risk of transmitting HIV to their infants. Pregnancy test should be performed at baseline and as indicated from counseling, especially for those on EFV regimens.
(b) If on AZT, Hb should be measured at week 8
(c) Repeat ALT at week 4 and week 8 if elevated at baseline, if hepatitis B or C coinfection, or if on other hepatotoxic drugs (e.g. TB medications)
(d) In adolescents, fasting tests for cholesterol, triglycerides and glucose should be performed at baseline and every 12 months when receiving EFV or LPV/r

7. ADHERENCE TO ART IN CHILDREN

- Greater than 95% adherence to the child's ARV drug regimen will ensure a good virologic response and prevent the likelihood of viral resistance.
- For a child taking medication twice daily, omitting more than 1 dose in 10 days (3 days 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.
    - Infants under 12 months must be started on ART without delay, preferably within 2 weeks of HIV diagnosis. It may be necessary to create intensive counseling schedules so that this important objective can be met. ART should not be unduly delayed in order to complete a specified number of pre-treatment counseling sessions.

    - 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.

8. TREATMENT FAILURE

- Treatment failure appears first as virologic failure, then as immunologic failure, and later as clinical failure.
- It is recommended to switch to second-line drugs before clinical failure occurs.
- As routine plasma viral load (VL) monitoring is rolled-out in Cambodia, virologic failure will determine the need to switch to second line.

8.1 CAUSES OF TREATMENT FAILURE

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

- Inadequate adherence:
  - Missing doses
  - 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
- Pre-existing viral resistance (as in the case of failed PMTCT)

It should not be concluded that an ARV regimen is failing until:

- The child has been on the current regimen for at least 6 months
- Adherence to therapy has been assessed and considered to be optimal
- Any opportunistic infections have been treated, 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.

Inadequate adherence is the most common cause of virologic failure. At each visit, adherence should be confirmed by pill counts or other means. Proper dosing should be confirmed and medication doses adjusted for any weight gain since the last visit.

8.2 CLINICAL FAILURE

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

- These events may include:

- Occurrence of new opportunistic infections or malignancies, or recurrence of infections, such as oral candidiasis that is refractory to treatment, or esophageal 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)

- When clinical failure is detected or suspected, **CD4 and viral load should be determined.**
- Results of HIV viral load testing will either confirm or rule-out treatment failure, and should be used to make the final decision regarding 2nd line treatment when possible.

See Table 7 for management options when new clinical events occur.

Table 7: Evaluation and management of WHO clinical events on ART

Clinical event after ≥24 weeks on ART	Evaluation and initial management	Follow-up management
Stage 1 event	• Do not switch regimen • Routine 3 month follow-up	• Consider 2nd line if 2 or more routine CD4 values reveal immunologic failure • Measure viral load if possible to confirm virologic failure prior to initiating 2nd line
Stage 2 event	• Treat event as appropriate • Do not switch regimen • Assess adherence and intensify counseling • Assess nutritional status and access to food • Follow-up in 1 month for repeat clinical staging and CD4 if not improved	• Consider 2nd line if 2 or more CD4 values reveal immunologic failure • Measure viral load if possible to confirm virologic failure prior to initiating 2nd line

Stage 3 event	• Treat event as appropriate • Assess adherence and intensify counseling • Assess nutritional status and access to food • Follow-up within 2 weeks to monitor for response • Check CD4 once acute phase of illness has stabilized or at 2 week follow-up, whichever is earlier • Check viral load	• Switch to 2nd line if CD4 reveals immunologic failure • Measure viral load if possible to confirm virologic failure prior to initiating 2nd line • If viral load is lower than detectable limit, do not switch to 2nd line • Do not delay 2nd line if viral load testing is unavailable
Stage 4 event	• Treat event as appropriate • Assess adherence and intensify counseling • Assess nutritional status and access to food • Follow-up closely or hospitalize as necessary • Check CD4 once acute phase of illness has stabilized • Check viral load • Begin planning for possible ART regimen switch	• Switch to 2nd line if CD4 reveals immunologic failure • If CD4 above the age-related threshold, obtain viral load if possible • If viral load is lower than detectable limit, do not switch to 2nd line

8.3 IMMUNOLOGIC FAILURE

- Immunologic failure is defined as inadequate response of the CD4 value to ≥24 weeks of adherent antiretroviral therapy.
- Age-related CD4 values that suggest immunologic failure are shown in Box 8
- Failure may occur either by an initial rise in CD4 that subsequently falls below the age-related threshold, or an inadequate rise of the CD4 to above these values despite therapy.
- In children <2 years of age suspected of immunologic failure, expert advice should be obtained.

Box 8: Age-related thresholds for immunologic failure

Age-related thresholds for immunologic failure

Age ≥ 2 years and less than 5 years:
- CD4 <200 cells/mm^3, *or*
- %CD4+ < 10%, *or*
- CD4 decrease of >30% in previous 6 months

Age ≥5 years:
- CD4 <100 cells/ mm^3, *or*
- CD4 decrease of >30% in previous 6 months

8.4 VIROLOGIC FAILURE

- The overall aim of treatment is to reduce viral load (VL) to levels below the lowest detection threshold (given by the laboratory, 50 to 400 copies/mL) as rapidly as possible and to maintain undetectable levels for as long as possible.
- Viral load will soon be a routine test in Cambodia.
- The recommended schedule is to determine the VL after 6 months of ART.
- If the VL is undetectable, continued monitoring every 12 months is recommended.
- If the VL is detectable, additional steps need to be taken to ensure adequate drug adherence and administration (see Table 8 and Annex J).
- If access to VL testing is limited, VL should be prioritized to confirming virologic failure in patients with suspected clinical or immunologic failure.

Box 9: When to send viral load testing

When to send viral load testing

- **Month 6 following start of 1st or 2nd line**
- **Every 12 months while on ART**
- **Any new clinical stage 3 or 4 event after ≥24 weeks of ART**
- **Any new immunologic failure after ≥24 weeks of ART**
- **Follow-up of prior elevated viral load as indicated in Annex J**

- Continuing an NNRTI-based regimen when viral replication is occurring leads to the development of resistance first to the NNRTI medication, followed rapidly by resistance to lamivudine. Thereafter, assuming an AZT or d4T based initial regimen, thymidine analog mutations (TAMs) accumulate.
- These TAMs also reduce the efficacy of abacavir, which is a major component of current 2nd line regimens in Cambodia. When >3 TAMs have accumulated, the likelihood of failing an abacavir-containing regimen increases.
- To avoid accumulation of resistance, early detection of virologic failure is critical to preserve the efficacy of the 2nd line regimen available in Cambodia.

Box 10: Viral load threshold for virologic failure

A VL consistently higher than 5,000 copies/mL despite >24 weeks of adherent NNRTI-based ART should lead to a switch to 2nd line therapy.

Table 8 and Annex J summarize the approach to a child with isolated virologic failure.

Table 8: Viral load monitoring in children receiving ART

Plasma viral load (VL)	Recommendation
Undetectable	• Repeat VL in 12 months
<1,000 copies/mL (1.7 - 3.0 log)	• Repeat VL in 6 months[1] • Assess adherence, increase counseling as needed
>1,000 – 5,000 copies/mL (3.0 – 3.7 log)	• Repeat VL in 3 months[2] • Intensify adherence counseling • Investigate for drug-drug interactions or inadequate dosing • Consider 2nd line therapy if repeat VL remains between 1,000 and 5,000 copies/mL *and* the child has evidence of clinical or immunological failure *and* adherence is >80% • Switch to 2nd line therapy if repeat VL is >5,000 copies/mL
>5,000 copies/mL (>3.7 log)	• Repeat VL in 3 months • Intensify adherence counseling • Investigate for drug-drug interactions or inadequate dosing • Switch to 2nd line therapy if repeat VL is >5,000 copies/mL and adherence is >80%

[1]If 3 successive VL measurements remain between 50 and 1,000 copies/mL without evidence of immunologic or clinical failure, decisions regarding 2nd line must be made on an individual basis. Discuss with an expert.

[2]VL >1,000 copies/mL on two repeat VL assays should prompt a switch to 2nd line. See Annex J.

- In case of clinical or immunological failure with the plasma VL undetectable, switching to 2nd line therapy will not improve the clinical or immunologic status of the child, and alternative explanations for the child's failure should be sought.

- It is very rare for children taking 1st-line PI therapy to develop resistance to LPV/r. Most children with extensive resistance to LPV/r have previously failed an unboosted PI regimen (such as nelfinavir).

- Children taking PI-based ART with plasma VL >1,000 copies/mL should be aggressively investigated for improper dosing, drug-drug interactions, or inadequate adherence. Repeat VL should be determined once appropriate adjustments have been made. If repeat VL is >5,000 copies/mL, the child should be referred for evaluation in a treatment center with expertise in this situation. When possible, genotype analysis should be performed to guide construction of an appropriate 2nd line regimen.

Table 9: Conversion of viral copies/ml and log

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)

9. CHOICES FOR SECOND-LINE TREATMENT

Children meeting the definition of treatment failure described in Chapter 8 require modification of their ART regimen to control viral replication and to prevent the further emergence of viral resistance mutations.

9.1 Failure on NNRTI-based Therapy for children <12 years of age

- In children failing standard 1st line NNRTI-based therapy, the preferred 2nd line therapy in Cambodia includes 2 NRTIs plus lopinavir/ritonavir.
- The choice of which NRTI drugs to select as the regimen backbone depends on the backbone that composed 1st line therapy.

Table 10: Recommended 2nd line regimens for children failing NNRTI-based ART

Failing **Regimen**	**Recommended 2nd line**
AZT *or* d4T + 3TC + NVP/EFV	ABC + 3TC + LPV/r
ABC + 3TC + NVP/EFV	AZT + 3TC + LPV/r

9.2 Choice of NRTIs for Second line regimen

- Abacavir (ABC) has been safely used to treat many infants and children in Europe and the United States. It is well tolerated in the majority of children and does not result in anemia, mitochondrial dysfunction, or lipodystrophy. Three-drug fixed-dose-combinations (FDCs) are not yet widely available. Abacavir appears to be as potent, and possibly more potent, than AZT when used as a first-line ART backbone in combination with 3TC. Its use has been limited by cost as well as concern regarding rare but serious hypersensitivity reactions (HSR), which are associated with the HLA B5701 gene. This gene is common in Caucasian races but uncommon in Asians and rare in Africans. Abacavir is the NRTI of choice in 2nd line regimens for children failing treatment with an AZT or d4T backbone.
- Tenofovir (TDF) is a potent nucleotide analog that can be dosed once daily. It retains significant activity even against virus with multiple thymidine analog mutations (TAMs) and therefore is the preferred 2nd line NRTI in children old enough to safely take this drug. Concerns about decreased bone mineral density in infants and young children, as well as a lack of a pediatric formulation, currently limit its use to adolescents ≥12 years or with Tanner stage ≥4. TDF is also active against hepatitis B virus. Toxicity is primarily limited to decreased bone mineral density and rare kidney tubule damage leading to the Fanconi syndrome (hyperphosphaturia, glucosuria, and elevated creatinine). Use of TDF in combination with ABC should be avoided, as their use together promotes the

emergence of viral K65R mutations that confer high-level resistance to both TDF and ABC.

9.3 Treatment failure in adolescents ≥12 years

- Children ≥12 years of age or Tanner stage ≥4 should receive tenofovir in place of ABC when failing an initial AZT or d4T-containing regimen. See Box 11.

Box 11: Second line ART in adolescents

Preferred 2nd line regimen for adolescents failing AZT or d4T + 3TC + NVP
TDF + 3TC (or FTC) + LPV/r

- Adolescents failing a 1st line regimen composed of ABC +3TC + NVP may be treated with the standard 2nd line of AZT + 3TC + LPV/r.
- In cases of ABC hypersensitivity or unavailability in second-line treatment, ABC should be replaced by ddI.

- **The following second-line regimens should be avoided**:
  - TDF + ddI Triple Combinations (lacks potency, drug-interaction)
  - ddI + d4T Triple Combinations (superimposed toxicity profiles)

IMPORTANT

When 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*).

9.4 Regimen selection after failure of PI-based therapy

- Children failing 1st-line LPV/r almost never have significant resistance to LPV/r. Infants will occasionally take longer than 6 months to fully suppress HIV virus on their initial regimen.
- Children with failure on a PI-based regimen should be evaluated in a referral center with expertise in the construction of salvage-regimens for HIV-therapy, preferably guided by viral genotype analysis.
- After genotype analysis, it will usually be recommended to continue the original regimen and strongly address adherence or dosing issues.
- Due to a lack of adequate evidence-based data and the variability of each

individual scenario, a standard 2nd line regimen for children failing PI-based ART cannot be recommended at the present time.

9.5 Treatment failure in special circumstances

- *Active tuberculosis*-
  - In a child with proven virologic failure who is receiving rifampicin-based TB treatment, initiating PI-based therapy will be complicated by drug-drug interactions.
  - When 2nd line is necessary during TB treatment, additional ritonavir must be added to coformulated lopinavir/ritonavir to bring the lopinavir/ritonavir ratio to 1:1. This is referred to as "super-boosting."
  - The additional ritonavir dose should be continued until 2 weeks after rifampicin is discontinued.
  - See the Chapter 10 section on TB/HIV coinfection for more details.

- *Chronic Hepatitis B*-
  - Abrupt discontinuation of hepatitis B treatment can precipitate a flare in hepatitis B activity.
  - Children with chronic hepatitis B who require 2nd line therapy should not stop either 3TC/FTC or tenofovir if included in the first line because of their activity on hepatitis B virus.
  - Construction of an appropriate NRTI backbone in this situation should be done in consultation with an expert in ART treatment for children with hepatitis B.

10. ART CONSIDERATIONS IN TB AND HEPATITIS CO-INFECTION

10.1 TB/HIV Co-infection

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

10.1.1 Diagnosis of TB

- In many cases, particularly in young children, diagnosis is presumptive and is based on a combination of clinical signs and symptoms, known contact with a household member with TB disease or positive TST, and findings on chest x-ray.
- Diagnosis of TB should be made according to the *National Guidelines for TB Treatment in Children* and the *National Guidelines for the Prevention and Treatment of Opportunistic Infections among HIV-exposed and HIV-infected Children*.
- Infants and children living with HIV/AIDS should be regularly screened for the following symptoms and referred for active TB diagnosis if any one of the following is present:
    - Living with active TB patients
    - Failure to thrive
    - Fever
    - Current cough
    - Enlarged cervical lymph nodes
- Children ≥12 months of age without any of the above symptoms should be provided **isoniazid preventive therapy (IPT)** per the 3 Is initiative as outlined in the *National Guidelines for the Prevention and Treatment of Opportunistic Infections among HIV-exposed and HIV-infected Children*.
- Children <12 months of age should be provided IPT when contact with a smear-positive TB case is discovered and no other symptoms of active TB are present.

10.1.2 When to start ART in children receiving TB treatment

- While the ideal timing of ART-initiation for all children with TB is not yet known, it is recommended that ART begin within two weeks of starting TB treatment. See Box 12.
- The child should have demonstrated initial stabilization on TB medications and be tolerating the regimen without adverse drug reactions.

Box 12: When to start ART in children receiving TB therapy

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

10.1.3 Selecting an ART regimen in children receiving TB treatment

- There are many interactions between ARVs and other medications, particularly TB drugs.
- The interactions between rifampicin and the NNRTI and PI classes are due to the fact that rifampicin stimulates the activity of the cytochrome P450 (3A4) liver enzyme system which metabolizes lopinavir, nevirapine, and to a lesser extent, efavirenz. Rifampicin decreases the blood levels of these drugs. PIs and NNRTIs can also modify this same enzyme system activity and lead to altered blood levels of rifampicin. The potential drug interactions may result in failure of ART or TB treatment or an increased risk of drug toxicity. Importantly, ritonavir specifically *inhibits* the CYP 3A4 enzyme, and for this reason is used to "boost" blood levels of lopinavir when given together.

- Specific interactions between rifampicin and ARV drugs available in Cambodia are outlined below:

  - *Nevirapine*- Rifampicin reduces NVP area under the curve (AUC) by 31%, although the clinical significance of this reduction is not clear. Small pediatric studies have variably suggested that trough levels are reduced to sub-therapeutic levels, although this reduction appears to be more dramatic in children of African origin than those from Asia.
    - When possible, efavirenz should be used in place of NVP when co-administration with rifampicin is necessary.
    - In the case of contraindications to efavirenz (age <3y, weight <10kg, or prior efavirenz intolerance), NVP may be used but should be dosed at the upper limit of 200 mg/m^2 per dose twice daily.
    - When NVP is begun in a child already receiving rifampicin, it may be initiated at the twice-daily maintenance dosing without a 14 day induction period.
  - *Efavirenz*- Rifampicin reduces EFV AUC by 22%. Most studies have suggested that trough levels remain in the therapeutic ranges in patients receiving both rifampicin and efavirenz. For this reason:
    - Efavirenz is the NNRTI of choice for use in patients receiving rifampicin-based TB therapy.
    - It is not necessary to increase the maximum daily dose of efavirenz above 600mg daily.

- *Lopinavir*- Rifampicin reduces LPV AUC by >50% and trough concentrations by >90% in adults and children.
    - For this reason, standard-dose LPV/r CANNOT be administered at the same time as rifampicin.
    - However, the addition of extra ritonavir "super-boosting" to standard LPV/r dosing has been shown to result in therapeutic lopinavir concentrations in children receiving TB therapy.
    - Challenges of this approach include increased regimen complexity, poor palatability of ritonavir, and diarrhea. Liver enzyme elevation may rarely occur.
    - Children are generally able to tolerate this drug dosing combination but should be followed closely.
    - The additional ritonavir "super-boosting" should be stopped 2 weeks after rifampicin discontinuation.
- *NRTIs*- There are no significant clinical interactions between rifampicin and the NRTI medications. This allows the use of a triple NRTI combination in children who are receiving TB therapy and are unable to receive NNRTI medications.

Table 11: Recommended initial ART regimen in children on TB therapy

Age	Suggested initial regimen
<3 years or <10 kg	AZT + 3TC + NVP [1,2,3]
≥3 years and ≥10 kg	AZT + 3TC + EFV

[1]Ensure NVP dosed at upper limit for weight.
[2]Begin at twice-daily maintenance dosing since CYP 3A4 already induced by rifampicin; close monitoring for NVP-related hypersensitivity is advised.
[3]Viral load should be checked at 6 months in all children starting NVP while on TB therapy to detect early failure

10.1.4 Considerations when TB develops on ART

- ART should continue in children already on a first-line ART regimen who are subsequently diagnosed with TB.
- Children >3 years of age and >10 kg in weight who are receiving NVP-based therapy should have NVP replaced with EFV to minimize the risk of subtherapeutic NVP levels and future virologic failure.
- Because of overlapping toxicities and drug-drug interactions, children <3 years or <10 kg who must remain on rifampicin and NVP should be followed up monthly to assess for signs of clinical hepatitis. ALT should be measured promptly if any evidence of hepatic injury arises.
- Children receiving lopinavir/ritonavir-based regimens should be given additional ritonavir boosting to achieve therapeutic serum lopinavir levels while rifampicin

is administered.

- For children receiving lopinavir/ritonavir solution, the additional ritonavir volume should equal 0.75x the regular lopinavir/ritonavir volume. Older children receiving lopinavir/ritonavir tablets should also receive additional ritonavir while on rifampicin (See Table 12 and Annex F).
- Some experts recommend that when additional ritonavir capsules are not available, older children on LPV/r tablets should have their LPV/r dose doubled for the duration of TB therapy. Data on this approach are extremely limited. Children should be monitored for medication intolerance and clinical hepatitis while receiving additional ritonavir boosting.

Table 12: Regimen adjustment when TB develops during ART

Age/weight	Initial regimen	Suggested change
≥3 years and ≥10 kg	2 NRTIs + NVP	2 NRTIs + EFV
<3 years and <10 kg	2 NRTIs + NVP	No change[1]
Any	2 NRTIs + LPV/r	2 NRTIs + LPV/R (1:1 ratio)[2]

[1]Ensure NVP dose is at the upper limit of 200 mg/m^2

[2]For dosing of additional ritonavir "super-boosting", see Annex F. Discontinue additional ritonavir two weeks after TB treatment is completed

10.1.5 TB-related Immune Reconstitution Inflammatory Syndrome (IRIS)

- IRIS has been observed in up to 1/3 of adult patients receiving anti-TB therapy and who have been initiated on ART within 8 weeks of TB diagnosis.
- This occurs as a result of a vigorous immune response to TB organisms in response to adequate ART.
- Two forms include:
  - "paradoxical" IRIS, in which there is a worsening of disease after initial improvement
  - "unmasking" IRIS in which unrecognized TB becomes evident shortly after the initiation of ART.
- 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 for several weeks.
- **Except in cases of severe, life-threatening decompensation, ART should be continued through the episode of IRIS.**
- TB treatment must continue, and correct dosing of TB medications should be ensured.

- For severe paradoxical reactions, prednisolone (1-2 mg/kg for 1-2 weeks, then gradually decreasing doses) may help, and some patients need to be hospitalized.
- IRIS is a diagnosis of exclusion, and it is important to rule out other causes of illness before deciding a child's illness is IRIS. This topic is discussed in further detail in the *National Guidelines for the Prevention and Treatment of Opportunistic Infections among HIV-exposed and HIV-infected Children.*

10.2 ART in 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.

- Because the selection of an appropriate ART regimen may depend upon a child's hepatitis B status, and because the incidence of medication-related liver toxicity is increased in children with chronic viral hepatitis, testing for hepatitis B surface antigen (HBsAg) and hepatitis C antibodies is recommended prior to initiation of ART.
- Formal diagnosis of chronic hepatitis B requires two HBsAg tests >6 months apart. However, any child with an indication for ART should be started on a regimen appropriate for HBV/HIV co-infection if the first HBsAg test is positive.

<u>Regimen selection in children with chronic hepatitis B</u>

- Tenofovir, 3TC, and FTC all have activity against HBV.
- In patients with HIV, the use of **two drugs with anti-HBV activity** is preferable when treating a child with chronic hepatitis B.
- Some experts recommend excluding 3TC from the ART regimens of children too young to receive tenofovir. This is to prevent the emergence of HBV resistance. 3TC when used alone for the treatment of hepatitis B is unlikely to result in HBV viral suppression. However, alternative HIV regimens suffer from additional toxicity and the lack of FDC formulations.
- At the present time, in children with chronic HBV who are too young to receive tenofovir, the recommended 1st line regimen is the same as for children without chronic hepatitis B.
- In children over 3 years of age with elevated baseline ALT, efavirenz is the preferred NNRTI. See Table 13.

Table 13: Recommended ART regimens in children with chronic hepatitis B

Age	Suggested initial regimen
<3 years or <10 kg	AZT + 3TC + NVP [1]
3 - 11 years and ≥10 kg	AZT + 3TC + (NVP or EFV)[1,2]

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

- **Children with chronic hepatitis B who are ≥ 12 years should receive tenofovir and either 3TC or FTC within their ART regimen to prevent long-term liver injury (Box 13).**
- These children may experience transient elevations of liver enzymes to ≤10N during treatment initiation which may be a sign of effective anti-HBV therapy. In general, medications should be continued through this period unless symptomatic hepatitis occurs.
- ALT should be measured monthly for several months, then 6 monthly (See Table 10).

Box 13: Preferred ART regimen in adolescents ≥12 years with chronic hepatitis B infection

Initial ART in adolescents ≥12 years of age with chronic hepatitis B infection
TDF + (3TC or FTC) + (EFV or NVP) [1]

[1]EFV preferred if baseline ALT is elevated ≥2N, and also allows once-daily dosing.

10.3 ART in 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. Studies from adults have shown that patients with HCV/HIV co- infection progress 3 times more rapidly to liver cirrhosis than those patients who have HCV alone.

- ARVs used for the treatment of HIV have no activity against hepatitis C.
- 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.**
- HCV co-infected children on ART should have liver enzymes monitored for drug toxicity monthly for the first 2 months, then every 6 months.

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 virologic 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.

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 may receive HIV medical care and treatment from pediatric AIDS care sites or from adult AIDS care sites. **Attempts should be made to avoid transition from pediatric to adult treatment sites during middle-adolescence, when a strong relationship between patient and provider is key to ensuring adequate adherence during this challenging time in children's lives.**

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ANNEXES

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

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

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

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

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

Annex A-2: Cotrimoxazole dosing for exposed-infant prophylaxis

Cotrimoxazole – 5 mg/kg trimethoprim component once daily	
<5 kg:	¼ tablet or 2.5 ml syrup
5-9kg:	½ tablet or 5 ml syrup
10-14kg:	1 tablet or 10 ml syrup
15-24kg:	1½ tablet or 15 ml syrup
>25kg:	2 tablets or 20 ml syrup

Annex B-1: WHO Clinical Staging

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

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

- **Clinical Stage 3:**
  - Unexplained 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:**
  - Unexplained severe wasting stunting or severe malnutrition not responding to
  - standard therapy
  - *Pneumocystis jiroveci* pneumonia
  - Recurrent severe bacterial infections (>2 episodes in 12 months, infections include empyema, pyomyositis bone or joint infection, meningitis but excluding pneumonia)
  - Chronic herpes simplex infection (orolabial or cutaneous of more than one month's duration or visceral at any site)
  - Esophageal candidiasis (or candidiasis of trachea, bronchi or lungs)

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

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

Annex B-2: HIV Staging in Children using Clinical and Immunologic 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: Immunologic Staging of HIV-Infected Infants and Children

C-1- Immunologic criteria:

Using CD4 count

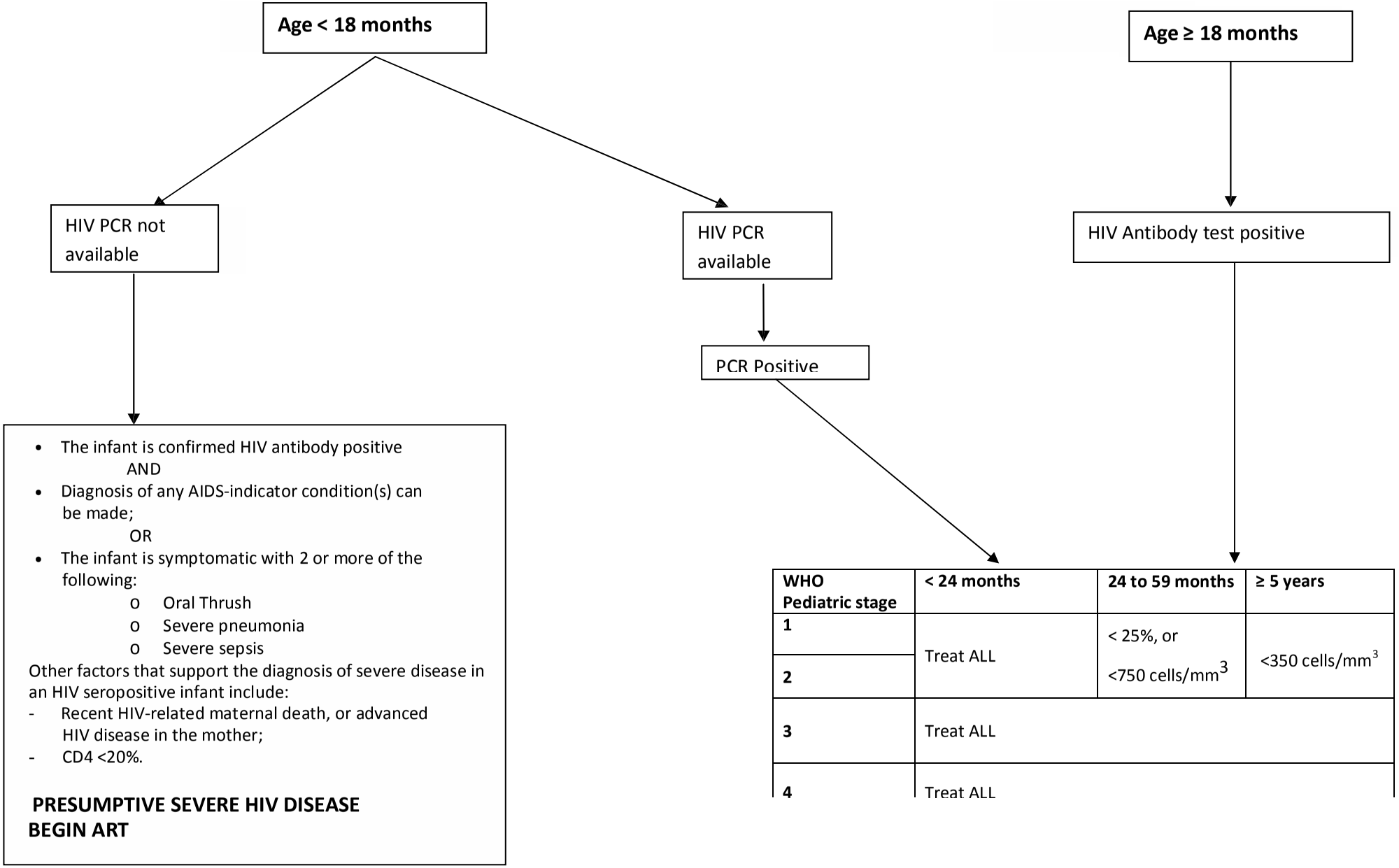
WHO Classification of HIV associated immunodeficiency using CD4 count				
Classification HIV-associated immunodeficiency	**Aged-related CD4 values**			
	≤ 11 months (%)	12-35 months (%)	36-59 months (%)	≥ 5 years (cells/mm3)
Not significant	> 35	>30	> 25	>500
Mild	30-35	25-30	20- 25	350-499
Advanced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

C-2- Immunologic 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: Algorithm for Initiation of Antiretroviral Therapy



Annex E: Formulations and Dosages of Anti-retroviral medications

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)	-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
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 crushed and 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 AZT:*** **(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)	-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 **<u>Notes:</u>** For children with suspected nervous system involvement, 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 onto small amount of food and immediately ingested. Tablets: Can be cut in half or may be crashed and combined with a small amount of food or water and immediately ingested.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)			
Efavirenz **(EFV)**	-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 or <10 kg.	-Storage at 15-30^{o}C -Capsules may be opened and added to liquid or food, but EFV 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**: BW <2.5 kg- 1 ml daily BW >2.5 kg- 1.5 ml daily -Dosing for extended breastfeeding prophylaxis *when mother not on ART*: Age 6 wks to 6 months: 2 ml daily Age 6 – 9 months: 3 ml daily Age 9 months to end of breastfeeding: 4 ml daily	-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 -Pediatric Tablet: 100mg lopinavir + 25mg ritonavir	Neonatal dose: -14 days to 6 months: 300mg/m^2 LPV/75m^2 ritonavir twice daily OR -16mg/kg lopinavir/4mg/kg ritonavir twice daily ->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/tables MUST NOT be opened or crushed!
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.

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

Fixed-dose combinations (FDCs):

Zidovudine (AZT) + Lamivudine (3TC)

- Tablet: AZT (60mg) + 3TC (30mg)
- 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)

Abacavir (ABC) + Lamivudine (3TC)

- Tablet : ABC (60mg) + 3TC (30mg)
- Tablet : ABC (600mg) + 3TC (300mg)

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

- Tablet : AZT (60mg) + 3TC (30mg) + ABC (60mg)
- Tablet: AZT (300mg) + 3TC (150mg) + ABC (300mg)
- Oral solution: not available

Zidovudine (AZT) + Lamivudine (3TC) + Nevirapine (NVP)

- Tablet : AZT (60mg) + 3TC (30mg) + NVP (50mg)
- Tablet : AZT (300mg) + 3TC (150mg) + NVP (200mg)

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 of Anti-retroviral Medications

	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 Lopinavir/ritonavir and additional Ritonavir boosting for TB therapy

	Lopinavir/ritonavir (LPV/r)								Ritonavir boosting (RTV)	
Target dosing	LPV: <15kg: 16-12mg/kg; >15kg:10mg/kg*								ONLY for boosting LPV/r when on Rifampicin	
Formulations	Sol: 80mg LPV + 20mg RTV/ml		Cap133.3/33.3mg LPV/r		Tab. 200/50mg LPV/r		Tab. 100/25mg LPV/r		Sol. 80 mg/ml	
Weight Range (kg)	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**
3-3.9	1ml	1ml							1ml	1ml
4-6.9	1.5ml	1.5ml	1 cap	1 cap					1.2 ml	1.2 ml
7-9.9	1.5ml	1.5ml	1 cap	1 cap					1.2 ml	1.2 ml
10-11.9	2ml	2ml	1 cap	1 cap			2 Tabs	1 Tab	1.5 ml	1.5 ml
12-14.9	2ml	2ml	1 cap	1 cap	1 Tab	1 Tab	2 Tabs	1 Tab	1.5 ml	1.5 ml
15-16.9	2.5ml	2.5ml	2 cap	2 cap	1 Tab	1 Tab	2 Tabs	2 Tabs	2 ml	2 ml
17-19.9	2.5ml	2.5ml	2 cap	2 cap	1 Tab	1 Tab	2 Tabs	2 Tabs	2 ml	2 ml
20-24.9	3ml	3ml	2 cap	2 cap	1 Tab	1 Tab	3 Tabs	2 Tabs	2.5 ml	2.5 ml
25-29.9	3.5ml	3.5ml	2 cap	2 cap	2 Tab	1 Tab			3 ml	3 ml
30-34.9	4ml	4ml	3 cap	3 cap	2 Tab	2 Tab			3 ml	3 ml
35-40	5ml	5ml	3 cap	3 cap	2 Tab	2 Tab			4 ml	4 ml

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			

Formulations	AZT 60mg + 3TC 30mg		AZT 60mg + 3TC 30mg + NVP 50mg		ABC 60mg + 3TC 30mg	
Weight range (kg)	AM	PM	AM	PM	AM	PM
3-3.9	1 Tab	1 Tab	1 Tab	1 Tab	1 Tab	1 Tab
4-4.9	1 Tab	1 Tab	1 Tab	1 Tab	1 Tab	1 Tab
5-5.9	1 Tab	1 Tab	1 Tab	1 Tab	1 Tab	1 Tab
6-7.9	1.5 Tabs	1.5 Tabs	1.5 Tabs	1.5 Tabs	1.5 Tabs	1.5 Tabs
8-9.9	1.5 Tabs	1.5 Tabs	1.5 Tabs	1.5 Tabs	1.5 Tabs	1.5 Tabs
10-10.9	2 Tabs	2 Tabs	2 Tabs	2 Tabs	2 Tabs	2 Tabs
11-11.9	2 Tabs	2 Tabs	2 Tabs	2 Tabs	2 Tabs	2 Tabs
12-13.9	2 Tabs	2 Tabs	2 Tabs	2 Tabs	2 Tabs	2 Tabs
14-16.9	2.5 Tabs	2.5 Tabs	2.5 Tabs	2.5 Tabs	2.5 Tabs	2.5 Tabs
17-19.9	2.5 Tabs	2.5 Tabs	2.5 Tabs	2.5 Tabs	2.5 Tabs	2.5 Tabs
20-24.9	3 tabs	3 Tabs	3 Tabs	3 Tabs	3 Tabs	3 Tabs

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

Formulations	AZT300mg + 3TC150mg		AZT 300mg + 3TC 150mg + NVP 200mg		d4T30mg+3TC150mg		d4T30mg + 3TC150mg + NVP200mg		AZT300mg + 3TC150mg + ABC300mg	
Weight range (kg)	AM	PM	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 Tab	1 Tab	1 Tab	1 Tab	1 Tab	½ Tab	½ Tab + ½ 3TC + ½ NVP	1 Tab	½ Tab
30-34.9	1 Tab	1 Tab	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	1 Tab	1 Tab

Formulations	AZT300mg + 3TC150mg		AZT 300mg + 3TC 150mg + NVP 200mg		d4T30mg+3TC150mg		d4T30mg + 3TC150mg + NVP200mg		AZT300mg + 3TC150mg + ABC300mg	
Weight range (kg)	AM	PM	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 Tab	1 Tab	1 Tab	1 Tab	1 Tab	½ Tab	½ Tab + ½ 3TC + ½ NVP	1 Tab	½ Tab
30-34.9	1 Tab	1 Tab	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	1 Tab	1 Tab

Formulations	**AZT300mg + 3TC150mg**		**AZT 300mg + 3TC 150mg + NVP 200mg**		**d4T30mg+3TC150mg**		**d4T30mg + 3TC150mg + NVP200mg**		**AZT300mg + 3TC150mg + ABC300mg**	
Weight range (kg)	**AM**	**PM**	**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 Tab	1 Tab	1 Tab	1 Tab	1 Tab	½ Tab	½ Tab + ½ 3TC + ½ NVP	1 Tab	½ Tab
30-34.9	1 Tab	1 Tab	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	1 Tab	1 Tab

Age/weight dosing of NVP Liquid for PMTCT

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

Annex G: ARV Toxicity Severity Grading

	Grade 1	Grade 2	Grade 3	Grade 4
Parameter	**Mild**	**Moderate**	**Severe**	**Severe and potentially life-threatening**
General guidance on estimating severity grade				
Characterization of symptoms and general guidance on management	Symptoms causing no or minimal interference with usual social and functional activities:[a] No therapy needed, monitor	Symptoms causing greater than minimal interference with usual social and functional activities: may require minimal intervention and monitoring	Symptoms causing inability to perform usual social and functional activities: 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*

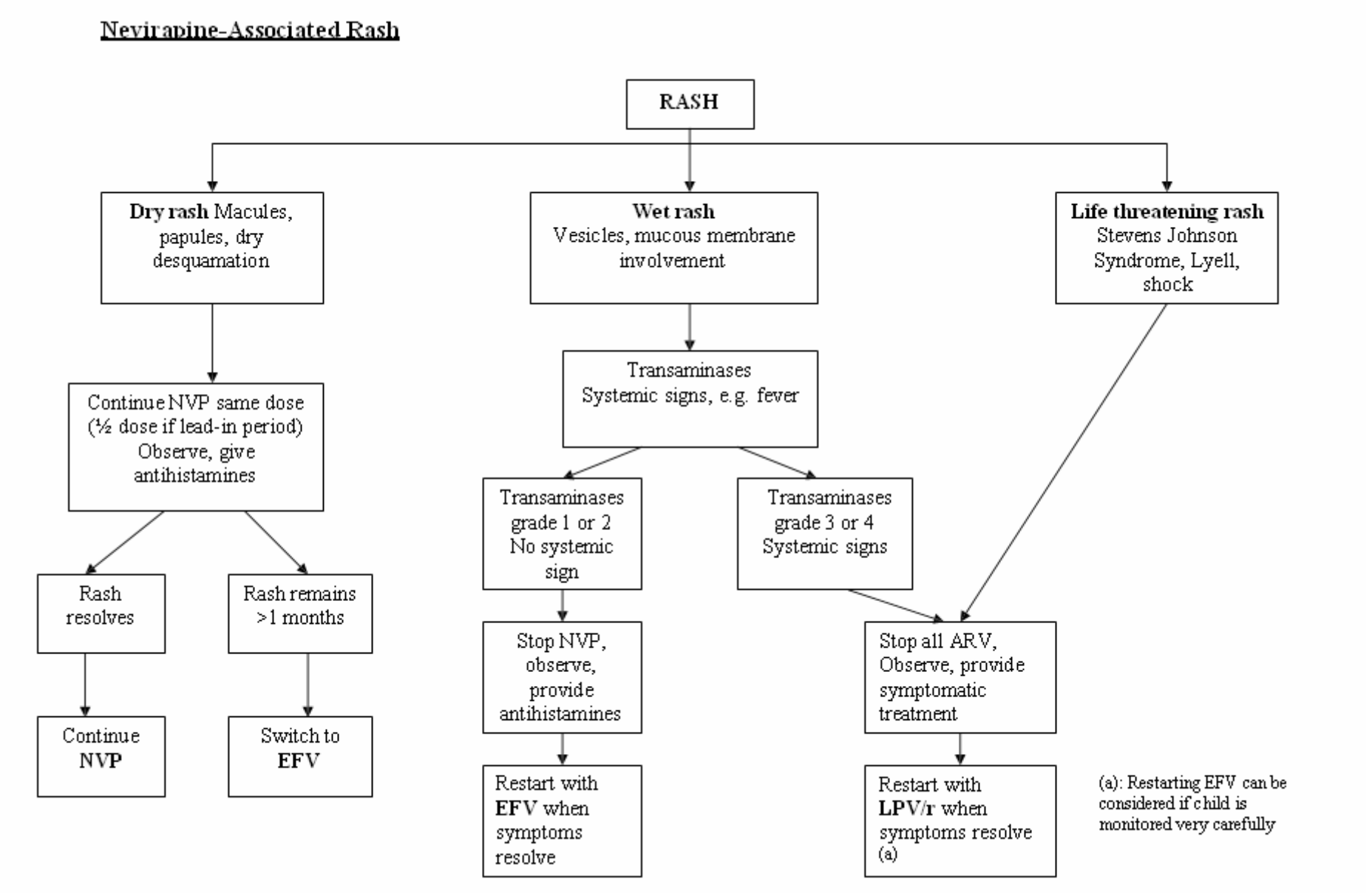
Source: Adapted from Division of AIDS, National Institute of Allergy and Infectious Diseases, Table for grading the severity of adult and pediatric adverse events, Bethesda, Maryland, USA; December 2004.

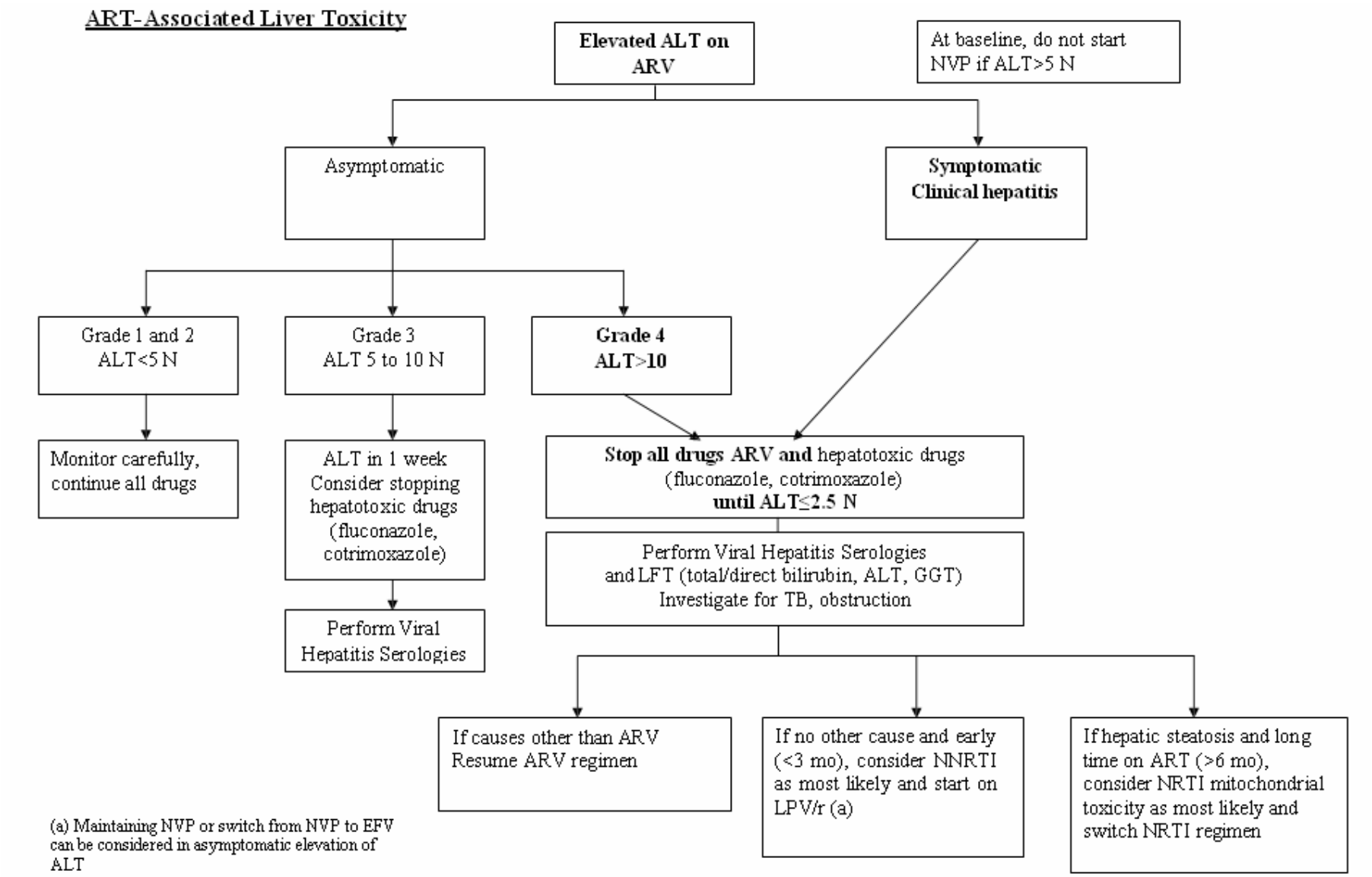
a Usual social and functional activities in young children include those that are appropriate to their age and culture (e.g. social interactions, play activities, learning tasks).

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

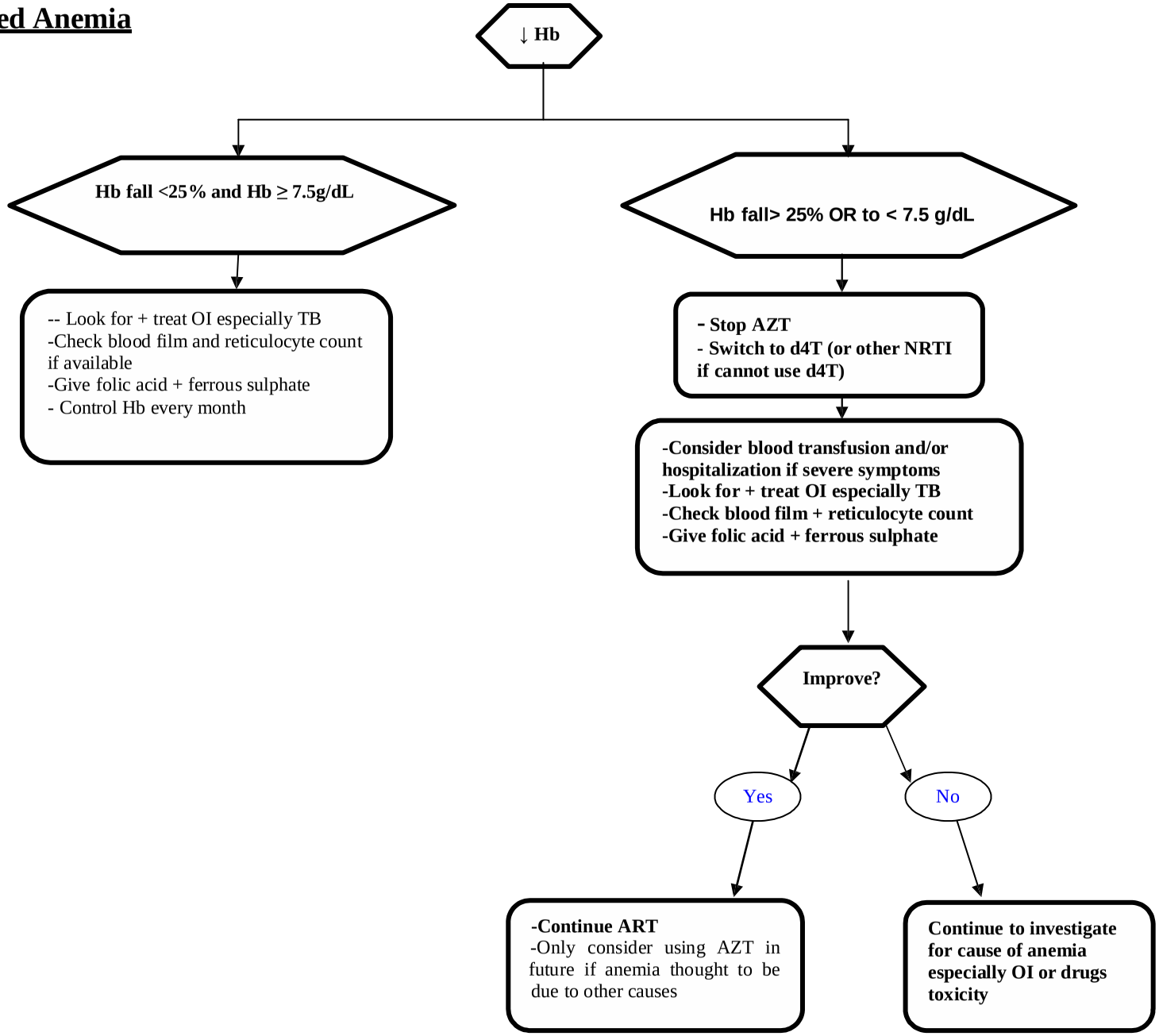
c Values are provided for children in general except where age groups are specifically noted.

Annex H: Flow Diagrams for Clinical Management of ARV Toxicities

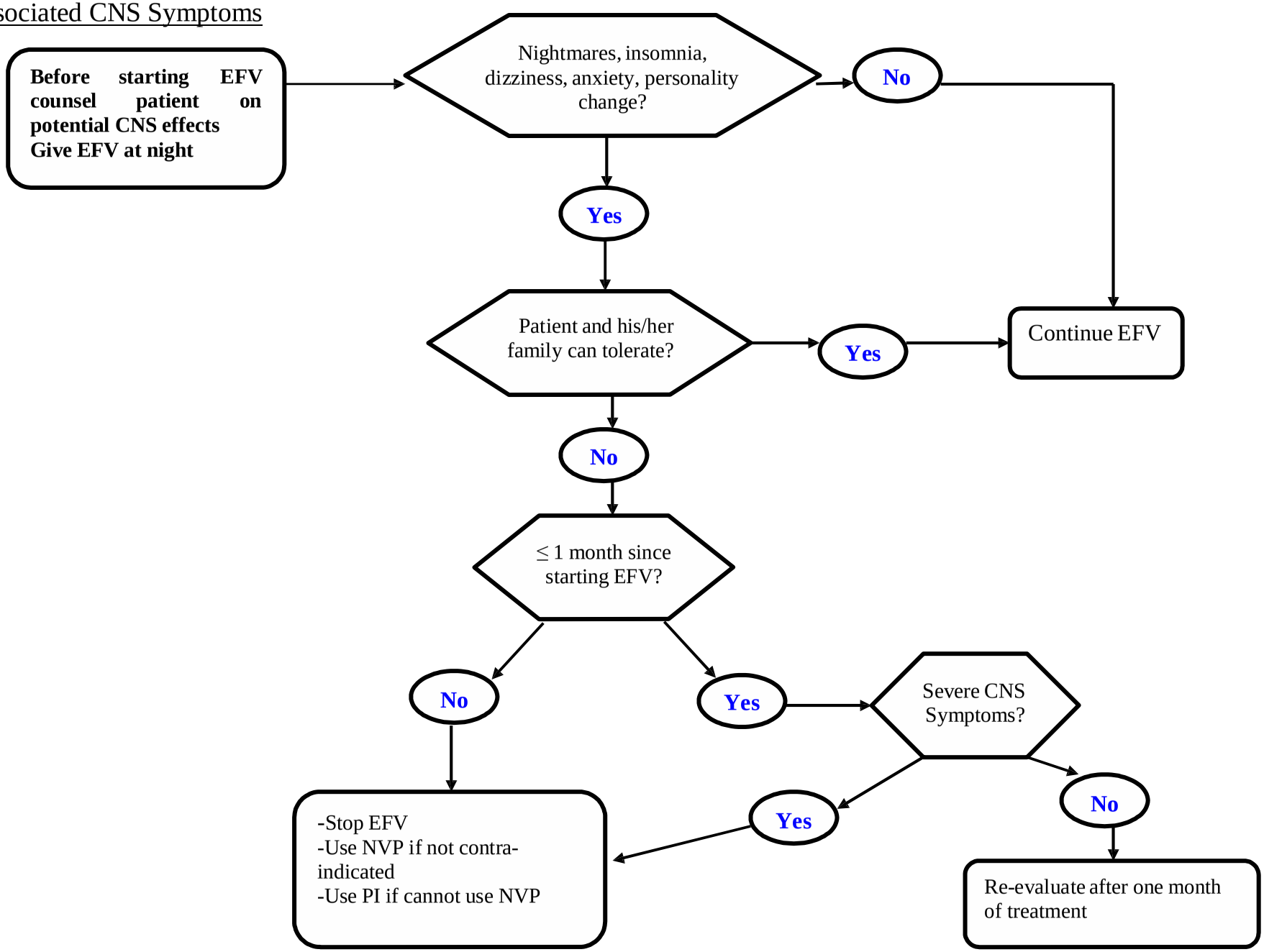


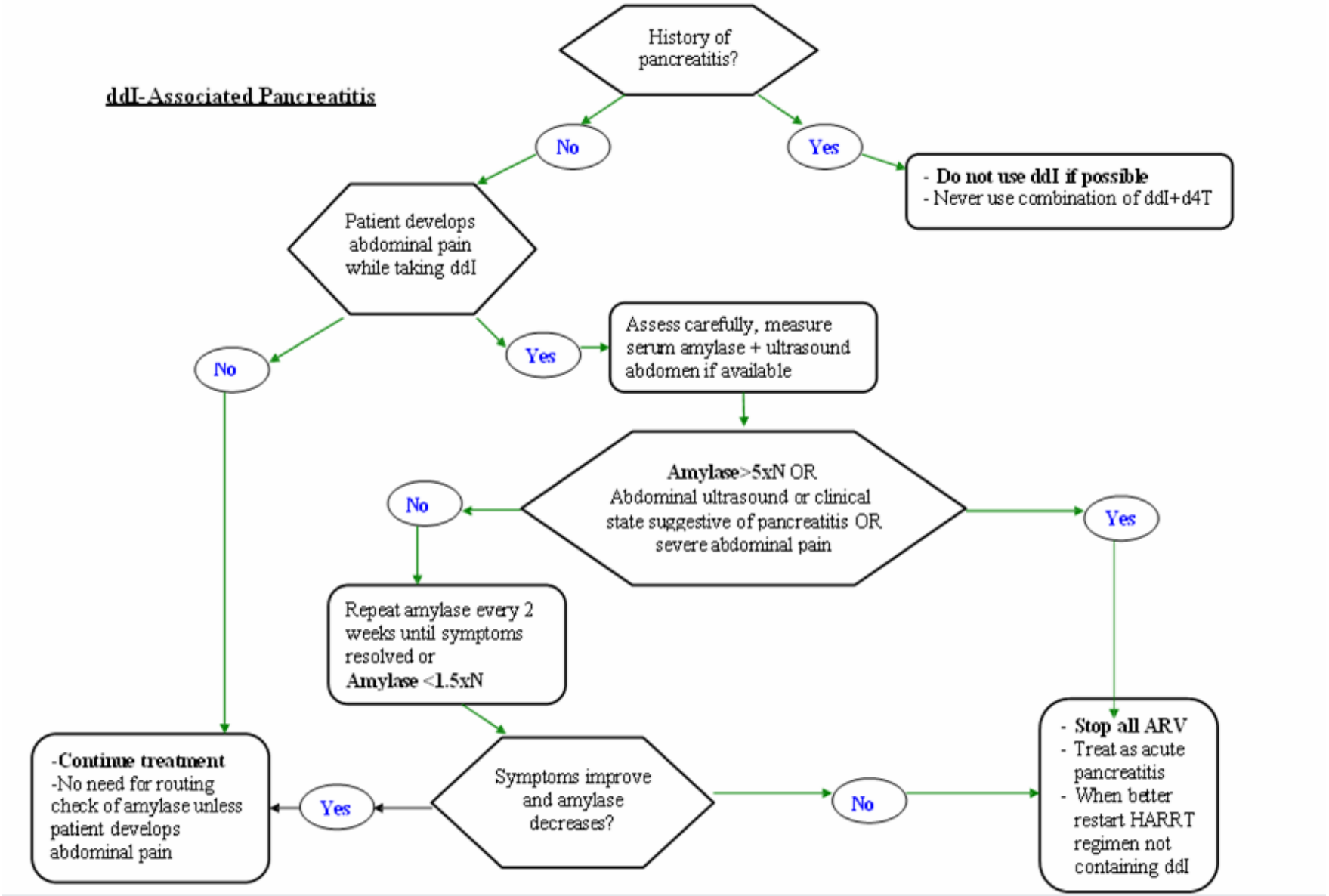

ART-Associated Liver Toxicity
Elevated ALT on ARV
At baseline, do not start NVP if ALT>5 N
Asymptomatic
Symptomatic Clinical hepatitis
Grade 1 and 2 ALT<5 N
Grade 3 ALT 5 to 10 N
Grade 4 ALT>10
Monitor carefully, continue all drugs
ALT in 1 week Consider stopping hepatotoxic drugs (fluconazole, cotrimoxazole)
Stop all drugs ARV and hepatotoxic drugs (fluconazole, cotrimoxazole) until ALT≤2.5 N
Perform Viral Hepatitis Serologies
Perform Viral Hepatitis Serologies and LFT (total/direct bilirubin, ALT, GGT) Investigate for TB, obstruction
If causes other than ARV Resume ARV regimen
If no other cause and early (<3 mo), consider NNRTI as most likely and start on LPV/r (a)
If hepatic steatosis and long time on ART (>6 mo), consider NRTI mitochondrial toxicity as most likely and switch NRTI regimen
(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
History of pancreatitis?
No
Yes
- Do not use ddI if possible
- Never use combination of ddI+d4T
Patient develops abdominal pain while taking ddI
No
Yes
Assess carefully, measure serum amylase + ultrasound abdomen if available
Amylase>5xN OR Abdominal ultrasound or clinical state suggestive of pancreatitis OR severe abdominal pain
No
Yes
Repeat amylase every 2 weeks until symptoms resolved or Amylase <1.5xN
Symptoms improve and amylase decreases?
Yes
No
-Continue treatment
-No need for routing check of amylase unless patient develops abdominal pain
- Stop all ARV
- Treat as acute pancreatitis
- When better restart HARRT regimen not containing ddI

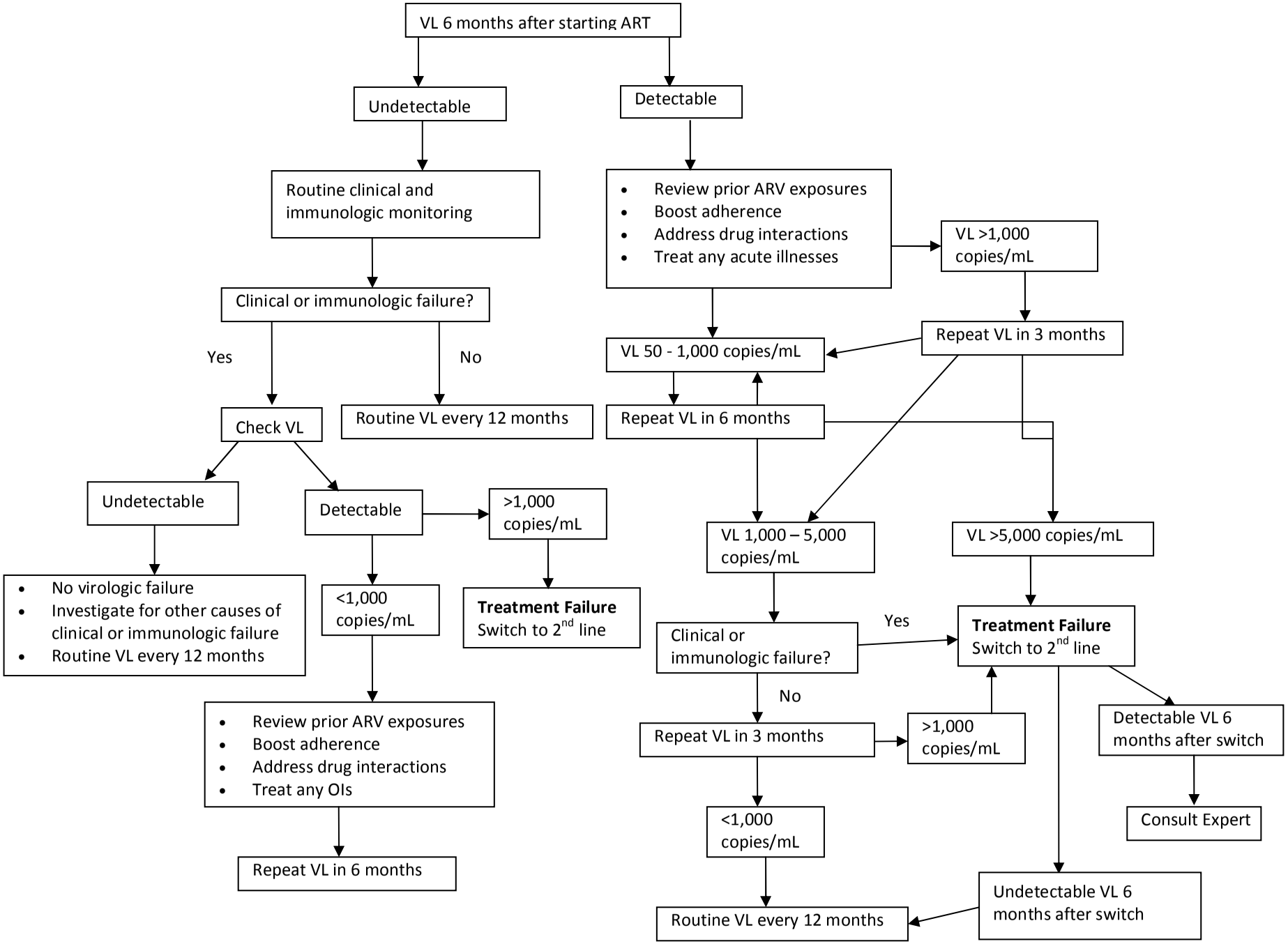
Annex I: Important ARV Drug Interactions

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

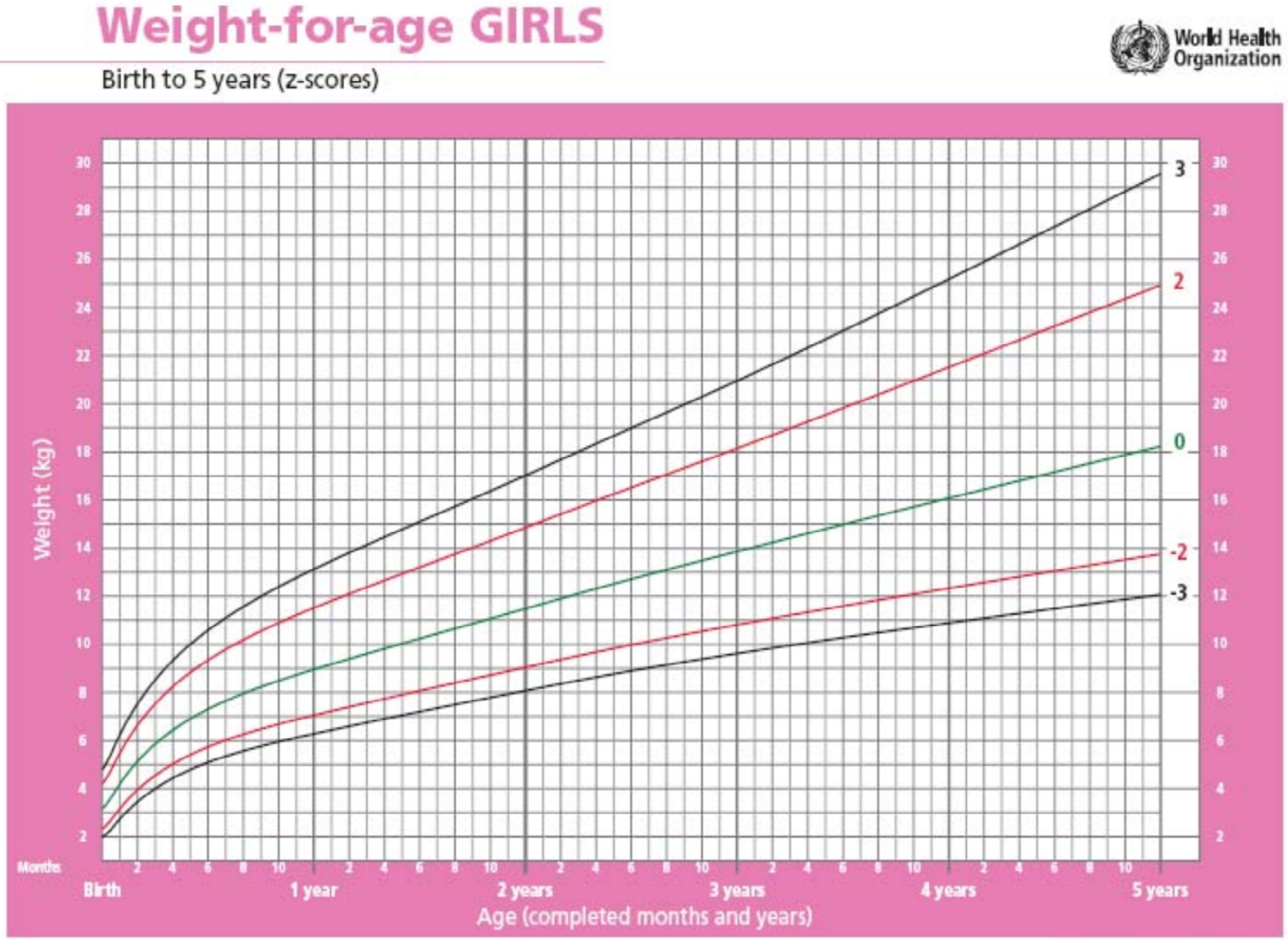
Interacting drug	**NVP**	**EFV**	**NFV**	**IDV/r**	**LPV/r**	**SQV/r**
Ketoconazole	X	+/-	OK			
Fluconazole	May cause ↑ NVP Level				OK	
Rifampicin	Use with caution	May increase EFV to 800mg/d	X	X	X	Give both drugs at full dose
Rifabutin	OK	RBT 450-600 mg/d	RBT 150mg/d NFV 1000mg tds			RBT 250mg 2-3/week
Clarithromycin	May decrease clarithro levels	X	?		Dose reduction of clarithro needed if renal failure	
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
SSRI Antidepressants	+/-	+/-			May cause ↑ SSRI level. Start at lowest dose	
Anti-epileptic drugs[3]	X	X		X	X	X
Benzodiazepines[4]	X	X		X	X	X
Other drugs that should not be co-administered	Garlic supplements	Astemizole Terfenadine Cisapride Midazolam Triazolam Ergotamine Dihydro-ergotamine Garlic	Astemizole Terfenadine Cisapride Midazolam Triazolam Ergotamine Dihydro-ergotamine Garlic	Astemizole Terfenadine Cisapride Midazolam Ergotamine Dihydro-ergotamine Garlic Flecanide Pimozide	Astemizole Terfenadine Cisapride Midazolam Ergotamine Dihydro-ergotamine Garlic Flecanide Pimozide	Astemizole Terfenadine Cisapride Midazolam Ergotamine Dihydro-ergotamine Garlic Flecanide Pimozide
Miscellaneous	Can lower steroid levels	Monitor warfarin if co-administered				

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

Annex J: Viral load monitoring in HIV-infected children



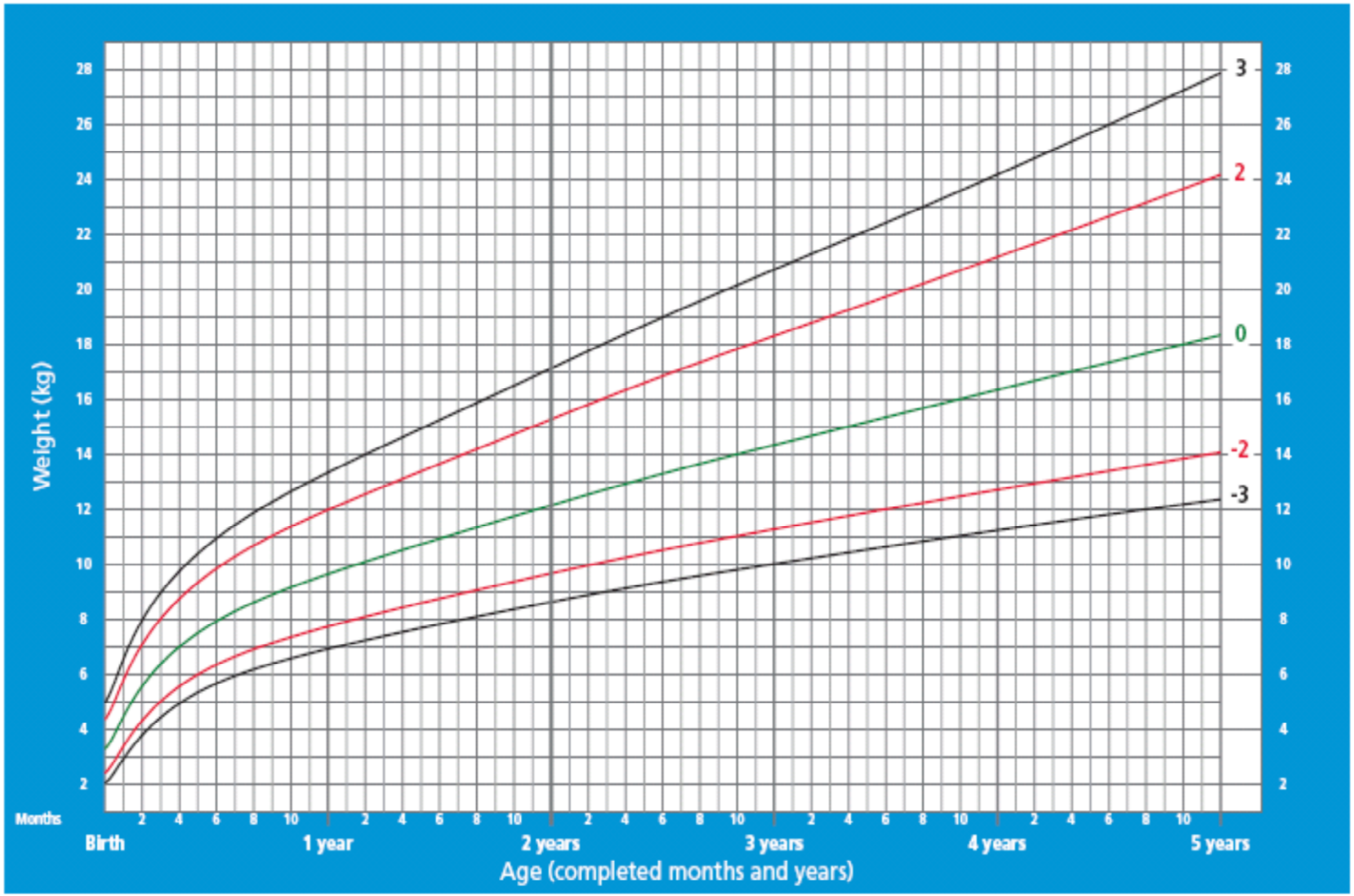
Annex K: Pediatric Weight-for-Age Growth Charts



Weight-for-age BOYS

World Health Organization

Birth to 5 years (z-scores)

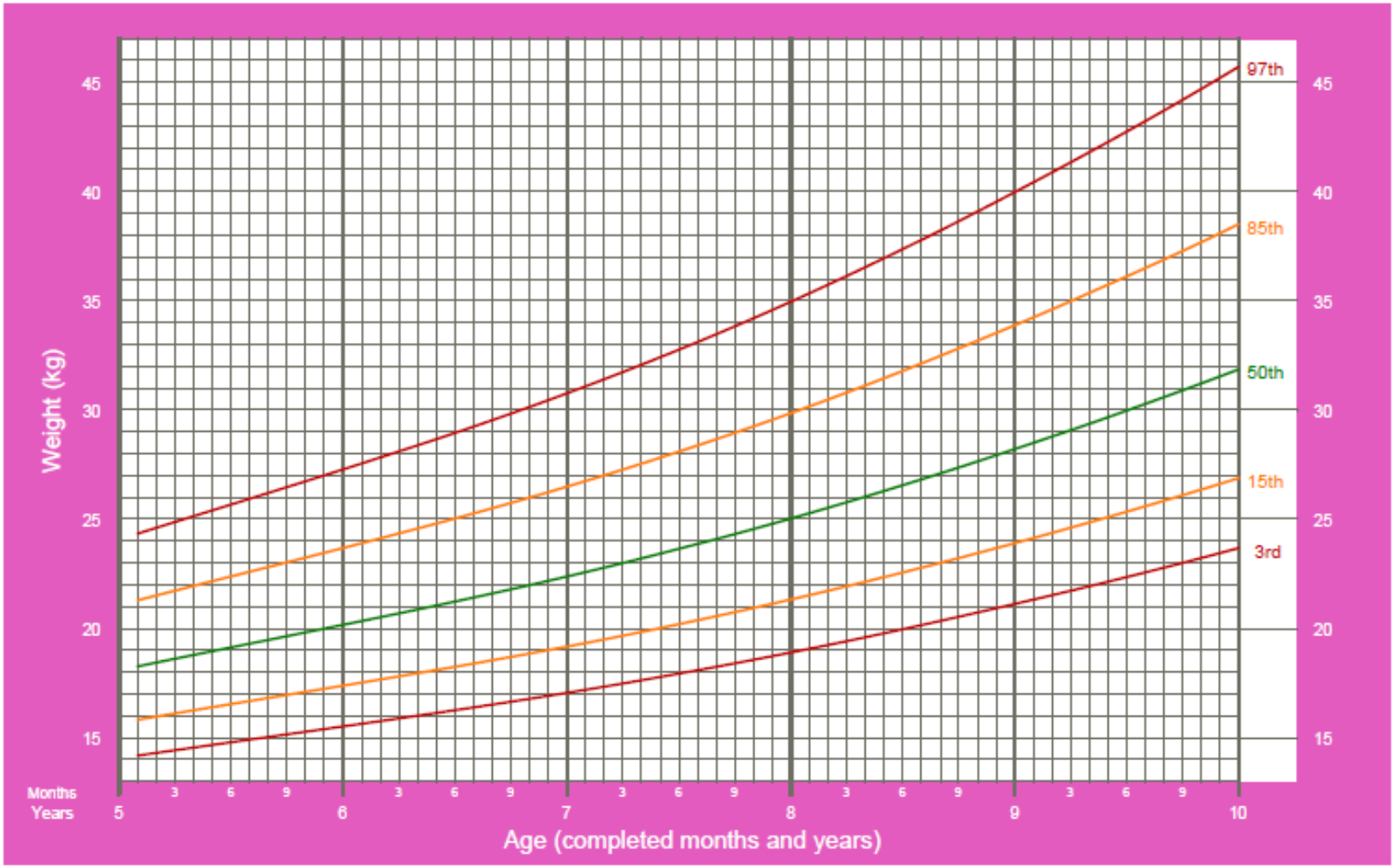


WHO Child Growth Standards

Weight-for-age GIRLS

5 to 10 years (percentiles)

World Health Organization

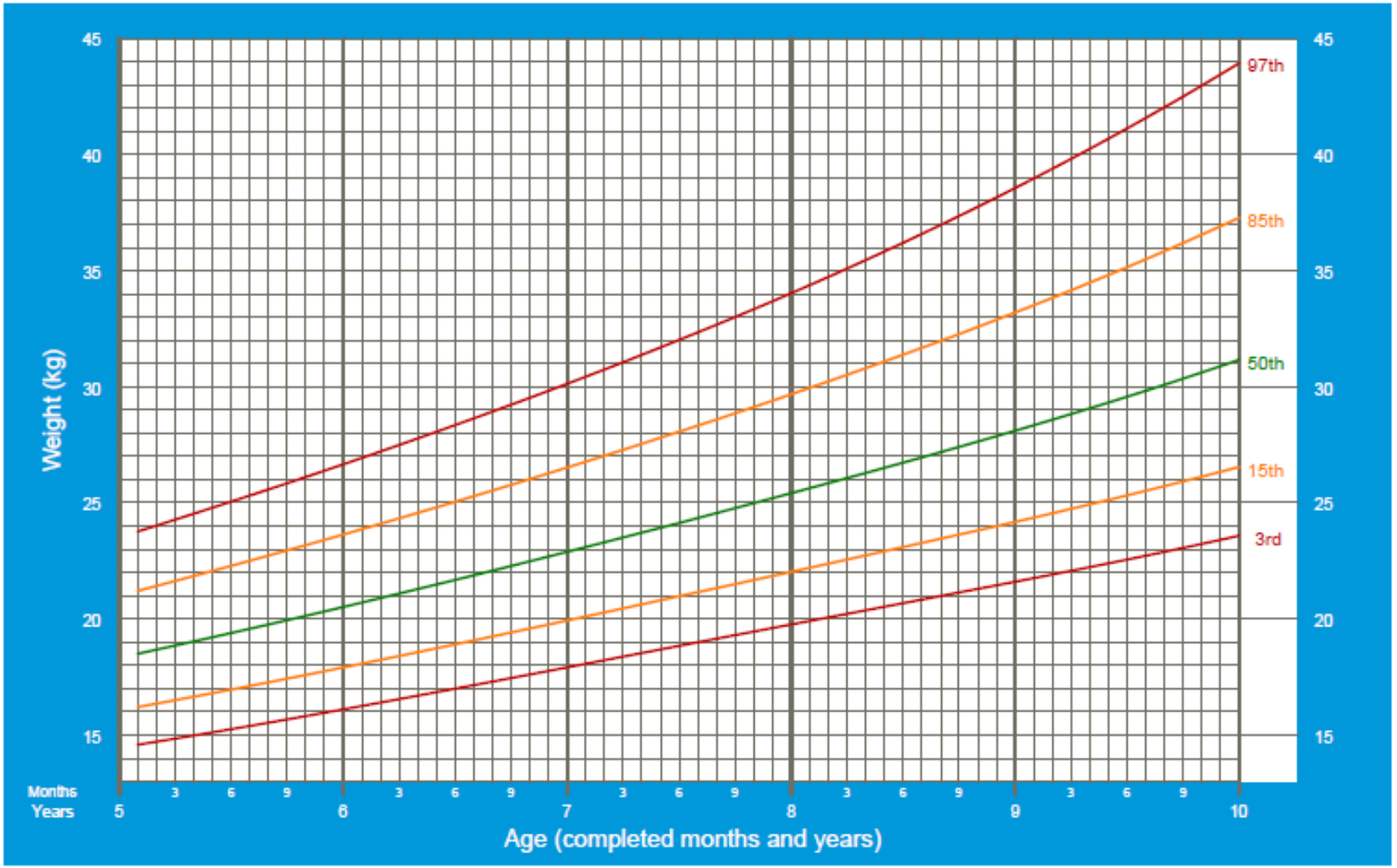


2007 WHO Reference

Weight-for-age BOYS

5 to 10 years (percentiles)

World Health Organization



2007 WHO Reference

ANNEX L: 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