Guidelines for HIV Care and Treatment in Infants and Children

November 2006

Indian Academy of Paediatrics

National AIDS Control Organisation

with support from
Clinton Foundation. UNICEF. WHO

Assessment and management at the first visit of a child with known HIV exposure or a sick child with unknown HIV exposure but suspected to have HIV infection

Child with known HIV exposure[a]

- Assess likelihood of acquiring HIV infection by checking for:
  - maternal HIV disease status;[b]
  - maternal and infants exposure to ARVs;[c,d]
  - mode of delivery and breastfeeding.[e]

- Perform history taking and physical examination. Evaluate if the child has signs and symptoms of HIV infection or opportunistic infections.
- Provide appropriate investigation/treatment for OI. *(see p59)*

- Identify needs for ART and cotrimoxazole to prevent PCP *(see p7)*

- Perform HIV diagnostic testing
- Methods used depend on the child's age *(see p9)*

Sick child with unknown HIV exposure but suspected to HIV infection

- Identify if there are HIV risk factors:
  - maternal HIV disease status;[b]
  - blood transfusion, injecting drug use, or sexual exposure.

- Perform history taking and physical examination and identify if the child has signs and symptoms of HIV infection or opportunistic infections.
- Provide appropriate investigation/treatment for OI. *(see p59)*

- Identified risk factor and/or signs/symptoms consistent with HIV infection or HIV-related opportunistic infections.
- Offer HIV diagnostic testing and counselling.
- Methods to use depend on the child's age *(see p9)*
- In cases where maternal HIV status cannot be confirmed and virologic testing is not available to diagnose HIV infection in a child younger than 18 months, HIV antibody testing should be performed.

PCP = Pneumocystis jiroveci pneumonia

Notes:

[a] All HIV-exposed children should be evaluated by a paediatrician

[b] Advanced clinical HIV disease or low CD4 count in the mother are risk factors for HIV transmission from mother to infant during pregnancy, delivery and breastfeeding.

[c] Successful chronic treatment with ART in mothers reduce the risk of HIV transmission.

[d] Use of antiretroviral drugs for the prevention of mother-to-child transmission (PMTCT) using AZT monotherapy alone, AZT monotherapy + NVP single dose, NVP single dose alone are associated with transmission rates of approximately 5–10%, 3–5%, 10–20% respectively in non-breastfeeding mothers.[i]

[e] HIV transmission can occur via breastfeeding. A child remains at risk for HIV acquisition as long as he/she is breastfed.

[i] Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants in resource-limited settings: Towards universal access. Recommendations for a public health approach, 2006.

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Abbreviations and Acronyms

3TC	lamivudine
ABC	abacavir
AFB	acid-fast bacillus
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransaminase
ARV	antiretroviral (drug)
ART	antiretroviral therapy
AST	aspartate aminotransferase
AZT	azidothymidine (also named zidovudine)
BAL	bronchoalveolar lavage
CD4	CD4+ T-lymphocyte
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
d4T	stavudine
ddI	didanosine
DNA	deoxyribonucleic acid
EFV	efavirenz
FBC	full blood cell count
FDC	fixed-dose combination
FTC	emtricitabine
Hb	haemoglobin
HCW	health-care worker
HIV	human immunodeficiency virus
HSV	herpes simplex virus
IDV	indinavir
IMCI	Integrated Management of Childhood Illnesses
INH	isoniazid
IPT	isoniazid preventive therapy
IRIS	immune reconstitution inflammatory syndrome
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LIP	lymphocytic interstitial pneumonia
LPV	lopinavir
LPV/r	lopinavir/ritonavir
MAC	Mycobacterium avium complex
MTCT	mother-to-child transmission (of HIV)
NFV	nelfinavir
NRTI	nucleoside reverse transcriptase inhibitor
NNRTI	non-nucleoside reverse transcriptase inhibitor
NVP	nevirapine
OHP	oral hairy leukoplakia
OI	opportunistic infection
PCP	Pneumocystis jiroveci pneumonia (previously Pneumocystis carinii pneumonia)
PCR	polymerase chain reaction
PI	protease inhibitor
PGL	persistent generalized lymphadenopathy
PML	progressive multifocal leukoencephalopathy
PMTCT	prevention of mother-to-child transmission (of HIV)
RTV	ritonavir
SD	standard deviation
SQV	saquinavir
STI	sexually transmitted infection
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
TLC	total lymphocyte count
TMP–SMX	trimethoprim–sulfamethoxazole
TST	tuberculin skin test
ULN	upper limit of normal
UNICEF	United Nations Children's Fund
VZV	Varicella zoster virus
WBC	white blood cell
WHO	World Health Organization
ZDV	zidovudine

Contents

Acknowledgements

Abbreviations and Acronyms

Introduction

Objectives of the Guidelines

Section A : Management of Infants and Children with HIV Infection and Paediatric Antiretroviral Therapy

A1. Management of HIV Exposed Children

1.1 HIV exposure in infants and young children 3

1.2 Care of exposed child immediately at birth 3

1.3 PPTCT: Prophylactic ARV for infants 4

1.4 Infant feeding choices 4

1.5 Care of the HIV exposed child 4

1.6 Counselling and psycho-social support 5

A2. Cotrimoxazole prophylaxis

2.1 Who should receive cotrimoxazole prophylaxis (CTX) 7

2.2 How long CTX should be given 7

A3. Diagnosis of HIV Infection in Children

3.1 Excluding HIV infection in infants and children 9

3.2 Diagnosis of HIV infection in children < 18 months 9

3.3 Diagnosis of HIV infection in children > 18 months 10

3.4 Presumptive diagnosis where there is no testing available 12

A4. Monitoring HIV-infected Children not on ART (Pre-ART Care) 13

A5. Antiretroviral Treatment in Infants and Children

5.1 Pre-enrollment details 15

5.2 Clinical staging in children using clinical and immunological criteria 16

5.3 When to start ART 18

5.4 What to start 18

5.5 How to select d4T-based vs AZT-based combinations 19

5.6 First-line regimens for children with TB co-infection 19

5.7 Hepatitis and HIV 19

5.8 ART in infants with prior ARV exposure 21

5.9 How much paediatric ARVs to give 21

A6. Monitoring and Follow-up after ART Initiation

6.1 Monitoring schedule after ART initiation 23

6.2 Evaluating response to ART on follow up visit 24

A7. Managing ARV Toxicity

7.1 Guiding principles in management of ARV toxicity in children 25

7.2 When do ARV side effects and toxicities occur 26

7.3 Severe toxicities in infants and children associated with specific ARV drugs and potential substitutions 27

A8. Differentiating IRIS and ARV Toxicity

8.1 Immune reconstitution inflammatory syndrome (IRIS) 29

8.2 Differential diagnosis of common clinical events developing during first 6 months of ART....30

A9. Failure of Treatment

9.1 Treatment failure definition....31

9.2 Protocol for assessment of treatment failure in children on ART 32

9.3 Plan before switching to second line regimen....34

A10. Adherence Counselling and Monitoring

10.1 Preparing to start ART 37

10.2 Ensuring long term adherence and good response to ART 38

10.3 Disclosure for children....40

A11 Nutrition in HIV-infected Infants and Children

11.1 Nutritional assessment and support 43

11.2 Severe malnutrition and ART initiation....44

A12. Adolescent Issues in Care and Treatment

12.1 Challenges with HIV-infected adolescents....45

12.2 Considerations in ART specific to adolescents 45

A13. Palliative Care in Children

13.1 What is palliative care: principles....47

13.2 Palliative care in children....47

13.3 Essential components in palliative care for children 48

13.4 Supporting family and child 49

13.5 Bereavement....49

Section B : Management of Opportunistic Infections in Infants and Children

B1. Management of OIs in HIV Children....53

B2. Opportunistic Infections – Bacterial, Fungal, Protozoal

2.1 Pneumocystis pneumonia (PCP) 59

2.2 Recurrent bacterial infections....62

2.3 Tuberculosis (TB)....63

2.4 Mycobacterium avium complex (MAC)....66

2.5 Toxoplasmosis 67

2.6 Diarrhoea....69

2.7 Candidiasis....71

2.8 Cryptococcal meningitis....73

B3. Opportunistic Infections – Viral

3.1 Cytomegalovirus....75

3.2 Herpes simples 76

3.3 Varicella infections 77

3.4 Herpes zoster....78

3.5 Penicilliosis 79

Section C : Annexes

Annex 1 : Diagnosis in Children > 18 months 83

Annex 2 : WHO Clinical Staging of HIV for Infants and Children with Confirmed HIV Infection 85

Annex 3 : Presumptive and Definitive Criteria for Recognizing HIV/AIDS-related Clinical Events in Infants and Children with Confirmed HIV Infection 87

Annex 4 : Pros and Cons of Various ARVs in Children 91

Annex 5 : Drugs that may have Interactions with ART 93

Annex 6 : Doses of the Common Antiretroviral Drugs for Children 97

Annex 7 : Serious Acute and Chronic Toxicities Due to ARV Drugs that may require Therapy Modification: Clinical Presentation, Laboratory Abnormalities, and Implications for ART Management 99

Annex 8 : Severity Grading of Selected Clinical and Laboratory Toxicities most commonly seen with Recommended Antiretroviral Drugs for Children 103

Annex 9 : Weight Bands in Kilograms with Dosing of Various Formulations 107

Annex 10 : Algorithms for Paediatric Pulmonary TB 109

Annex 11 : Developmental Milestones 111

Annex 12 : Tanner Staging (Sexual Maturity Rating) 113

Annex 13 : Growth Monitoring Chart 115

Annex 14 : Estimation of Body Surface Area 119

Annex 15 : Immunization Chart for Children Living with HIV 121

List of Tables

Table 1 : Estimated risk and timing of MTCT in the absence of interventions 3

Table 2 : Indications for CTX prophylaxis 7

Table 3 : How long cotrimoxazole should be given : discontinuing CTX 7

Table 4 : TMP/SMX (CTX) prophylaxis for PCP 8

Table 5 : Clinical criteria for presumptive diagnosis of severe HIV disease in infants and children less than 18 months of age requiring ART in situations where virological testing is not available 12

Table 6 : Monitoring and follow-up schedule for children on pre-ART care 14

Table 7 : Details of history and physical examination to be done 15

Table 8 : WHO classification of HIV-associated clinical disease 16

Table 9 : Formula for calculating CD4% when only CD4 absolute count is available 16

Table 10 : Revised classification of immune suppression in children 17

Table 11 : Clinical and immunological criteria for starting ART 17

Table 12 : Formulations of FDCs available for Pediatric HIV use in India 18

Table 13 : Recommendations for the timing of ART following initiation of TB treatment with rifampicin-containing regimen in HIV-infected infants and children 20

Table 14 : Toxicities in infants and children associated with specific ARV drugs and potential substitutions 27

Table 15 : Differential diagnosis of common clinical events developing during first 6 months of ART 30

Table 16 : Using the WHO Pediatric Clinical Staging System to guide decision-making regarding switching to second-line therapy for treatment failure 35

Table 17 : Decision-making regarding switching to second line therapy for treatment failure based on availability of CD4 measurementa 36

Table 18 : Recommended second-line regimens in infants and children in the event of treatment failure of first-line regimens 36

Table 19 : Summary of clinical diagnosis and management of common opportunistic infections in HIV-infected children 53
Table 20 : Summary of Guidelines for Primary OI prophylaxis in children 56
Table 21 : Summary of Guidelines for Secondary OI prophylaxis in children 57
Table 22 : Treatment of Pneumocystis jiroveci (PCP) infection 61
Table 23 : Drugs used for the treatment of tuberculosis 64
Table 24 : Recommended TB treatment regimens under RNTCP 64
Table 25 : Induction and continuation phase of anti-TB treatment 65
Table 26 : Treatment of Mycobacterium avium complex (MAC) 66
Table 27 : Indications for MAC prophylaxis 67
Table 28 : Drugs for MAC prophylaxis 67
Table 29 : Treatment of Toxoplasmosis 68
Table 30 : Prophylaxis for Toxoplasmosis 69
Table 31 : Treatment of chronic diarrhoea 70
Table 32 : Treatment of candida infection 72
Table 33 : Prophylaxis for candidiasis 73
Table 34 : Treatment of cryptococcal meningitis 74
Table 35 : Prophylaxis for cryptococcal meningitis 74
Table 36 : Treatment of cytomegalovirus (CMV) 76
Table 37 : Prophylaxis for CMV 76
Table 38 : Treatment of Herpes simplex 77
Table 39 : Treatment of chickenpox 78
Table 40 : Prophylaxis for chickenpox 78
Table 41 : Treatment of Herpes zoster 79

Introduction

Children of today are the youth of tomorrow. HIV affects this very precious generation and bear grave consequences to our future, our nation, the continent and the world at large. It will adversely impact the health statistics, economic growth and above all the morale of nations. Although children represented only 6% of all people infected with HIV/AIDS as of December 2005, they accounted for 18% of the 3.1 million AIDS deaths in 2005. Only 40,000 or 4% of the one million people now on antiretroviral treatment are children. This means that one in every six AIDS deaths each year is a child, yet children represent less than one of every twenty-five persons getting treatment in developing countries today.

India has an estimated 202,000 children infected by HIV/AIDS (UNAIDS 2004). Using a conservative vertical transmission rate of 30%, a new cohort of approximately 56,700 HIV infected infants, is added every year (NACO, 2005). As of Sept 2006, the programme has about 45,000 individuals on ART through public, private, and NGO supported ART centers (NACO 2006). There are 2,300 children, who are currently receiving ART in India (NACO Oct, 06) however, half of HIV-positive children die undiagnosed before their second birthday. The reasons for lack of access for treatment of children with HIV/AIDS are manifold and include among others, issues of diagnosis in infants (early diagnosis), lack of clear guidelines for the treatment of children, lack of access to appropriate pediatric ART formulations, inadequate capacity and knowledge of service providers in clinical management of Paediatric HIV/AIDs, lack of surveillance and data in this age group (<15 years), nutrition in young infants, inadequate follow up of infants born to mothers from the PPTCT programme and other programmatic issues such as convergence with RCH services and the lack of a minimum package for care and support of children affected and infected with HIV. Enhancement of health care systems' ability to address health needs of infected children, resulting in effective management of common childhood illnesses and prevention and treatment of opportunistic infections.

Children have specific needs for growth and development, and of early diagnosis of infection besides needing a strong family support. Orphaned and vulnerable (OVC) children, both uninfected and infected add to the complexity of the issue in terms of vulnerability, social security, livelihood, poverty etc.

The main thrust areas of this document include the newborn component of PPTCT, follow up of the HIV-exposed infant, counselling mothers to decide the right infant feeding choices, PCP prophylaxis and appropriate diagnosis of infected children. Once HIV infection is confirmed and for the older children, who have contracted HIV through other routes, the areas of importance include correct diagnosis, nutritional support, immunization- both routine and special vaccines, antiretroviral therapy, prevention and management of opportunistic infections (OIs), and last but not the least, access to appropriate counselling services. There is also a need to focus on adolescents and HIV, especially with regard to primary prevention of HIV amongst teens by providing them with the life skills, family life education and right messages on prevention of HIV.

Objectives of the Guidelines

These guidelines are intended to guide pediatricians prescribing ART as well as the team in the ART centers, on the practical issues regarding care and treatment of HIV in infants and children. The guidelines describe recommendations for practice in the national programme as well as guidance in dealing with special cases, in view of the role of the private sector in provision of ART.

This guideline is part of a series of NACO guidelines:

- National ART Guidelines including post-expsoure prophylaxis (PEP)
- National Guidelines for prevention of parent-to-child transmission
- National Guidelines for management of Opportunistic infections
- National Guidelines for HIV care and treatment in children
- National Guidelines for Laboratory Diagnosis of OIs.

The guidelines are based on the *WHO 2006 guidelines on ART in infants and children in resource limited setting: towards universal access, recommendations for a public health approach* as well as a review of current literature on HIV and children. The field of HIV/AIDS and in particular, antiretroviral therapy is rapidly evolving. This guideline will evolve over time and updated as more evidence becomes available.

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SECTION A

Management of Infants and Children with HIV Infection and Paediatric Antiretroviral Therapy

SECTION

A1

Management of HIV Exposed Children

1.1 HIV exposure in infants and young children

Mother to Child Transmission (MTCT) is by far the most significant route of transmission of HIV infection in children below the age of 15 years. In 2005 alone, 700,000 children were reported to have acquired HIV infection. HIV can be transmitted during pregnancy, during childbirth, or breast-feeding. Without intervention, the risk of transmission from an infected mother to her child ranges from 15% to 25% in developed countries and from 25% to 45% in developing countries. This difference is largely attributed to breast-feeding practices (Table 1).

Table 1: Estimated risk and timing of MTCT in the absence of interventions	
During pregnancy	5–10%
During labour and delivery	10–15%
During breast-feeding	5–20%
Overall without breast-feeding	15–25%
Overall with breast-feeding to 6 months	20–35%
Overall with breast-feeding to 18 to 24 months	30–45%

The proportion of HIV transmission attributable to breast-feeding depends on feeding practices. Exposure to HIV transmission continues for as long as a child is breastfed. Prolonged breast-feeding up to 18 to 24 months accounts for increased risk of HIV transmission to infant compared to shortened breast -feeding up to 6 months. Mixed feeding, the norm for the majority of women in India (>90%), has been shown to double the risk of postnatal HIV transmission.

With approximately 27 million pregnancies a year and an overall estimated 0.7% prevalence rate of HIV infection among pregnant women, it is estimated that about 189,000 HIV infected women are delivering every year in India. However, with the current uptake coverage of HIV testing pregnant women in India, over 90% of these exposed infants remain unknown. Even when the HIV status of the mother is known, only 6% of all infants are followed up at 8 weeks of age.

Women who are HIV positive are at increased risk of opportunistic infections such as tuberculosis, herpes simplex, cytomegalovirus and invasive bacterial infection such as *streptococcus pneumonia* and salmonellosis. HIV infection is difficult to diagnose in infants, as most infected babies appear healthy and exhibit no signs and symptoms at birth. Maternal predictors of infant disease progression include maternal viral load, maternal CD4 count (< 200), rapidly progressing maternal disease, maternal death. Care of the neonate and infants will need to include adequate referral linkages between the maternal and child units and adult care facilities.

1.2 Care of exposed child immediately at birth

Definition of HIV-exposure: infants and children born to mothers living with HIV, until HIV infection in the infant or child is reliably excluded and the infant or child is no longer exposed through breast-feeding.

Care of HIV-exposed infants should follow standard neonatal care according to safe motherhood guidelines including the following:

- The baby's mouth and nostrils should be wiped as soon as the head is delivered
- Infants should be handled with gloves until all blood and maternal secretions have been washed off (early baby bathing)
- The cord should be clamped soon after birth,

but milking should be avoided. Cover the cord with gloved hand and gauze before cutting to avoid blood splattering.

- Initiate feeding within the first hour of birth according to the mother's preferred and informed choice

1.3 PPTCT: Prophylactic ARV for Infants

ARV prophylaxis to the infant must be given according to the current National PPTCT Programme Guidelines. This includes single dose (SD) NVP to mother during labour and to the baby within 72 hours after birth. However, PPTCT regimens for India are being reviewed to include different regimens and a new guideline for PPTCT will be available soon.

(See WHO 2006 Guidelines for prevention of mother to child transmission for reference.)

1.4 Infant Feeding Choices

Breast-feeding provides the infant with all required nutrients and immunological factors that help to protect against common infections. This protection is reduced when the child is given water or any other substance during exclusive breast-feeding. Mixed feeding i.e. breast milk and formula feeds combined is the most hazardous form of infant feeding. Exclusive replacement feeding is the ideal option but it may not be affordable and feasible, where safe drinking water, fuel or clean utensils are scarce. In such scenario HIV—infected women should be counseled during the antenatal period about infant feeding choices and to make an informed decision.

Where exclusive replacement feeding is **AFASS — acceptable, feasible, affordable, sustainable and safe,** avoidance of all breast feeding is recommended. The mother who has chosen not to breast-feed must be able to prepare feeds hygienically and should be advised to use cup feeding and not bottle feeding. In case replacement feeding is not possible, **exclusive breast-feeding** for the first six months of life with early cessation is recommended. The risks of HIV transmission especially if combined with ART may be less than 0.5%, if exclusive breast-feeding is done. If family support is not present, exclusive breast feeding may be difficult and the parent(s) may need consistent psycho-social support.

When the child reaches the age of six months or earlier, breast-feeding should be stopped within two weeks while ensuring the comfort level of both mother and infant. At the same time, good quality complimentary foods should be introduced, ensuring adequate amounts of energy proteins and micronutrients.

HIV infected mothers should be counseled about infant-feeding choices during pregnancy (ante-natal period) and to decide before delivery. During the post-natal period, she should be counseled again to support her decision and to note if there is a change of decision on infant feeding options. As with the PPTCT recommendations, HIV positive women are counseled on feeding options in order for them to make an informed decision on how they would like to feed their infants.

1.5 Care of the HIV exposed child

1.5.1 Immunization and Vitamin A supplementation

HIV-exposed children should be immunized according to the routine national immunization schedule with the following notes:

- BCG should not be given in symptomatic HIV-infected children.
- HiB vaccine should be given to all who are confirmed HIV-infected on the basis of 2 positive DNA PCR tests done at 6 weeks of age.
- Additional vaccines such as Pneumcoccal, Varicella, Hepatitis A, Influenza Virus etc. may be given as necessary.
- Vitamin A supplementation should be as per the UIP schedule.

1.5.2 Cotrimoxazole (CTX) prophylaxis for all HIV exposed infants

Cotrimoxazole prophylaxis protects the infant from PCP, toxoplasmosis and other bacterial diseases. It is the standard component of HIV care to reduce the morbidity and mortality of children less than five years of age:

- All HIV-exposed infants should get CTX prophylaxis from age of 4–6 weeks.
- The recommended dose is 5 mg/kg/day as a single daily dose.

(See section A2 for cotrimoxazole recommendations)

1.5.3 Follow-up of HIV exposed children

Follow-up will be according to the India UIP schedule starting at 6 weeks. The road to health card for HIV-exposed children will include information on maternal HIV status, cotrimoxazole prophylaxis, infant HIV diagnosis and infant feeding information.

What should be done at each visit?

1. Give information to the mother or care-giver on potential common HIV related features, address psycho-social concerns; reinforce the need for cotrimoxazole prophylaxis; infant feeding and the importance of follow up and adherence to treatment.
2. Growth monitoring: If the child's growth curve is flattening, intensify assessment for HIV related features and also screen for treatable causes e.g. nutritional deficiency, chronic infections such as respiratory, gastro-intestinal, urinary tract infection and TB.
3. Review for TB at each visit

In order to pick up more mother-infant pairs, the RCH programme should be linked to the PPTCT and paediatric HIV p rogramme to utilise the strengths of each programme at grass roots in order to provide for and incorporate HIV care into the package of care for mothers and children.

1.6 Counselling and psycho-social support

Appropriate counselling is ultimately the responsibility of the paediatrician and the ART center staff. The counselling task can be delegated to counselors, and must make sure that the psychosocial issues have been dealt with appropriately.

If the child is infected, the parent or the care giver must be told what to expect with regard to the health of the child, and how to take care of the child. Counselling and psychosocial support is the cornerstone of the management of HIV infected or affected families.

(See section A10 for counselling support in Children)

SECTION

A2 Cotrimoxazole Prophylaxis

Cotrimoxazole prophylaxis (CPT) is now considered standard of care for HIV. Children with a history of severe adverse reaction (grade 4 reaction) to CTX or other sulfa drugs and children with G6PD (glucose-6-phosphate dehydrogenase deficiency) should not be prescribed CTX. The alternative drug is dapsone 2 mg/kg once daily, if available. Some children cannot tolerate both, in this case, there are no other alternatives.

2.1 Who should receive cotrimoxazole prophylaxis

Table 2: Indications for CTX prophylaxis	
Group	**Give cotrimoxazole**
All HIV-exposed infants	• from 4–6 weeks of age (or at first encounter with health services) until HIV infection can be excluded.
All HIV-infected infants < 1 year of age	• irrespective of symptoms or CD4 counts
All HIV-infected children between 1 and 5 years of age	• WHO stage 2,3 and 4 or CD4 < 25 %
All symptomatic HIV-infected children > 5 years of age	• WHO Stage 2, 3 and 4 if CD4 counts not available *or* • WHO Stage 3 and 4 irrespective of CD4 *or* • CD4 < 350 cells/mm3 irrespective of WHO staging
As secondary prophylaxis	• After initial treatment for PCP – < 5 years old: do not stop – > 5 years old: may consider stopping as per Table 3 below.

2.2 How long cotrimoxazole should be given

Table 3: How long cotrimoxazole should be given : discontinuing CTX	
Group	**Discontinue CTX when-**
HIV-exposed children	Give CTX until HIV infection has been ruled out and the mother is no longer breast-feeding.
Infants and children living with HIV < 5 years	Maintain on CTX prophylaxis until age 5 years irrespective of clinical and immune response
HIV-infected children on ART and > 5 years old	CTX can be stopped only when clinical or immunological indicators confirm restoration of the immune system for more than 6 months i.e. in a child > 5 years of age with a CD4 count of > 350 cell/mm3 on two occasions not less than 3 months apart (as per adult guidelines).

Table 4: TMP/SMX (CTX) prophylaxis for PCP					
Weight (kg)	Approx. Age	CTX once a day			
		Syrup 5ml (40 TMP/ 200 SMX)	Child tablet (20 TMP, 100 SMX)	Single strength adult tablet (80 TMP/400 SMX)	Double strength adult tablet (160 TMP/800 SMX)
< 5	6 wk–2 months	2.5 ml	1 tablet	-	-
5–10	2–12 months	5 ml	2 tablet	½ tablet	-
10–15	1–2 years	7.5 ml	3 tablet	½ tablet	-
15–22	2– 5 years	10 ml	4 tablet	1 tablet	½ tablet
> 22	> 5 years	15 ml	-	1½ tablet	½ to 1 tablet depending on weight
Dosage: 5mg/kg of TMP/day PO daily * splitting of tablets into quarters is not recommended, unless there is no syrup available.					

CTX prophylaxis (or dapsone if the child cannot tolerate cotrimoxazole) should be restarted if the CD% falls below the age-related initiation threshold or if new or recurrent WHO clinical stage 2,3 or 4 conditions occur.

Patients and families should understand that cotrimoxazole does not treat and cure HIV infection. Counsel caregivers well for side-effects to CTX (although this is not common).

SECTION

A3 Diagnosis of HIV Infection in Children

3.1 Excluding HIV infection in infants and children

As maternal HIV antibody transferred passively during pregnancy can persist for as long as 18 months in children born to HIV-infected mothers, the interpretation of positive HIV antibody test results is more difficult in children below this age. Also, children who are breastfed have ongoing risk for HIV acquisition; therefore HIV infection can only be excluded after breast-feeding is stopped for > 6 weeks. In India, antibody tests and ELISA can be used for infants > 18 months as per adults; and for infants < 18 months, DNA PCR will be done using dried blood spots (DBS).

There are two ways to exclude HIV infection in infants and children:

1. A child has negative virologic test result and > 6 weeks after complete cessation of breastfeeding.

    - HIV- DNA PCR can be done ideally at age 6–8 weeks to exclude HIV infection acquired during delivery. The infection can only be ruled out by DNA PCR test done at more than 6 weeks after stopping breast-feeding.

2. A child has negative HIV antibody test result at ≥ 18 months of age if not breast-feeding and more than 6 weeks after complete cessation of breast-feeding.

    - A child who has negative HIV antibody test result at the age of ≥ 9 months and at least 6 weeks after complete cessation of breast-feeding is HIV-uninfected. Confirm by repeat HIV antibody testing at 18 months.

HIV antibody testing can be done as early as 9 to 12 months of age; by then 74% and 96% of HIV-uninfected children will have negative HIV antibody test at age 9 and 12 months respectively. However, it is recommended that if the infant is diagnosed at 9–12 months, a confirmatory test should be done after 18 months of age and the infant should have stopped breast-feeding for more than 6 weeks.

3.2 Diagnosis of HIV infection in children < 18 months

For children < 18 months old, both breastfed and non-breastfed, born to a HIV positive mother — the following testing strategy applies according to the NACO programme:

- The first HIV DNA PCR shall be conducted at 6 weeks of age. If the PCR test is positive, the test is to be repeated immediately (or as early as possible) for confirmation.

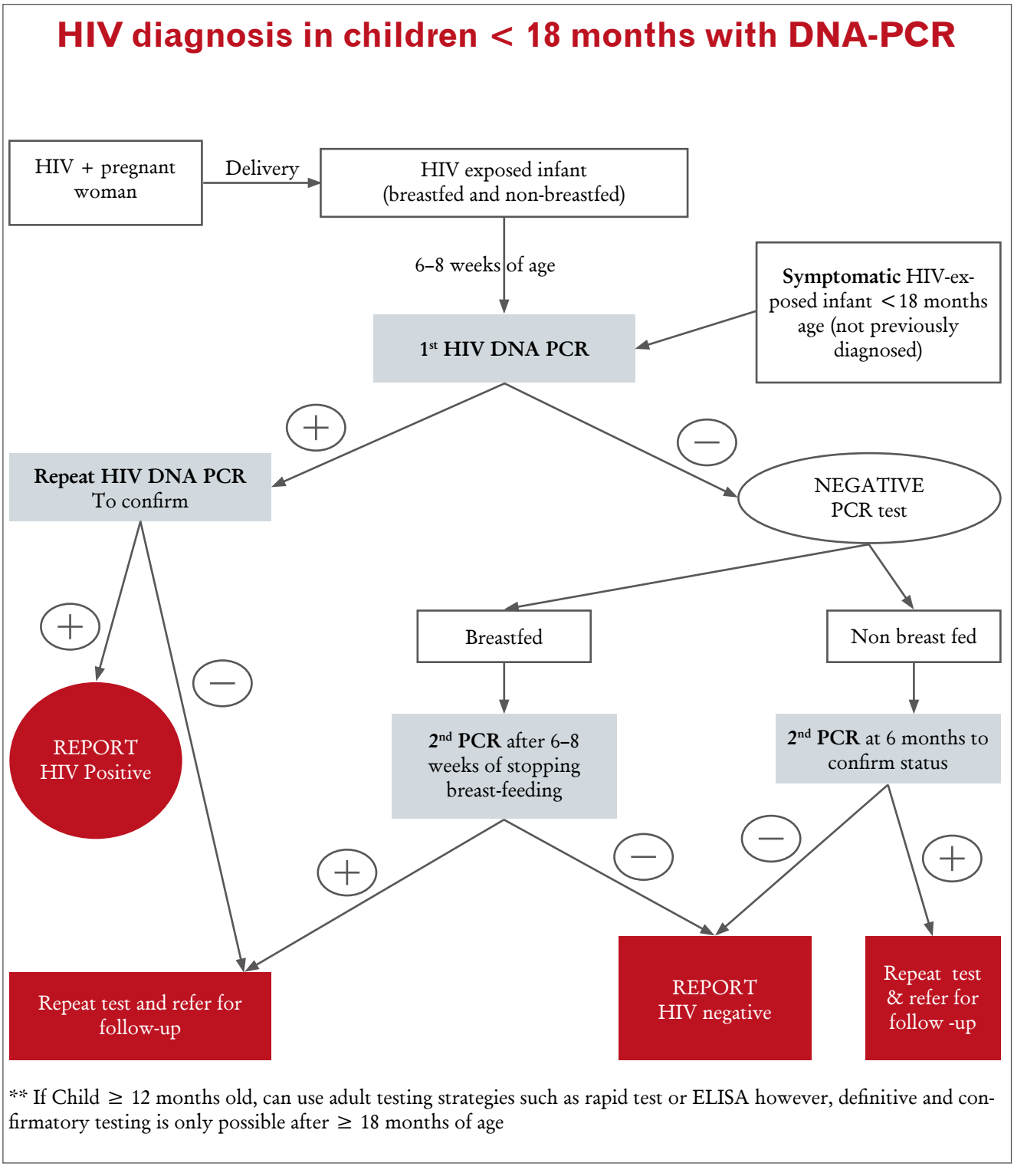
- If the first PCR is negative in a non-breastfed baby, confirm with a second PCR test at 6 months.

- If the child is breastfed and initial PCR test at 6 weeks is negative, PCR testing should be repeated at 6–8 weeks after cessation of breast-feeding to rule out HIV infection.

- In case of mixed -feeding the same strategy to be applied as for a breast fed baby.

- If symptoms develop at any time, the child should be tested appropriately (PCR or ELISA/rapid) at that age.

- A report of "HIV Positive" is given when 2 PCR tests are positive; and a report of "HIV negative" is given when 2 PCR tests are negative.



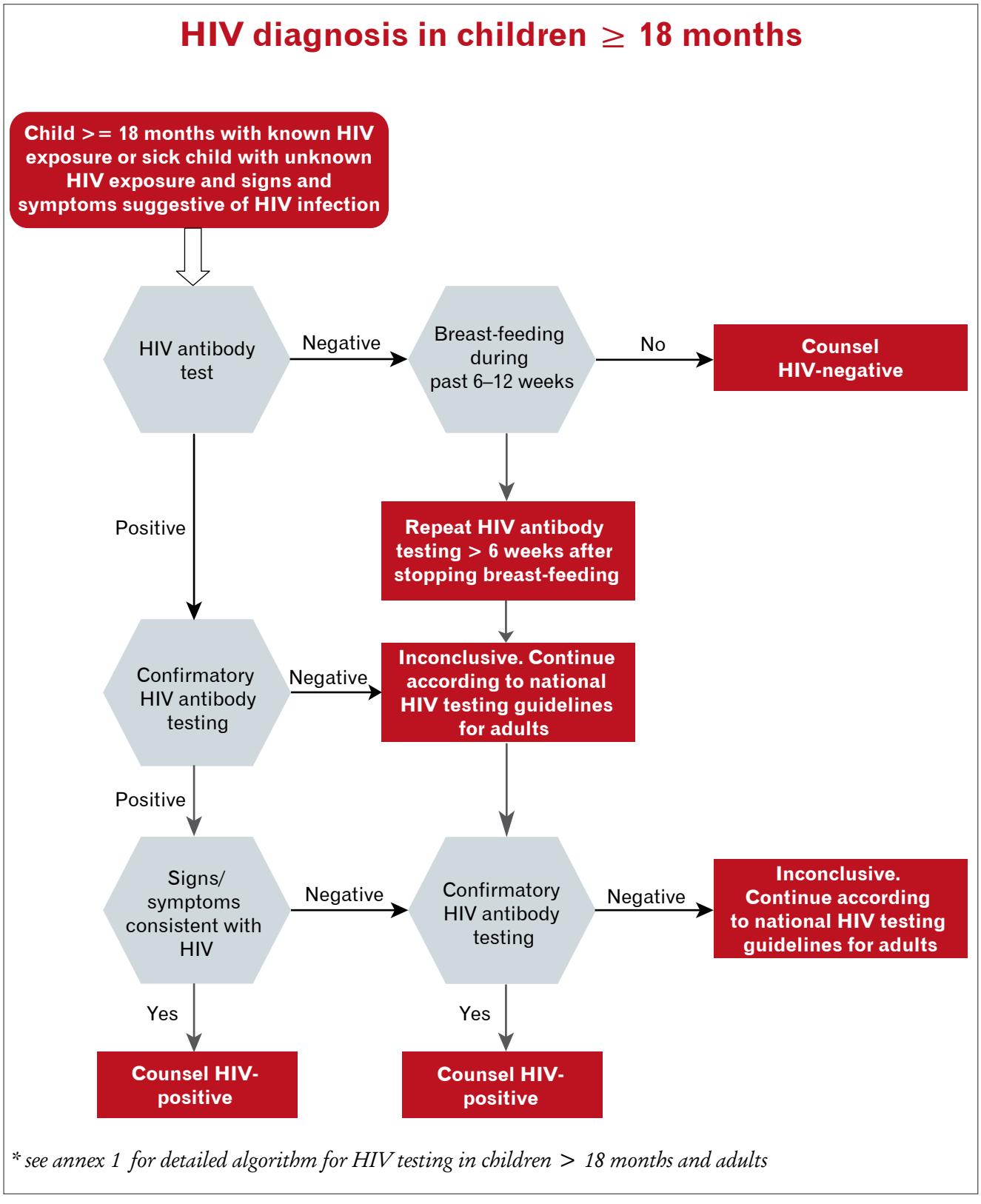
** If Child ≥ 12 months old, can use adult testing strategies such as rapid test or ELISA however, definitive and confirmatory testing is only possible after ≥ 18 months of age

3.3 Diagnosis of HIV infection in children ≥ 18 months

For children ≥ 18 months old, test according to adult national testing strategies:

- If an infant is positive at 12 months, a confirmation with a second HIV test should be done be done at 18 months of age to exclude a positive test result due to passively transferred maternal antibodies.

Two positive HIV antibody test results (done sequentially) in a clinically symptomatic child (suggestive of HIV infection) more than 18 months indicate HIV infection in the child.



** see annex 1 for detailed algorithm for HIV testing in children > 18 months and adults*

Three positive HIV antibody test results (done sequentially) in a clinically asymptomatic child more than 18 months old indicate the child has HIV infection.

Two positive HIV antibody test results and one negative result (done sequentially) in an asymptomatic child more than 18 months old is indeterminate HIV status result. Follow up testing should be done in such a child to resolve the HIV status.

3.4 Presumptive Diagnosis where there is no testing available

If the child is < 18 months and has symptoms and signs that are suggestive of HIV infection and there is no virologic testing available, it is possible to make a presumptive diagnosis by addressing the following issues:

- Is there evidence of HIV exposure mother or baby's serology is HIV positive?
- Is there evidence of immuno-suppression (low CD4 count/%) and symptoms or illness consistent with HIV infection?
- Does the child meet the clinical criteria for presumptive diagnosis of severe HIV infection?

Refer :

Annex 2: WHO Clinical staging for infants and children with established HIV infection

Annex 3: Presumptive and Definitive Criteria for recognizing HIV-related clinical events in infants and children with established HIV infection

Table 5 : Clinical criteria for presumptive diagnosis of severe HIV disease in infants and children less than 18 months of age requiring ART in situations where virological testing is not available

A presumptive diagnosis of severe HIV disease should be made if:

- The infant is confirmed HIV antibody positive;

and

- Diagnosis of any AIDS-indicator condition (s) can be made;

or

- The infant is symptomatic with two or more of the following:
  - Oral thrush[a];
  - Severe pneumonia[a];
  - Severe sepsis[a].

Other factors that support the diagnosis of severe HIV disease in an HIV sero-positive infant include:

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

Confirmation of the diagnosis of HIV infection should be sought as soon as possible.

Notes:

As per IMCI definition:

1. Oral thrush: Creamy white to yellow soft small plaques on red or normally coloured mucosa which can often be scraped off (pseudo membranous), or red patches on tongue, palate or lining of mouth, usually painful or tender. Not responding to topical antifungal treatment.
2. Severe pneumonia: Cough or difficult breathing in a child with chest indrawing, stridor or any of the IMCI general danger signs; i.e., lethargic or unconscious, not able to drink or breast-feed, vomiting, and presence or history of convulsions during current illness; responding to antibiotics.
3. Severe sepsis: Fever or low body temperature in a young infant with any severe sign such as fast breathing, chest indrawing, bulging fontanelle, lethargy, reduced movement, not feeding or sucking breast milk, convulsions, etc.

a. It is unclear how often CD4 is lowered in the above conditions in HIV-uninfected children.

Summary points for HIV diagnosis in infants:

- For infants < 18 months: confirm with PCR and check status of breast-feeding
- For infants > 18 months: ELISA testing as per adult diagnostic guidelines
- If testing if not available for infants < 18 months, then diagnose clinically using presumptive diagnosis method.

SECTION

A4 Monitoring HIV-infected Children not on ART (Pre-ART Care)

Assessment and management after confirmed HIV diagnosis include the following:

- Assess growth and nutritional status, and intervention needs.
- Assess immunization status and provide appropriate immunization.
- Assess for signs and symptoms of opportunistic infections and TB exposure. If opportunistic infection is suspected, diagnosis and treatment of OIs take priority over ART initiation.

- Assign WHO clinical stage
- Ensure that the child is on cotrimoxazole prophylaxis
- Identify any concomitant medication use that may have drug interactions with ART.

- Staging of HIV disease using immunological criteria (see WHO stage from "not significant" to "severe immune suppression")
  - Perform CD4 (%CD4 is preferred in children < 5 years and CD4 count is preferred in children ≥ 5 years).
  - In order to calculate %CD4, full blood cell count (FBC) needs to be performed as well (ideally automated).

- Assess whether the child fits the criteria for starting ART
- Assess family situation including but not limited to number of persons with or at risk for HIV infection and their current health/treatment status.
  - Identify primary caregiver for the child and his/her ability and willingness to adhere to follow up and HIV treatment especially ART
  - Assess family member's understanding of HIV disease and treatment
  - Assess disclosure status of HIV diagnosis within the family (whether the child knows his/her diagnosis and whether anyone else knows, and also if the child knows the parent(s)' HIV status)
  - Assess family financial status including ability to pay for transportation to clinic, ability to afford adequate food/nutritional supplements for the child, ability to pay for any treatment needed etc.

* Caregivers should be advised to bring back the child if sick. If child has missed a visit, attempts should be made to call or visit the child's home to see what has happened.

Regular monitoring of children not requiring ART yet (Pre-ART care) is essential in order to maintain a healthy positive living status until they require therapy:

Good pre-ART care of the infected child with support to the family as comprehensive care for the family unit is important as this sets the stage for future care and better response to treatment.

Table 6 : Monitoring and follow-up schedule for children on pre-ART care						
Items	**Baseline**	**Month 1**	**Month 2**	**Month 3**	**Month 6**	**Every 6 months**
Clinical						
Clinical evaluation[a]	X	X	X	X	X	X
Weight, height	X	X	X	X	X	X
Nutritional status and needs	X	X	X	X	X	X
Cotrimoxazole needs and adherence[b]	X	X	X	X	X	X
Counselling for prevention of STIs and pregnancy in adolescents	X				X	X
OI prevention and treatment needs[e]	X	X	X	X	X	X
Laboratory						
Hb and WBC	X					X
ALT[c]	X					
CD4% or count[d]	X					X

Notes

[a] Includes history taking and physical exam and assessment of neurodevelopment. Children <12 months of age have a higher risk of HIV disease progression and should be followed more frequently than older children.

[b] See section A2 for cotrimoxazole prophylaxis.

[c] ALT at baseline is the minimum monitoring for possible liver impairment. Children with high ALT (> 5 times upper limit of normal) should have full liver function test performed as well as assessment for hepatitis B, hepatitis C or other hepatic disease. Other chemistry tests depend on symptoms.

[d] CD4% is used in children < 5 years of age. For children ≥ 5 years of age, CD4 count is mainly used.

[e] Counselling and access to birth control measures and sexually transmitted infections prevention in teenagers should be part of every visit. Counselling should also include prevention of transmission of HIV to others, and in girls who are in reproductive age, the risk of transmitting HIV to their infants

[f] Assessing TB exposure is important.

Refer:

Annex 11: Developmental milestones

Annex 12: Tanner staging (sexual maturity rating)

Annex 13: Growth monitoring Chart for children

SECTION

A5

Antiretroviral Treatment in Infants and Children

The goals of the National Pediatric Initiative are:

- Provide prevention, care and treatment for children infected or affected by HIV/AIDS.
- Provide ART to at least 40,000 children living with AIDS by 2011
- Prevent HIV infection through PPTCT programme scale up

5.1 Pre- enrollment details

Antiretroviral therapy once started not only has to be taken lifelong, but also has to be taken strictly as per schedule. Besides, it requires regular monitoring. All these factors demand careful patient selection and thorough counselling to ensure adherence. Before enrollment, it is necessary to have 2 to 3 counselling visits to confirm their preparedness for ART and ensure long-term adherence to the therapy. Thus, a detailed history and examination including clinical staging are mandatory prior to enrollment into ART as below:

Table 7: Details of history and physical examination to be done

History	Physical Examination
• Current symptoms and concerns of the patient • Co-existing medical conditions and their treatments • Developmental milestones • History suggestive of any opportunistic infections (OI) • History of contact with tuberculosis • Current and past OI prophylaxis • Ability to adhere to OI prophylaxis and /or anti-tuberculous treatment (ATT) / ART in the past • Past history of ART and details thereof • Ability to keep scheduled appointments in the past • Psychosocial, financial and family support status	• Nutritional and growth status • Brief developmental assessment • Neurological examination • Detailed general physical examination with emphasis on cutaneous manifestations such as herpes zoster, papular pruritic eruptions (PPE), diffuse skin dryness, warts, molluscum angular cheilitis and parotitis • ENT examination • Lymphadenopathy • Oropharyngeal mucosa examination – candidiasis, oral hairy leucoplakia (OHL) etc. • Exclude active tuberculosis: respiratory system, abdominal lymphadenopathy etc. • Hepatosplenomegaly • Examination of eye and optic fundus • Examination of genito-urinary tract

5.2 Clinical staging in children using clinical and immunological criteria

5.2.1 Using clinical criteria

Table 8: WHO classification of HIV-associated clinical disease

Classification of HIV-associated clinical disease	WHO Clinical Stage
Asymptomatic	1
Mild	2
Advanced	3
Severe	4

Notes:

- Clinical staging in HIV-infected children not yet taking ART predicts disease progression and mortality
- Clinical staging can be used to guide when to start cotrimoxazole and when to start ART particularly in situations where CD4 count is not available

Stabilize any opportunistic infection before starting ART

5.2.2 Using immunological criteria

CD4 count is used to assess the immunological status of the HIV-infected child. CD4 counts are higher in infants compared to that of adults, and falls to adult values by age 5 years. There are variations due to diurnal change, intercurrent illness, steroid treatment, splenectomy and after immunization. Repeated measurements are more informative than one value.

CD4 % varies less than CD4 counts, hence considered more valuable in children < 5 years of age. CD4 cell counts for children under the national care and treatment programme shall be done at baseline and subsequently every 6 months; more frequently if clinically indicated eg. 3–6 months.

CD4 % in children is done by using:

- FACS Calibur / Guava / EPICS XL (automated machines) or
- Calculating percentage of CD4 cells using formula when only the CD4 absolute count is available. See Table 9 below.

Table 9: Formula for calculating CD4% when CD4 absolute count is available

$$\%\ \text{CD4 count} = \frac{\text{Absolute CD4 T-lymphocyte count}}{\text{Total lymphocyte count}} \times 100$$

Absolute CD4 +T-lymphocyte count: as obtained by the flowcytometer

- Total lymphocyte count (TLC) can be obtained by a cell counter or alternatively obtained using the following formula:

$$TLC = \frac{\textit{Total no. of lymphocytes (DLC)} \times \textit{total leukocyte count}}{100}$$

- Total leukocyte count can be obtained either through a counting chamber or using a hematology analyzer with the blood sample drawn at the same time as CD4 sample

Table 10: Revised classification of immune suppression in children (CD4 levels in relation to severity of immune suppression)

Classification of HIV-associated immuno-deficiency	Age-related CD4 cell values			
	< 11 months (%)	12 - 35 months (%)	36-59 months (%)	≥ 5 years (cells/mm³)
Not significant (normal CD4 cells)	> 35	> 30	> 25	> 500
Mild	30 – 35	25 – 30	20 – 25	350 – 499
Advanced	25 – 30	20 – 25	15 – 20	200 – 349
Severe	< 25 % or < 1500 cells/mm³	< 20 or < 750 cells/mm³	< 15 or < 350 cells/mm³	< 15% or < 200 cells/mm³

Notes:

- CD4 is the best measurement for assessing immune deficiency.
- CD4 should be used in conjunction with clinical assessment; however, CD4 allows an earlier detection of worsening of HIV disease as CD4 decline usually occurs prior to clinical progression.
- CD4 monitoring can aid in the decision to initiate or switch ART.
- Younger children normally have higher CD4 than older children and adults.
- %CD4 cells varies less in children < 6 years old and is the preferred measurement.
- At age ≥ 6 years, either %CD4 and/or absolute CD4 count can be used.
- The threshold CD4 cell levels for severe immuno-deficiency in children age 1 year and up corresponds with a 12-months mortality risk of ≤ 5%. In children younger than 1 year and especially < 6 months, CD4 is less predictive of mortality and there is high risk for death even at high %CD4.
- Normal CD4 count/% in children are:
  - [a] <12 months: >1500 cells/mm3 (> = 25%)
  - [b] 1-5 years: >1000 cells/mm3 (> = 25%)
  - [c] > 6 years: >500 cells/mm3

Table 11: Clinical and immunological criteria for starting ART

WHO Paediatric Stage	Availability of CD4 cell measurements	Age-specific treatment recommendation	
		< 12 months	≥ 12 months
4[a]	CD4	Treat all	
	No CD4[b]		
3[a]	CD4	Treat all	Treat all, CD4 guided in those children with TB[c], LIP, OHL, thrombocytopenia
	No CD4[b]		Treat all[c]
2	CD4	CD4 guided[d]	
	No CD4	Don't Treat	
1	CD4	CD4-guided[d]	
	No CD4[b]	Do not treat	

LIP - lymphocytic interstitial pneumonia; OHL- oral hairy leukoplakia; TB – tuberculosis

Notes:

[a] Stabilize any opportunistic infection prior to initiation of ARV therapy.

[b] Baseline CD4 estimation is useful to monitor ART even if it is not required to initiate ART.

[c] In children with pulmonary or lymph node tuberculosis, the CD4 level and clinical status should be used to determine the need for and timing of initiation of ART in relation to tuberculosis treatment (see Table 13).

[d] For CD4 count %, refer to Table 10 and below.

5.3 When to start ART

Under the national programme, CD4 counts/% will be done to screen the medical eligibility for ART however, where CD4/% is not available, there should be no delay in offering ART based on clinical staging as in Table 11.

When to start ART in children, guided by CD4

< 11 month infants : if CD4 < 1500 cells/mm^3 (< 25%)

12–35 months : if CD4 < 750 cells/mm^3 (<20%)

36–59 months : if CD4 <350 cells/mm^3 (15%)

> 5 years old : follow adult guidelines ie start ART if < 350 cells/mm3 especially if symptomatic. Initiate ART before CD4 drops below 200 cells/ mm^3.

Reminder: CTX prophylaxis should be given to all HIV-exposed infants until HIV infection is excluded; and to all HIV-infected children with symptomatic confirmed HIV infection

5.4 What to start

Paediatric formulations will be provided at all ART centers. The drugs supplied are fixed dosed combinations (FDC) available in India which are stavudine-based regimens. It has been recommended that in order to scale up the treatment of children, this will be used until zidovudine (AZT) –based regimens are available, recommended globally, as the preferred choice for children.

As NACO will supply drugs to be used for children in the national programme, it is recommended NOT to cut adult drugs once paediatric formulations are available at ART centers.

FDC Tablets supplied under the national initiative, will cover > 5 kg children (based on weights). For children < 5 kg body weight, ARVs have to be in form of syrups or suspension. Contact SACS to make a special arrangement for these individual cases.

In the 2006 WHO guidelines for treatment of infants and children, several drugs have been recommended for use, based on evidence – NRTI (d4T, 3TC, AZT, ABC) ; NNRTI (NVP, EFV) and PIs (LPV/r, NFV, SQV). There is little data on other ARV drugs for use in children.

The recommended preferred first-line ARV regimens for infants and children are:

Regimen of 2 NRTI plus 1 NNRTI

AZT* + 3TC + NVP or EFV**

D4T + 3TC + NVP or EFV**

* AZT should not be given in combination with d4T.

** EFV is not currently recommended for children <3 years of age or < 10kg, and should be avoided in post-pubertal adolescent girls who are either in 1st trimester of pregnancy or are sexually active and not receiving adequate contraception. EFV is used to substitute NPV when anti-tuberculous treatment has to be provided concomitantly. However, after 2 weeks of completion of ATT, EFV should be switched back to NVP.

*** ABC+ 3TC + NVP or EFV is an alternative however, in the national programme – ABC is not available and is still costly.

Table 12 : Formulations of FDCs available for pediatric HIV use in India

Formulation	Stavudine (d4T)	Lamivudine (3TC)	Nevirapine (NVP)
FDC 6 (baby tablet)	6 mg	30 mg	50 mg
FDC 10 (tablet)	10 mg	40 mg	70 mg
FDC 12 (junior tablet)	12 mg	60 mg	100 mg
FDC 30 d4T (adult tablet)	30 mg	150 mg	200 mg
FDC -30 AZT (adult tablet)	300 mg	150 mg	200 mg

5.5 How to select d4T-based versus AZT-based combinations

Since no AZT based FDC pediatric formulations are available at present for children < 20 kg, d4T based FDCs are considered as the first choice drugs for all children below 15 kgs weight. Studies have increasingly shown long term adverse effects with d4T based therapy and hence, with availability of pediatric formulations of FDCs with AZT, these would be preferred except in those with moderate to severe anemia.

(See annex 4: pros and cons of each ARV drug)

Currently only d4T and AZT based regimens are available under the National Pediatric Initiative. second line regimen has been mentioned in the current guidelines for the sake of completeness only.

5.6 First-line regimens for children with TB co-infection

Tuberculosis and HIV are the commonest co-infections encountered in our country. TB drugs alter the p450 inducer enzymes in the liver which affects the therapeutic levels of several of the commonly prescribed antiretroviral drugs. It is important that children with suspected TB be referred to the RNTCP programme (i.e. to the nearest TB microscopy centre or joint management of TB-HIV can be done)

If TB is diagnosed, anti-TB treatment should be started first and ART should be started 2–8 weeks after anti-TB treatment is tolerated and to decrease the risk of inflammatory immune reconstitution syndrome (IRIS).

1. **For children on rifampicin-containing anti-TB treatment and starting ART**
   - Preferred regimen: 2 NRTI + EFV (in children ≥ 3 years old)

After 2 weeks of completing rifampicin-based anti-TB treatment, switch back to standard first line regimen with 2NRTI + NVP.

2. **Children on first-line ART and starting rifampicin-containing anti-TB treatment**

Current first line regimen	Preferred regimen
2NRTI + EFV	Continue the same regimen
2NRTI + NVP	Switch to 2NRTI + EFV (if age > 3 years and weight > 10 kg)

Notes:

- There is no drug interaction between NRTI and rifampicin.
- Rifampicin lowers NVP drug level by 20-58% and EFV drug level by 25%. In children, there is no information on appropriate dosing of NVP and EFV when used with rifampicin.
- Apart from rifampicin, other anti-TB drugs do not have drug interaction with ART.
- Rifampicin is the best bactericidal anti-TB drug and should be part of anti-TB regimens especially during the first 2 months of treatment. Consideration to change from rifampicin-based to non-rifampicin-based anti-TB treatment during the maintenance phase is up to the discretion of the treating physician and should follow the National TB treatment guidelines.
- Both Anti-TB drugs and NNRTI (especially NVP) can cause hepatotoxicity; therefore, close monitoring is required.
- After 2 weeks of completing rifampicin-based anti-TB treatment, switch back to standard first line regimen with 2NRTI + NVP

It is of utmost importance that TB infection be stabilized. Hence, for management of HIV children co-infected with TB, the recommendations are as in Table 13.

5.7 Hepatitis and HIV

Hepatitis and HIV may often co-exist in those children who have transfusion transmitted infection as well as in adolescents who may be IDUs. In these children and adolescents, one has to exercise caution with the drugs that cause hepatotoxicity, especially ZDV and ddI amongst the NRTIs, nevirapine amongst NNRTIs and PIs in general especially higher doses of ritonavir. The desired choice of drugs would be lamivudine and tenofovir based

regimen preferably with efavirenz. In the presence of active hepatitis B infection, this regimen would also help treat HBV. Tenofovir are currently not available under the national programme.

(See annex 5: drug interactions with ARVs)

Table 13 : Recommendations for the timing of ART following initiation of TB treatment with rifampicin-containing regimen in HIV-infected infants and children

Clinical stage of child with TB (as an event indicating need for ART)	Timing of ART following initiation of TB treatment (rifampicin-containing regimen)a	Recommended ARV Regimen
WHO Pediatric Clinical Stage 4[b]	• Start ART soon after initiating TB treatment (between 2 - 8 weeks)	In children < 3 years: Standard first-line regimen of 2 NRTI + NVP[d] In children >3 yearse: Standard first-line regimen of 2 NRTI + EFV[e] Following completion of TB treatment, it is recommended to change from EFV to NVP after 2 weeks of completion of ATT unless other contraindications. • Regimens as recommended above • Where ART can be delayed until after completion of TB treatment, initiation with a standard 2 NRTI + NNRTI first line regimen is recommended.
WHO Pediatric Clinical Stage 3[c]	With clinical management alone: • Start ART soon after initiating TB treatment (between 2 - 8 weeks) • If excellent clinical response to TB treatment in first 2 to 8 weeks of TB therapy, and child is stable and on co-trimoxazole preventive therapy (CPT)[a], it may be reasonable to delay initiation of ART.	
	Where CD4 cell estimation is available: • Evaluate possibility to delay initiation of ART depending on assessment of clinical status and CD4 cells, and clinical and immunological response to TB therapy: – Severe and advanced immuno-deficiency[f]: initiate ART soon after initiating TB treatment (between 2-8 weeks) – Mild or no immuno-deficiency[g]: Initiation of ART may be delayed until after completion of TB therapy; monitor closely response to TB therapy and re-assess for ART after TB therapy; if no improvement, consider starting ART.	

Notes:

[a] Administration of CPT is important in children with TB/HIV co-infection.

[b] All children with Pediatric Clinical Stage 4 should be initiated on ART regardless of CD4 cell count/% criteria.

[c] Except for lymph node TB.

[d] Careful clinical monitoring with laboratory support if available is recommended where NVP is administered concurrently with rifampicin.

[e] EFV is not currently recommended for children <3 years of age or < 10kg, and should not be given to post pubertal adolescent girls who are either in 1st trimester of pregnancy or are sexually active and not using adequate contraception.

[f] Severe immunodeficiency as per Table 10, advanced immuno-deficiency is assumed to be up to 5% above age-specific CD4 threshold for severe immuno-deficiency or CD4 200–349 cells/mm^3 for children ≥5 years of age

[g] Mild or not significant immuno-deficiency is assumed at CD4 levels above those levels defining advanced immuno-deficiency.

5.8 ART in infants with prior ARV exposure

- Infants who are exposed to ARV for PPTCT, either the maternal or infant component

and/ or

- Breast-feeding infants who are exposed to ART because of maternal ART

} Should be considered eligible for the standard first-line ART regimen using the same doses and criteria.

Research is urgently needed to identify the efficacy of ART in infants with previous or continuing exposure to ARVs.

Globally, there is data that resistance strains are detected in infants with exposure through PPTCT regimens (NVP single dose or 2-drug regimen with 3TC and with exposure to ART in the breast milk of mothers on ART). As with resistance in mothers, these also disappear over time but may exist as minor viral sub-populations. It is currently not known of the ART options in these groups of exposed infants. Research is underway to address these questions. It is recommended for the infants as such to be considered eligible for the standard first-line ART regimen as above.

5.9 How much Paediatric ARVs to give

NACO Paediatric HIV Dosing Guide 2006*

NVP Lead-in period for first 2 weeks:

Weight band (kg)	Stavudine 6 mg containing FDCs		Stavudine 10 mg containing FDCs		Adult FDCs (Stavudine -30)		Adult FDC (zidovudine- 300)	
	Morning 2-drug FDC-6 Sta 6 + Lam 30	Evening 3-drug FDC-6 Sta 6 + Lam 30 + NVP 50	Morning 2-drug FDC-10 Sta 10 + Lam 40	Evening 3-drug FDC-10 Sta 10; Lam 40 + NVP 70	Morning 2-drug FDC-30 Sta 30 + Lam 150	Evening 3 drug FDC-30 Sta 30 + Lam 150 + NVP 200	Morning 2-drug AZT 300 + Lam 150 -drug	Evening 3 drug AZT 300 + Lam 150 + NVP 200
5–5.9	*1*	*1*						
6–6.9	*1*	*1*						
7–7.9	*1.5*	*1*						
8–8.9	*1.5*	*1.5*						
9–9.9	*1.5*	*1.5*						
10–10.9	*2*	*2*						
11–11.9	*2*	*2*						
12–13.9			*1.5*	*1*				
14–16.9			*1.5*	*1.5*				
17–19.9			*2*	*1.5*				
20–24.9					*1*	*0.5*	*1*	*0.5*
25–29.9					*1*	*1*	*1*	*1*
30–34.9					*1*	*1*	*1*	*1*

Subsequent follow-on regimen for NVP:

Weight band (kg)	FDC-6 Sta 6; Lam 30; NVP 50		FDC-10 (tab) Sta 10; Lam 40; NVP 70		Adult FDC-30 Sta 30; Lam 150; NVP 200		Adult FDC AZT 300; Lam 150; NVP 200	
	Morning	Evening	Morning	Evening	Morning	Evening	Morning	Evening
5– 5.9	1	1						
6–6.9	1	1						
7–7.9	1.5	1						
8–8.9	1.5	1.5						
9–9.9	1.5	1.5						
10–10.9	2	2						
11–11.9	2	2						
12–13.9			1.5	1				
14–16.9			1.5	1.5				
17–19.9			2	1.5				
20–24.9**					1	0.5	1	0.5
25–29.9					1	1	1	1
30–34.9					1	1	1	1

* Paediatric ARV Dosing Guide, Meeting report 19 July 2006 – NACO/IAP/WHO

** > 20 kg : option of using either Stavudine based regimen or Zidovudine-based regimen

Alternative 1st line EFV based regimen:

Weight band (kg)	Stavudine 6 mg containing 2- drug FDC			Stavudine 10 mg containing 2- drug FDC				Adult 2-drug Stavudine containing FDC			
	Morning	Evening		Morning	Evening			Morning	Evening		
	FDC-6 2-drug	FDC-6 2-drug	EFV 200 mg tablet	FDC-10 2-drug	FDC-10 2-drug	EFV 200 mg tablet	EFV syrup top up	FDC-30 2-drug	FDC-30 2-drug	EFV 200 mg tablet	EFV syrup top up
	Sta 6 + Lam 30	Sta 6 + Lam 30		Sta 10 + Lam 40	Sta 10 + Lam 40			Sta 30 + Lam 150	Sta 30 + Lam 150		
10–10.9	*2*	*2*	*1*								
11–11.9	*2*	*2*	*1*								
12–13.9				*1.5*	*1*	*1*					
14–14.9				*1.5*	*1*	*1*					
15–16.9				*1.5*	*1.5*	*1*	*2.5 ml*				
17–19.9				*2*	*1.5*	*1*	*2.5 ml*				
20–24.9								*1*	*0.5*	*1.5*	
25–29.9								*1*	*1*	*1.5*	*2.5 ml*
30–34.9								*1*	*1*	*2*	

* EFV for weights > 10 kg

2.5 ml syrup is equivalent of 50 mg of Efavirenz

TOP-UP with efavirenz syrup is necessary in some weight bands. Intensive Counselling of the caregiver of the infected child is required to educate how to give top-up syrup.

* A simple paediatric HIV dosing disk and desktop reference is available on dosing ARVs in children for the national programme.

SECTION

A6 Monitoring and Follow-up after ART Initiation

6.1 Monitoring schedule after ART initiation

Tasks	Baseline	Mo 1	Mo 2	Mo 3	Mo 4	Mo 5	Mo 6	Every 2–3 months	Symptom -directed
Clinical									
Clinical evaluation	X	X	X	X	X	X	X	X	X
Weight, height	X	X	X	X	X	X	X	X	
Development milestones	X			X				X	X
Calculation of ART dose[1]	X	X	X	X	X	X	X	X	
Concomitant medications[2]	X	X	X	X	X	X	X	X	
Check ART adherence[3]		X	X	X	X	X	X	X	
Laboratory									
Hb and WBC[4]	X								X
Full chemistry[5]									X
Pregnancy test in adolescent girls[6]	X								
CD4% or count[7]	X							X	X

[1] Children may have rapid weight and height gain after ART in addition to expected normal growth; therefore, re-calculation of ART dose should be done at every visit. Under dosing of ART can lead to rapid development of resistance. **WHO Clinical staging for clinical monitoring after ART initiation must be done at all visits**

[2] Check for concomitant drug intake at every visit such as appropriate cotrimoxazole prophylaxis (if indicated) and other drugs. Check for potential drug interactions with ART (Annex 5).

[3] ART adherence assessment can be done by asking child and parent/caregiver questions about missed dose and times the child take ARV. Performing pill count is time consuming but may be a better measurement for adherence, if done correctly.

[4] Hemoglobin (Hb) and white blood cell count (WBC) monitoring may be considered in children on AZT at 1, 2 and 3 months.

[5] Full chemistry includes liver enzymes, renal function, glucose, lipids, serum electrolytes, amylase, lipase (if available),. Monitoring depends on symptoms and regimens. Regular monitoring of liver function tests during the first three months of treatment may be considered for certain children using NVP -based regimens, in particular for adolescent girls with CD4 cell > 250 cells/mm^3 and infants and children co-infected with hepatitis B virus (HBV), hepatitis C virus (HCV), or other hepatic diseases.

[6] Pregnancy test should be done in adolescent girls especially those who are going to start EFV and provide family planning counselling.

[7] If signs of clinical progression of disease are seen, CD4 should be done earlier. TLC is not suitable for monitoring of ART. If CD4 is not available, clinical monitoring alone is used.

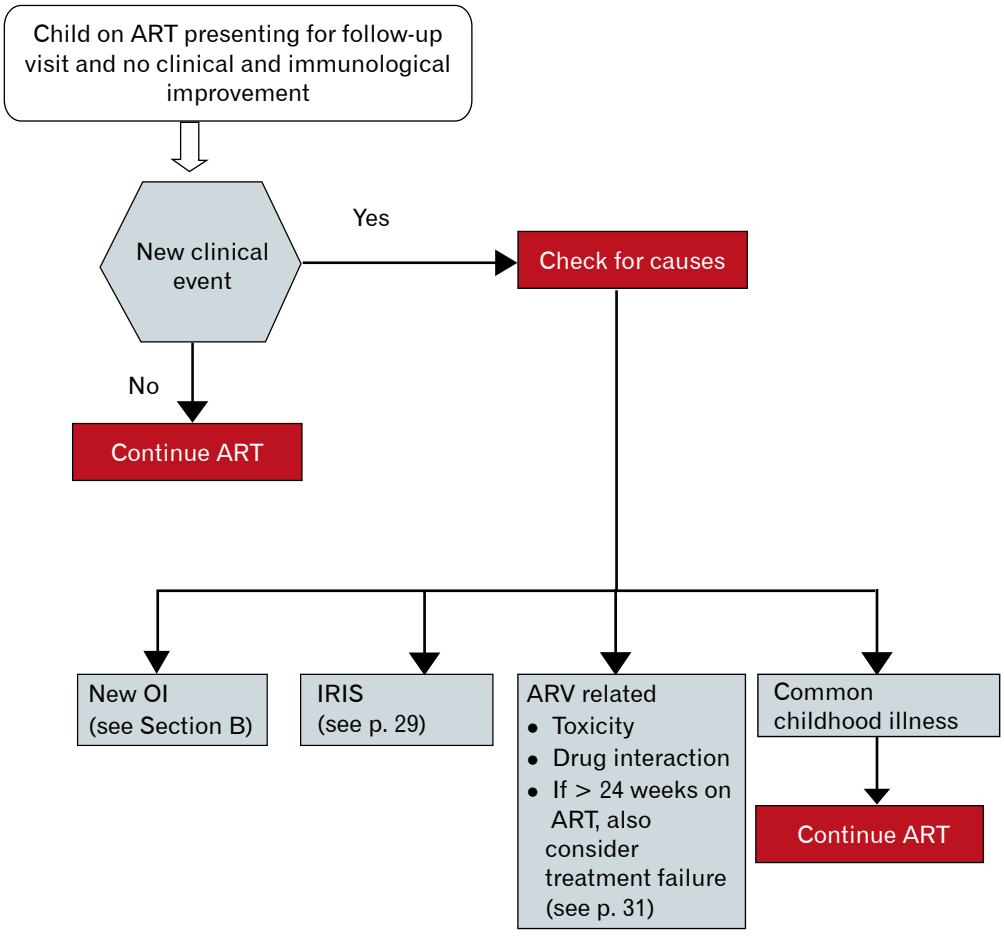
If the child has missed a visit, attempts should be made to contact parent/ caregiver (e.g. call or home visit). In addition to these suggested appointments, caregivers should be encouraged to bring the child in if he/she is sick and especially during the first few months of ART when the child may experience ART side effects and intolerance.

6.2 Evaluating response to ART on the follow-up visit

The following needs to be done at regular intervals in all children on ART:

- Counselling monthly and at every contact
- Adverse events monitoring
- Treatment efficacy evaluation: clinical improvement and/or CD4 count /% improvement, clinical staging using the WHO T staging for clinical monitoring after ART initiation should be done every visit
- Detecting Opportunistic infections, if any – review for TB at every visit
- Diagnose Immune reconstitution syndrome (IRIS)
- Adherence monitoring

For children with no clinical and immunological improvement in spite of good adherence and good nutritional support at follow-up visit, the protocol is:



Clinical staging using the WHO T staging for clinical monitoring after ART initiation must be done at all visits

SECTION

A7 Managing ARV Toxicity

7.1 Guiding principles in management of ARV toxicity in children

1. Determine the seriousness of the toxicity, as below.

2. Evaluate concurrent medications, and establish whether the toxicity is attributable to an ARV or due to other drugs taken at the same time.

3. Consider other diseases (e.g. viral hepatitis in a child on ARV who develops jaundice, as not all problems that arise during treatment are caused by ARVs)

4. Manage the adverse event according to severity.

5. Stress maintaining adherence despite toxicity for mild and moderate reactions.

In general:

If there is a need to discontinue ART because of life-threatening toxicity, all ART drugs should be stopped until the patient is stabilized. Most ARV drug toxicities are not severe and can be managed by giving supportive treatment. Minor side effects can lead to non-adherence; therefore, health care professionals must counsel patients and provide supportive treatment.

Grade	Severity	Response
Grade 4	***Severe life-threatening reactions*** *(Annex 8)*	Immediately discontinue all ARV drugs and manage the medical event (i.e. symptomatic and supportive therapy) and re-introduce ARVs using a modified regimen (i.e. with an ARV drug substitution for the offending drug) when patient is stabilized.
Grade 3	***Severe reactions***	Substitute the offending drug without discontinuing ART
Grade 2	***Moderate reactions***	Some moderate reactions (e.g. lipodystrophy or peripheral neuropathy) do require substitution. For other reactions consider continuation of ART as long as feasible; if patient does not improve on symptomatic therapy, consider single drug substitution.
Grade 1	***Mild reactions***	Are bothersome but they do not require change in therapy.

7.2 When do ARV side effects and toxicities occur

Time	Side effects / notes
Within first few weeks	• Gastro-intestinal toxicities include nausea, vomiting and diarrhoea. These side effects are usually self-limiting and require only symptomatic treatment. • Rash and liver toxicity are more common with NNRTI drugs but also seen in certain NRTI drugs such as ABC and some PIs
	Notes: • NVP lead-in dose is used in order to lower the risk of toxicity. • In mild to moderate rash and liver toxicity, ARV can be continued under close supervision, symptomatic treatment and supportive care. • Severe rash and liver toxicity (ALT > 5 ULN) can be life threatening and NVP should be substituted (see annex 7) • CNS toxicity from EFV can be self-limiting. Because EFV can cause dizziness, advise to take it at night. • ABC hypersensitivity usually occurs within the first 6 weeks and can be life threatening. ABC must be stopped and never re- challenged.
From 4 weeks onwards	• Drug-induced bone-marrow suppression such as anemia and neutropenia are most commonly seen with AZT. • Other causes of anemia should be evaluated and treated. • Asymptomatic mild anemia is common.
	Notes: • If there is severe anemia with Hb < 7.5 g/dl and neutropenia with neutrophil count < 500 /mm^3 AZT should be switched to either ABC or d4T (see Annex 8)
6–18 months	• Mitochondrial dysfunction is primarily seen with the NRTI drugs including lactic acidosis, hepatic toxicity, pancreatitis, peripheral neuropathy, lipoatrophy, and myopathy. • Lipodystrophy is frequently associated with d4T use and can cause permanent disfiguring. • Lactic acidosis is rare and can occur at any time. It is particularly associated with d4T use. Severe lactic acidosis can be life threatening. • Metabolic disorders are more common with PIs and include hyperlipidaemia, fat accumulation, insulin resistance, diabetes and osteopenia.
	Notes: • Substitute NRTI to other drug with different toxicity profile (see annex 7).
After one year	• Nephrolithiasis is commonly seen with IDV. • Renal tubular dysfunction is associated with TDF.
	Notes: • Substitute the PI to other drugs with different toxicity profile

Currently only d4T and AZT based regimens are available under the National Pediatric Initiative. Second line regimen has been mentioned in the current guidelines for the sake of completeness.

7.3 Severe toxicities in infants and children associated with specific ARV drugs and potential subsitutions

Table 14: Toxicities in infants and children associated with specific ARV drugs and potential substitutions

First-line ARV drug[a]	Most frequent significant toxicity for the ARV drug	Suggested first-line ARV drug substitution
ABC	Hypersensitivity reaction	AZT
AZT	Severe anaemia or neutropaenia[b,c]	d4T or ABC
	Lactic acidosis	ABC/AZT
	Severe gastrointestinal intolerance[d]	d4T or ABC
d4T	Lactic acidosis	AZT/ABC[e]
	Peripheral neuropathy	AZT or ABC
	Pancreatitis	
	Lipoatrophy/metabolic syndrome[f]	
EFV	Persistent and severe central nervous system toxicity[g]	NVP
	Potential teratogenicity (adolescent girl in 1st trimester pregnancy or of childbearing potential not receiving adequate contraception)	
NVP	Acute symptomatic hepatitis[h]	EFV[i]
	Hypersensitivity reaction	Preferred substitution by NRTI to: • a third NRTI (disadvantage- may be less potent) or • PI (disadvantage premature start of 2nd line ARV drug)
	Severe or life-threatening rash (Stevens-Johnson Syndrome[j])	

Notes:

a 3TC - associated pancreatitis has been described in adults but is considered very rare in children.

b Exclude malaria in areas of stable malaria.

c Defined as severe haematological abnormality that can be life-threatening and that is refractory to supportive therapy.

d Defined as severe, refractory gastro-intestinal intolerance that prevents ingestion of ARV drug regimen (e.g. persistent nausea and vomiting).

e ABC is preferred in this situation; however, where ABC is not available AZT may be used.

f Substitution of d4T typically may not reverse lipoatrophy. In children, ABC or AZT can be considered as alternatives.

g Defined as severe central nervous system toxicity such as persistent hallucinations or psychosis.

h Symptomatic NVP-associated hepatic toxicity is very rare in HIV-infected children prior to adolescence.

i EFV is not currently recommended for children < 3 years of age or < 10kg, and should not be given to post pubertal adolescent girls who are either in 1st trimester of pregnancy or are sexually active and not using adequate contraception.

j Severe rash is defined as extensive rash with desquamation, angioedema, or serum sickness-like reaction; or a rash with constitutional findings such as fever, oral lesions, blistering, facial oedema, conjunctivitis; Stevens-Johnson syndrome can be life-threatening. For life-threatening rash, most clinicians would not substitute EFV due to the potential for NNRTI-class specific toxicity.

k The premature introduction of the PI class of drugs in first-line regimens leads to limitations in the choice of drugs in the event of treatment failure

(See annex 7 : Serious acute and chronic toxicities due to ARV drugs that may require therapy modification: clinical presentation, laboratory abnormalities and implications for ART management)

SECTION

A8 Differentiating IRIS and ARV Toxicity

8.1 Immune reconstitution inflammatory syndrome (IRIS)

Definition	• A collection of signs and symptoms resulting from the ability to mount an immune response to antigens or organisms associated with immune recovery on ART.[i]
Frequency	• 10% of all patients initiating ART. • Up to 25% among patients initiating ART with a CD4 cell count < 50 cells/mm3 or severe clinical disease (WHO clinical stage 3 or 4).[ii iii]
Timing	• Typically within 2–12 weeks of initiation of ART but may present later.
Signs and symptoms	• Unexpected deterioration of clinical status soon after commencing ART. • Unmasking of sub-clinical infections such as TB, which present as new active disease and development of abscess at BCG vaccination site. • Worsening of co-existing infections such a flare of hepatitis B or C.
Most common IRIS events	• M. tuberculosis, Mycobacterium avium complex (MAC) and cryptococcal disease.
Management	• Continue ART if the patient can tolerate it. • Treat unmasked active OI. • In most cases the symptoms of IRIS resolve after a few weeks, however some reactions can be severe or life-threatening and may require a short course of corticosteroid treatment to suppress exaggerated inflammatory responses. • Prednisone 0.5 – 1 mg/kg/day for 5–10 days is suggested in moderate to severe cases of IRIS.[iv]

Notes:

i Robertson J, Meier M, Wall J, Ying J, Fichtenbaum C. Immune reconstitution syndrome in HIV: validating a case definition and identifying clinical predictors in persons initiating antiretroviral therapy. *Clin Infect Dis* 2006, 42:1639–46.

ii French MA, Lenzo N, John M, et al. Immune restoration disease after the treatment of immunodeficient HIV-infected patients with highly active antiretroviral therapy. *HIV Med* 2000, 1:107–15.

iii Breen RAM, Smith CJ, Bettinson H, et al. Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection. *Thorax* 2004, 59:704–7.

iv McComsey G, Whalen C, Mawhorter S, et al. Placebo-controlled trial of prednisone in advanced HIV-1 infection. *AIDS* 2001, 15:321–7.

8.2 Differentiating IRIS and ARV side effects

Table 15 : Differential diagnosis of common clinical events developing during first 6 months of ART

Symptoms	Side effects of ARV or OI prophylaxis	Immune reconstitution inflammatory syndrome (IRIS)
Nausea, vomiting	**ART:** • AZT, usually self-limiting after 2 weeks **OI prophylaxis:** • Cotrimoxazole or INH	• Hepatitis B and C can occur with IRIS. • Suspect if nausea, vomiting plus jaundice.
Abdominal or flank pain, and/or jaundice	**ART:** • d4T or ddI may cause pancreatitis. • NVP (and EFV less commonly) may cause liver dysfunctions which require stopping these drugs. **OI prophylaxis:** • Cotrimoxazole or INH.	• Hepatitis B and C can occur with IRIS. • Suspect if nausea, vomiting plus jaundice
Diarrhoea	**ART:** • NFV commonly causes diarrhoea	• IRIS from MAC or CMV may cause diarrhoea.
Headache	**ART:** • AZT or EFV usually self-limiting but can last 4-8 weeks.	• Assess for toxoplasmosis and cryptococcal meningitis
Fever	**ART:** • ABC hypersensitive reaction or NVP adverse drug reaction	• IRIS due to several organisms e.g. MAC, TB, CMV, Cryptococcus *neoformans*, herpes zoster
Cough, difficulty in breathing	**ART:** • NRTIs-associated lactic acidosis	• IRIS can be associated with PCP, TB, fungal or bacterial pneumonia
Fatigue, pallor	**ART:** • AZT, which is usually developed during 4 to 6 weeks after initiation	• Suspect MAC IRIS if fever, fatigue and anaemia.
Skin rash, itch	**ART:** • NVP or ABC • Should assess carefully and consider stopping the drug in case of severe reaction. EFV rash is often self limiting. **OI prophylaxis:** • Cotrimoxazole or INH	• Skin conditions which can flare up due to IRIS in the first 3 months of ART – Herpes simplex and zoster – Papilloma virus (warts) – Fungal infections – Atopic dermatitis

SECTION

A9 Failure of Treatment

9.1 Treatment failure can be defined as follows:

Type	Definitions
Clinical failure	• Clinical disease progression with progressive neuro-developmental deterioration, growth failure despite adequate nutritional support and/or • Development of an opportunistic infection or malignancy, when the drugs have been given sufficient time (at least for six months) to induce a protective degree of immune restoration. This needs to be differentiated from immune reconstitution syndrome (IRIS)
Immunologic failure	Defined as a return of CD4 cell count to pre-therapy baseline or below, after initial immune recovery, without any other concomitant infection to explain transient CD4 cell decrease or a greater than 50% fall from on therapy CD4 cells peak level without any other concomitant infection to explain transient CD4 cell decrease.
Virologic failure	The definition of virological failure is more complex and a consensus has not yet been reached. It is therefore currently not recommended to use viral loads routinely in decision-making on treatment failure.

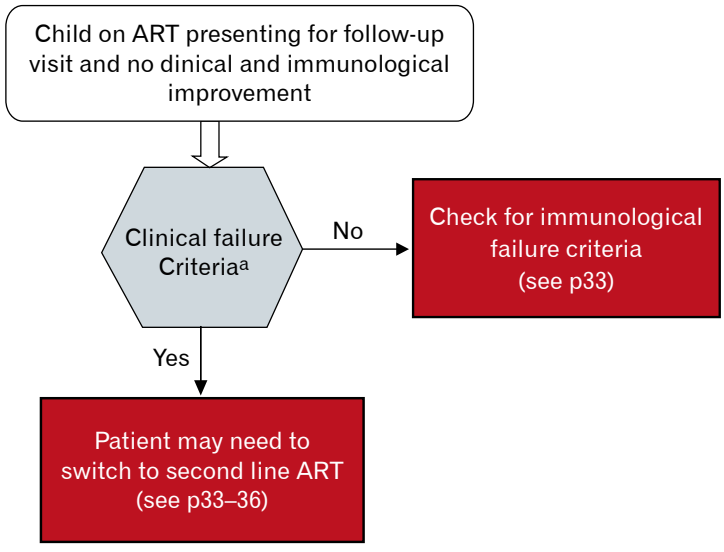
Causes of treatment failure other than drug resistance are:

- Non – adherence
- Impaired drug absorption
- Drug interactions
- Altered drug pharmacokinetics.

Clinical staging using the WHO T staging for clinical monitoring after ART initiation must be done at all visits

9.2 Protocol for assessment of treatment failure in children on ART

Step 1 : Assess clinical criteria for treatment failure



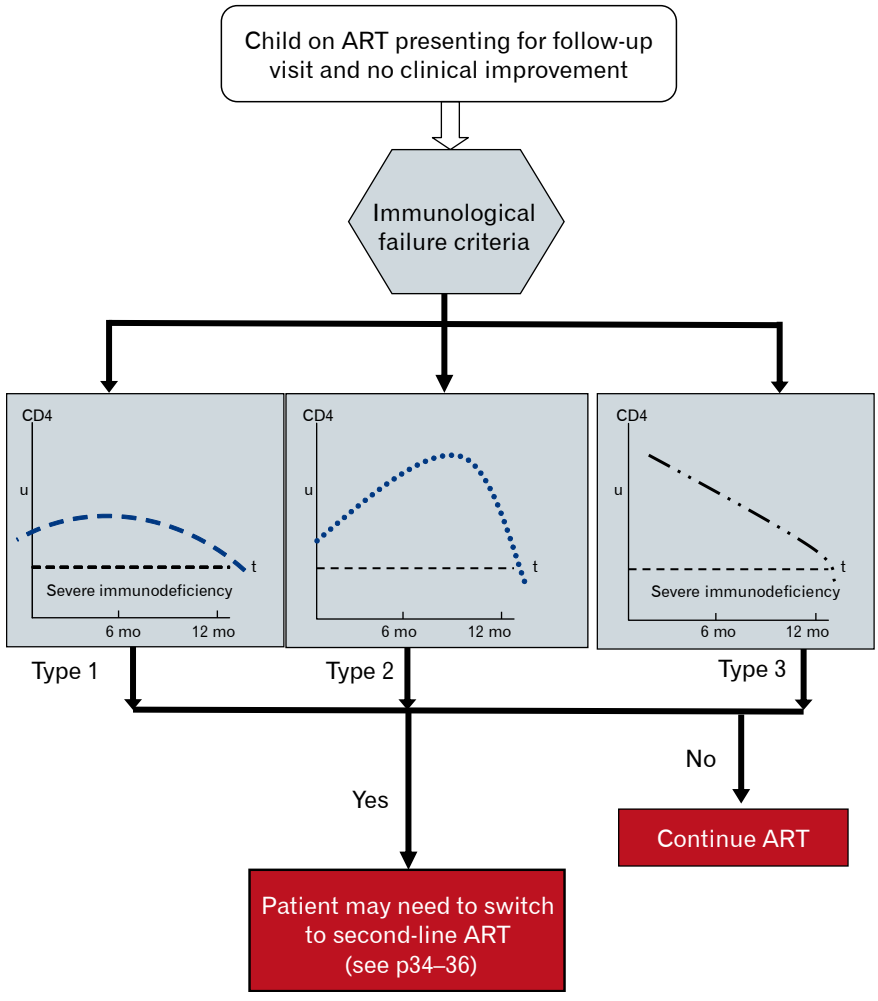
Notes:

[a] **Clinical failure criteria**

Does the child fulfil any of these failure criteria?

- Lack of for decline in growth rate in children who initially respond to treatment
- Loss of neurodevelopmental milestones or development of encephalopathy
- Occurance of new OIs or malignancies or recurrence of infections such as oral candidiasis that is refractory to treatment or oesophageal candidiasis

Step 2: Assess Immunological criteria for treatment failure



Type 1

Development of age-related severe immuno-deficiency after initial immune recovery.

Type 2

New progressive age-related severe immunodeficiency, confirmed with at least one subsequent CD4 measurement.

Type 3

Rapid rate of decline to below threshold of age-related severe immuno-deficiency.

9.3 Plan before switching to second line regimen

- The most common reason for failure is poor adherance. Adherence must be investigated and supportive mechanisms reinforced prior to any change in regimen.
- These cases should be managed by expert HIV paediatrician with full counselling and NGO support
- Switching to second-line is not an emergency
- Ensure that the child is on appropriate OI prophylaxis
- A failing regimen usually retains some anti-HIV activity, therefore – in general- a child should continue the failing regimen until he/she is ready to switch to second-line
- Use the WHO Pediatric Clinical Staging System to guide decision-making regarding switching to second-line therapy for treatment failure

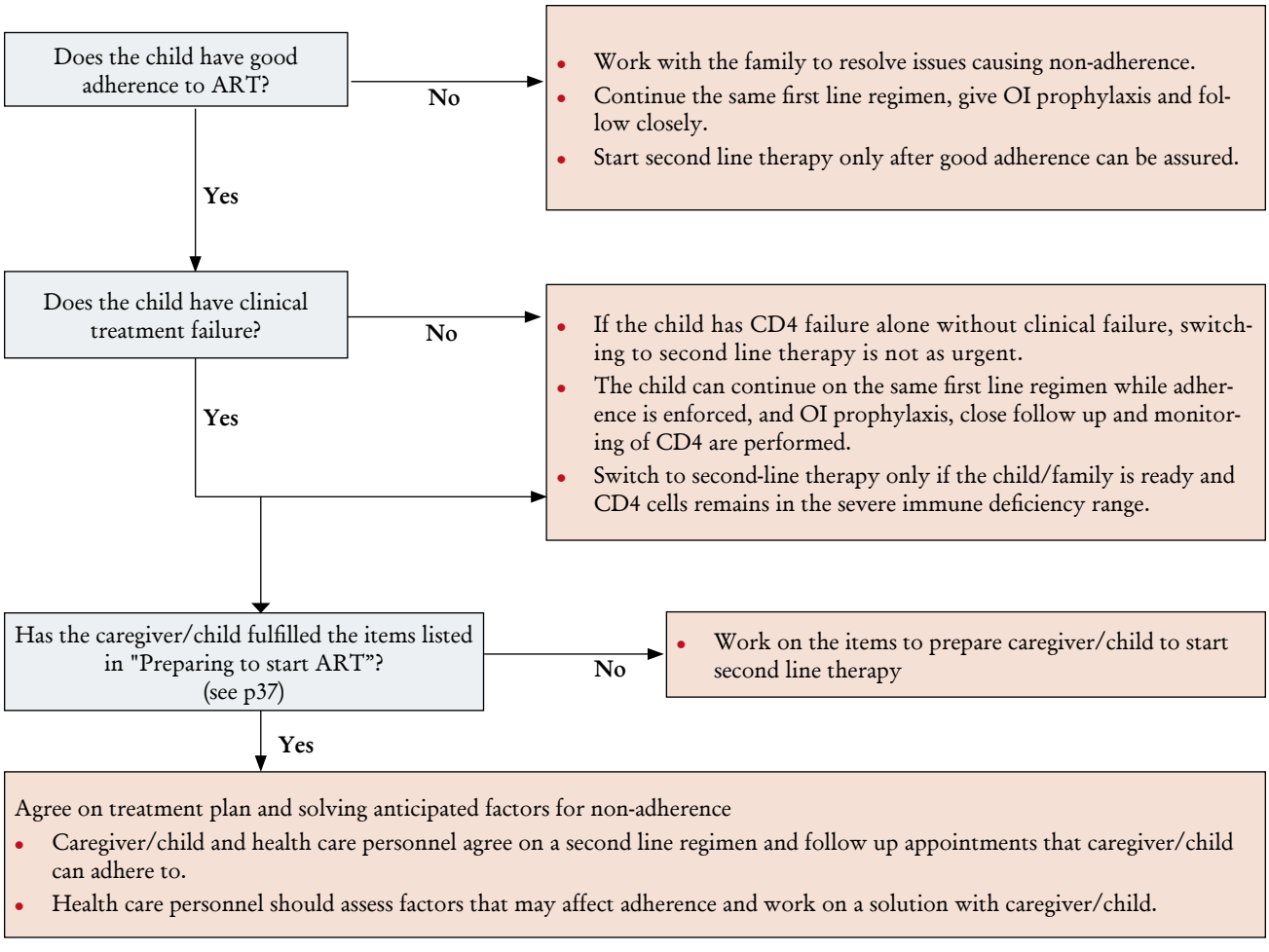


Table 16: Using the WHO Pediatric Clinical Staging System to guide decision-making regarding switching to second-line therapy for treatment failure	
WHO clinical stage on ART[a]	Management options[b]
T 1	• **Do not switch to other regimen** • Maintain scheduled follow up visits including CD4
T 2	• **Treat and manage staging event** • **Do not switch to new regimen** • Assess and offer adherence support • Assess nutritional status and offer support • Schedule earlier visit for clinical review and consider CD4
T 3	• **Treat and manage staging event and monitor responsec,** [c,d,e] • Check if on treatment 24 weeks or more • Assess and offer adherence support • Assess nutritional status and offer support • Check CD4 - where available • **Consider switching regimen** • Institute more frequent follow up
T 4	• **Treat and manage staging event** • Check if on treatment 24 weeks or more • Assess and offer adherence support • Assess nutritional status and offer support • Document CD4 - where available • **Switch regimen**

Notes:

[a] Clinical stages in this table refer to the WHO clinical stage as per revised classification while on ART (a new or recurrent stage at the time of evaluating the infant or child on ART).

[b] It needs to be ensured that the child has had at least 24 weeks of treatment trial, adherence to therapy has been assessed and considered to be adequate prior to considering switching to second-line regimen.

[c] Differentiation of opportunistic infections from immune reconstitution syndrome is important.

[d] In considering changing treatment because of growth failure, it should be ensured that the child is not failing to grow due to lack of adequate nutrition, and that any intercurrent infections have been treated and resolved.

[e] Pulmonary or lymph node TB, Clinical Stage 3 conditions, may not be an indication of treatment failure, and thus not require consideration of second-line therapy; response to tuberculosis therapy should be used to evaluate the need for switching of therapy.

In order to guide switching therapy due to treatment failure in children, CD4 counts/% is essential. Expert HIV paediatrician guidance is recommended.

The national programme currently does not provide for second-line treatment. However, the below recommendations are given for sake of completeness. PIs should not be used as first-line, as there is no known efficacious salvage therapy for children once resistance to PI develops.

Table 17 : Decision-making regarding switching to second line therapy for treatment failure based on availability of CD4 measurement[av]		
WHO Pediatric Clinical Stage on ART[b]	Availability of CD4 cell measurements[c]	Management options
T1 and T2[d]	No CD4	• Do not switch regimen
	CD4	• Consider switching regimen only if 2 or more values below age-related threshold for severe immuno-deficiencye are available • Increase clinical and CD4 follow up if CD4 approaches age-related threshold for severe immuno-deficiency
T3 [d]	No CD4	• Consider switching regimen[f]
	CD4	• Switching regimen is recommended if CD4 at or below age-related threshold for severe immuno-deficiency[e] and particularly if child initially had good immune response to ART
T4	No CD4	• Switch regimen, regardless of CD4
	CD4	

Notes:

[a] It needs to be ensured that the child had at least 24 weeks of treatment trial, adherence to therapy has been assessed and considered to be adequate prior to considering switching to second-line regimen. Additionally, in considering changing treatment because of growth failure, it should be ensured that the child has adequate nutrition, and that any intercurrent infections have been treated and resolved.

[b] Clinical stages in this table refer to a new or recurrent stage at the time of evaluating the infant or child on ART.

[c] Where CD4 cell count/% is available, at least two CD4 cell measurements should be compared.

[d] Do not switch regimen if CD4 cell values are above age-related threshold for severe immunodeficiency.

[e] Age-related severe immunodeficiency values; if serial CD4 cell values are available, the rate of decline should be taken into consideration.

[f] Some T3 conditions (i.e. pulmonary or lymph node tuberculosis and severe recurrent presumed bacterial pneumonia) may need to be treated and the need to switch regimens decided based on re-evaluation of the child in question.

Table 18 : Recommended second-line regimens in infants and children in the event of treatment failure of first-line regimens			
Recommended 2nd line regimen: boosted PI component + 2 RTI components (NRTI/NNRTI)			
1st line regimen at failure	**Preferred 2nd line regimen**		
	Choose 2 new RTI components (NRTI/NNRTI)		**Choose 1 PI component[a]**
2 NRTI[b] + 1 NNRTI AZT or d4T + 3TC	ddI[c] + ABC	**plus**	Preferred: LPV/r[e] *or* SQV/r[f] Alternative: NFV[g]
ABC + 3TC	ddI[c] + AZT		
AZT or d4T + 3TC + ABC	ddI[c] + EFV[d] *or* NVP		

Notes:

[a] PI components are listed in order of potency/acceptability;

[b] Continuation of 3TC in second line regimens may be considered;

[c] ddI is not available in India at present. Till such time a suitable formulation of ddI is available, 3TC is to be continued even in a failing regimen. ddI does not need to be taken on an empty stomach in children;

[d] EFV is not currently recommended for children <3 years of age or < 10 kg, and should be avoided in post pubertal adolescent girls who are either in 1st trimester of pregnancy or are sexually active and not using adequate contraception;

[e] LPV/r is available co-formulated as solid and liquid; requires cold chain.

[f] SQV/r should not be used in children or adolescents weighing less than 25kg;

[g] Unboosted NFV may need to be used where no cold chain in place; for liquid LPV/r or SQV/r; it should be taken with food to improve bioavailability and high doses are needed in young children (e.g., >150 mg/kg per day).

SECTION

A10 Adherence Counselling and Monitoring

10.1 Preparing to start ART

- Starting ART is not an emergency.
- Starting ART when child/caregiver is not ready can result in poor adherence and ART resistance

Prepare caregiver

Care giver should be able to:

- understand natural history of HIV infection in children, benefits and side effects of ART;
- understand the importance of taking ART on time every day and able to ensure adherence to treatment;
- assume the primary responsibility to directly observe daily ARV intake of the child;
- assume the primary responsibility to ensure compliance in adolescents. Direct observation of drug intake may not be needed in adolescents. The care giver may allow the adolescent to be responsible for taking the ART.
- appropriately store ARV;
- correctly demonstrate mixing/measuring of the selected ART regimen; and
- afford ART and necessary laboratory monitoring as well as transportation to the hospitals in a sustainable manner (if self paid)

Prepare child

Children who know their HIV status (explanation is given by health care personnel according to child's maturity level) should be able to:

- understand natural history of HIV infection, benefits and side effects of ART
- understand the importance of taking ART on time every day and is able to adhere to treatment
- Children who do not know their HIV status should be explained why they need to take ART by using culturally- and age-appropriate explanations and by avoiding the words "HIV" or "AIDS". They should be:
  - ready and agree to take ART (depending on maturity but mostly in children > 6 years. Explanation is given by health care personnel according to child's maturity level); and
  - understand the importance of taking ART on time every day and is able to adhere to treatment

Agree on treatment plan

Caregiver/child and health care personnel agree on an ART regimen and follow up appointments that caregiver/child can adhere to

Assess treatment preparedness and factors that may affect adherence

- Assess caregiver/child's understanding of the reason for taking ART, anticipated treatment response, side effects of ART and how ART is taken (dose, time and food requirements)
- Assess likelihood and factors that may affect adherence and work with the caregiver/child in finding solutions for these anticipated problems.
- Assess readiness of HIV disclosure. HIV disclosure is not a prerequisite to start ART but disclosure is encouraged when caregiver is ready and child is deemed to be mature and can keep secrets. Preparation for and performing disclosure is a process that takes time. Health care personnel's role is to help prepare and support caregiver and child.

10.2 Ensuring long term adherence and good response to ART

A team effort of health care personnel, caregiver and child is required to ensure long term adherence and good response to ART

- It is important for health care personnel to understand the child/caregiver's problems and provide positive reinforcement.
- Taking ART on-time every day is not an easy task.
- Health care professionals should never reprimand caregiver/child for being non-adherent but rather work with them to solve issues affecting adherence.
- Child-focused counselling principles should be used. NACO/WHO is developing modules/ tools/charts for use in HIV in children particularly to support treatment adherence.

Reasons for non-adherence

(a) Missed doses

The health care worker (HCW) should ask about missed doses at every visit :

- Ask whether the child has missed any dose in the past 3 days and since the last visit
- Ask what times the child take ART
- Ask for reasons for non-adherence
- Missed doses may occur
  - If the dosing time is inconvenient/does not fit well with caregiver/child's lifestyle
  - if the regimen is hard to take because of high pill/ liquid load and bad taste
  - if there are ART supply issues (lack of money, inadequate ART prescribed)
  - if the child refuses to take the medicines (especially an older child who is tired of taking medications or who does not know his/her HIV status)

(b) Incorrect dosing

- HCW should check at every visit:
  - dosing of each ARV
  - preparation of each ARV
  - storage of each ARV
- HCW should check at every visit if the child needs an increase in dosing according to growth.

(c) Side effects

- Severe side effects should be taken seriously and treated promptly;
- Minor side effects that are non-life threatening can be easily overlooked and may be reason for non-adherence; and
- Lipodystrophy can cause adolescent to discontinue ART.

(d) Others

- There are many possible reasons why a child cannot adhere to treatment. Examples are a bad relationship between health care personnel and the family, OIs/other conditions and their treatments which cause the child to feel ill, a large pill burden and social issues – change of caregiver, primary caregiver is sick etc.

Proposed management

(a) Management

- Find out why ARV schedule cannot be adhered to:
  - Find out the time when doses are usually missed
  - Check reasons why doses are missed at that time
  - Work with the family to adjust towards a suitable schedule
  - Consider using tools such as a pill box and alarm clock
- Find out why the ARV regimen is hard to take
  - Work with the family in adjusting the regimen/ formulation.
  - Consider training the patient to swallow pills to decrease the volume of liquid.
- Find out if ARV supply is interrupted and why
  - Help the caregiver solve this problem
- Find out reasons for child refusing to take ART:
  - Counselling, especially peer group counselling can help reinforce adherence.
  - If the child does not know his/her HIV status and questions need to take ART, the HCW should work with the caregiver/child in preparing the child for disclosure of the HIV status.

(b) Management

- Consider using tools such as pill box.
- Written /pictorial cards with details of regimens.
- Go over the dosing and have the caregiver/child demonstrate preparing ART.
- Adjust dose according to weight/height.

(c) Management

- Side effects should be treated promptly regardless of their severity.
- The HCW needs to pay attention to minor side effects and how the child feels.
- If relevant, consider switching to an ART regimen that causes less lipodystrophy.

(d) Management

- The HCW needs to provide an environment that is supportive and friendly so that the caregiver/child can feel comfortable discussing reasons for non-adherence.
- Treatment of OI takes priority and stopping/modifying ART may be needed.
- Involving community and support groups, and providing support outside the clinic environment such as home visits, may help.

10.3 Disclosure for children

Disclosure of HIV diagnosis to infected children is a complex process that presents a challenge to both families and health care providers. Obstacles to disclosure of HIV diagnosis to children include:

- Fears regarding a decrease in the child's will to live
- Fears regarding retaliation or discrimination based on stigma
- Parental guilt about prenatal transmission of HIV infection
- Child's difficulty keeping a secret
- Parent's denial and/or difficulty confronting their own illness.

Disclosure of HIV infection status to children should take into consideration

- Their age, psychosocial maturity, the complexity of family dynamics, and the clinical context.
- The exact diagnosis and prognosis of the disease.
- Child's ability to cope with knowledge of life-threatening infection
- Child's circumstances- e.g. When informing school going children- discrimination in schools, communities, and families remains a serious problem.

Disclosure of HIV status to children should include continued counselling about disclosure and its impact, for both the child and parents. Disclosure may be partial or complete depending on the age and level of functioning of the child. Partial disclosure aims to describe what's happening to the body and what treatments will help to resolve this, rather than naming the virus or illness. Complete disclosure involves open discussion about the virus, infection, and all other issues relating the HIV infection. This must be done together with the child and parent/caregiver.

Counselling for disclosure is an ongoing process and the health care provider needs to work with the child on every visit. Ideally the caregiver should be the one to disclose information to the child. Disclosure to children should be done little by little, encouraging questions, providing truthful answers, and making the child understand they can come back with more questions at any time. Counselling the caregiver for guidance on disclosure of HIV status is important component of the counselling process. Counselling techniques used should be individualized, based on the child's age, maturity, clinical and social circumstances; and should facilitate the child's capacity to cope with their illness.

(Refer to Paediatric HIV Counselling Module, NACO.)

Age-specific advice on disclosure

Up to 2 years	2–3 years	3–5 years	6–9 years
• Talk to the child simply and naturally about his/her health. • Avoid transmitting anxiety to the baby through body language or voice tone.	• Be aware of children's sensitivity to adult's feelings through body language. • Talk openly and naturally about child's health without transmitting anxiety. • If the child is sick talk gently about his/her illness, and provide constant loving care.	• Stimulate questions by asking the child what s/he understands about having to go to the clinic, taking medicine, being often sick, and what s/he fears. • Listen carefully and answer truthfully and naturally, giving little information at a time, as the child seems ready to take it in. • Use simple language, such as "a virus (or germ) inside you that can make you sick", "medicine will make the body stronger to fight against the virus", "the same virus your mother has and sometimes make her sick". • Answer questions about dying: "everyone will die one day, no one knows when. Meanwhile all children need to look forward to playing, learning new skills, making friends and growing up". • Provide ongoing loving re-assurance and support. Tell the child that s/he can play with, hug and hold hands with other children without giving them the virus, and that if some adults seem afraid it is because they don't know enough about this. • In that case, advise the child to go back to playing with her friends.	• Start disclosure process as soon as possible, paying attention to non-verbal expressions of anxiety and dental. • Encourage and stimulate questions by the child. If the child does not ask questions, ask him about his fears. • Talk about the illness openly and simply, giving information a little at a time, as the child seems ready to take it in. • Provide information about the infection/ illness, its name, its causes and whether it will lead to death (see 3–5 yrs). • Explain that medicine will fight against the infection and make him/her feel better, but that it needs to be taken very regulary. • Reassure the child that s/he must lead a life like all children, and can go to school, play games, hold hands and hug other children without transmitting the infection.

SECTION A11

Nutrition in HIV-infected Infants and Children

Malnutrition is a common condition in HIV-infected children and is major contributor to mortality in both HIV-uninfected and HIV-infected children. In HIV-infected children, wasting (i.e. low weight for height/ length) has been associated with reduced length of survival, while weight loss has resulted in increased infectious complications in children with AIDS. Conversely, HIV has been associated with nutritional disorders, and immune status and level of viral replication may be important in predicting growth outcomes.

Growth (i.e. a composite of weight, length or height, and head circumference) is a sensitive indicator of optimal nutrition and of HIV disease progression. In HIV-infected children, severe growth problems (i.e. growth failure and severe malnutrition/wasting criteria for clinical stage 3 and 4 disease, respectively) not attributable to inadequate nutritional intake may point to the need for ART to be initiated. Growth is also useful in the evaluation of the response to ART. Conversely, potential adverse effects of ARV drugs or opportunistic infections may affect food intake and nutrition in general, with limited improvements in growth and/or adherence to therapy as a consequence.

Following is a brief summary of key nutritional interventions relevant to the care of HIV-infected infants and children before or during ART. For more details, refer to NACO guidelines on nutrition.

11.1 Nutritional assessment and support

In view of the close interrelationship between HIV infection, nutritional status and growth, it is strongly recommended that early nutritional intervention (i.e. nutritional assessment and support) should be an integral part of the care plan of HIV-infected children.

Nutritional assessment, i.e. the systematic evaluation of current nutritional status, diet and nutrition-related symptoms, is critical in the early identification of malnutrition and poor growth as well as in the monitoring of HIV disease progression and treatment efficacy for children on ART. As for all infants, HIV-infected infants should follow the below protocol:

- Be measured monthly, using the standardized growth curves.
- Thereafter, children should be weighed at each review and full nutritional assessments should be made every three months unless the child in question requires particular attention because of growth problems or special nutritional requirements.

A proactive approach to nutritional support in HIV-infected children is important because of the increased energy needs associated with the infection:

- In asymptomatic HIV-infected children, resting energy expenditure is increased by about 10%, while increases in energy needs of between 50% and 100% have been reported in HIV-infected children experiencing growth failure.
- Increased utilization and excretion of nutrients in HIV infection can lead to micronutrient deficiencies.

Nutritional support should thus include early efforts to continue exclusive breastfeeding until 6 months old if replacement feeding is not done; ensure adequate nutrient intake on the basis of locally available and affordable foods and a daily intake of micronutrients equivalent to one recommended daily allowance (RDA).

It is recommended

- To increase the energy intake of HIV-infected infants and children by 10% of the RDA for their age and sex if they are asymptomatic, and
- By 20–30% of the RDA if they are symptomatic or recovering from acute infections.

These requirements are considered minimal and more may be needed in children with nutritional deficiencies. Increased protein requirement exceeding that required in a balanced diet to satisfy the total energy requirements (12 to 15% of the total energy intake) is not needed.

For all HIV-infected children, the comprehensive approach is:

- Assess nutritional status and growth/ development
- Nutritional counselling for micro- and macro-nutrient deficiency, selection of locally available good foods (by trained dietician/ nutritionist, ideally)
- Ensure Vitamin A supplementation
- Counselling of mothers who are breastfeeding and of caregivers/children about food and water hygiene
- If necessary, refer to NGO nutrition support programme (if available), ideally for support for the family unit
- Counsel on selection of specific high-energy foods for children with conditions that interfere with normal digestion or ingestion (eg sore throat or mouth, oral thrush, diarrhoea) may help reduce suffering and ensure enough energy intake.

11.2 Severe malnutrition and ART initiation

Severe wasting is a common clinical presentation of HIV infection in children. All children with severe malnutrition are at risk for a number of life-threatening problems and urgently require therapeutic feeding. The phase of malnutrition treatment at which to start ART is not known. Expert opinion therefore suggests that HIV-infected children with severe malnutrition be stabilized before decisions are made on the initiation of ART.

The initial treatment of severe malnutrition lasts until the children have stabilized on this treatment and their appetites have returned. In HIV-uninfected children this initial phase should not take longer than 10 days, whereas experts suggest that in HIV-infected children the response to initial treatment of severe malnutrition may be delayed or very limited. Following successful initial treatment of severe malnutrition and any underlying infections or conditions, the children's clinical condition should be re-evaluated.

For ART initiation in HIV-infected children who are slow to improve on malnutrition treatment, a decision may be taken (either for inpatients or outpatients) at around 6-8 weeks if they have not achieved 85% weight for height (i.e. cure).

In children who rapidly gain weight because of adequate nutrition and ART, dosages of ARVs should be frequently reviewed. The recurrence of severe malnutrition that is not caused by a lack of food in children receiving ART may indicate treatment failure and the need to switch therapy.

SECTION

A12 Adolescent Issues in Care and Treatment

WHO considers adolescence as the period between 10 and 19 years of age, during which healthy adolescents pass through well-described stages of physical, psychological and sexual maturation that have implications for the provision of appropriate treatment and care.

There are distinct groups of HIV-infected adolescents who may require ART:

- Adolescents who have been infected around birth
- Those who become infected during adolescence.

12.1 Challenges with HIV-infected adolescents

Adolescents with perinatal infection who began ART during early childhood because of rapid progression of HIV disease have some years of contact with health services and are likely to have experienced various ARV treatments; their parents are often aware of their HIV status. In respect of these adolescents, challenges may relate mainly to:

- The disclosure of HIV status to them if this has not been done by their parents;
- Developmental delays;
- The transition from paediatric to adult care, including the choice of appropriate ARV regimens; and adherence.

HIV-infected adolescents (i.e. those infected around birth, as infants or young children) often face considerable physical challenges:

- They may experience delayed growth and development, often resulting in late puberty and, in girls, delayed or irregular menstrual cycles.
- Stunting and/or wasting caused by progressing HIV illness, frequently exacerbated by malnutrition, may further complicate decision-making on whether to follow ARV treatment guidelines for adults or children.

12.2 Considerations in ART specific to adolescents

WHO recommends basing the choice of ARV regimens and dosages for adolescents on sexual maturity rating (i.e. Tanner staging, annex 12):

- Adolescents in Tanner stage I, II or III should be started on the paediatric schedule and should be monitored with particular care because they are at the time of hormonal changes associated with the growth spurt.
- Adolescents in Tanner stage IV or V are considered to be adults and the same recommendations as for adults.

In considering ART initiation and regimen in adolescent, several issues to consider:

- Maturity (as above)
- Simplify the treatment regimen
- Need to anticipate long term adherence and full psycho-social support
- Use of EFV in adolescent girls (who may be at risk of pregnancy)
- Use of NVP in females: Symptomatic NVP-associated hepatic or serious rash toxicity,

while uncommon, is more frequent in females than in males, and is more likely to be seen in antiretroviral-naive females with higher absolute CD4 cell counts (>250 cells/mm3). NVP should therefore be used with caution in adolescent girls with absolute CD4 counts between 250 and 350 cells/mm3; if used in such adolescent girls, careful monitoring is required during the first 12 weeks of therapy, preferably including liver enzyme monitoring. In situations where both EFV and NVP should not be included in first-line regimens for adolescent girls the use of a triple NRTI regimen may be indicated.

Adherence to long-term therapy is particularly difficult among adolescents. In addition to providing routine adherence assessment and support, health care providers may want to consider issues that are particularly relevant to adolescents and impair optimal adherence to ART

- possibly including the adolescents' perception of being immortal
- their desire for independence
- lack of disclosure of HIV status and stigma.

The parents of adolescents who have become infected as infants or young children may find it hard to share the diagnosis of HIV with their children because of fear of stigma or blame from their own children. However, without this knowledge it is impossible for adolescents to progress completely through the transition process into adult care. Sharing this diagnosis with peers is difficult for adolescents who are aware of their HIV status. For these reasons it is especially important that young people:

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

Simple ARV regimens will maximize adherence. Hence, it is important to establish a mutual trusting relationship between the child/adolescent and the counselor/physician.

SECTION

A13 Palliative Care in Children

13.1 What is palliative care: principles

WHO defines palliative care as an "approach which improves the quality of life of patients and their families facing life-threatening illness, through prevention, assessment, and treatment of pain, psychological and spiritual problems".

Eight guidelines by WHO describes what palliative care should, and should not, aspire to accomplish. These guidelines describe that palliative care:

- Provides relief from pain and other distressing symptoms
- Affirms life and regards dying as a normal process
- Intends neither to hasten nor postpone death
- Integrates the psychological and spiritual aspects of patient care
- Offers a support system to help the patient live as actively as possible until death
- Offers a support system to help the family cope during the patient's illness and in their own bereavement
- Uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated
- Will enhance the quality of life, and may also positively influence the course of illness

Palliative care, whether provided in resource-rich or limited settings, is multi-disciplinary.

13.2 Palliative care in children

Palliative care for children represents a special, albeit closely related field to adult palliative care. WHO's definition of palliative care appropriate for children and their families is as follows; the principles apply to other paediatric chronic disorders (WHO 1998):

- Palliative care for children is the active total care of the child's body, mind and spirit, and also involves giving support to the family.
- It begins when illness is diagnosed, and continues regardless of whether or not a child receives treatment directed at the disease.
- Health providers must evaluate and alleviate a child's physical, psychological, and social distress.
- Effective palliative care requires a broad multi-disciplinary approach that includes the family and makes use of available community resources; it can be successfully implemented even if resources are limited.
- It can be provided in tertiary care facilities, in community health centres and even in children's homes.

Palliative care in HIV-infected children may be needed from infancy and for many years for some children, while others may not need it until they are much older and for a shorter time period. Also, transition between aggressive treatment to prolonging quality of life and palliative care may not be clear.

13.3 Essential components in palliative care for children

Care and support as below is integral to palliative care:

- Prevention of opportunistic infections (cotrimoxazole prophylaxis)
- Relief of symptoms and the management of pain need to continue, even when the option to stop ART may have to be considered.
- Establishing a mutual trusting relationship between the child and family with the clinical team (counselor/paediatrician/nurse/NGO volunteer etc)

Child development: physical, emotional and cognitive development influences all aspects of care from drug dosages to communication skills and understanding of their disease and of death.

Care at home: most children are cared at home. If the parent (if still alive) is present, the family unit needs to be given support and be taught appropriate skills.

Assessing symptoms in children: Healthcare providers must provide an environment where children:

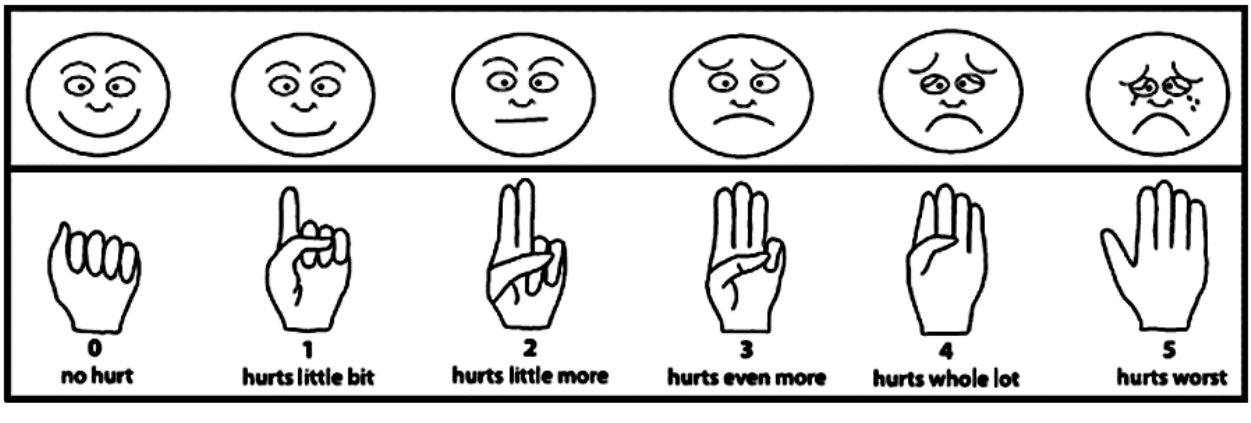
- Do not fear repercussions from their honest expressions (especially if there is an authority figure like doctors/parents)
- Understand that there is possibility to reduce pain, if present
- Learn to trust providers and express future feeling and symptoms

Pain and symptom management: Symptoms and pain are a major cause of discomfort and poor quality of life during the course of HIV infection in infants and children. Many of these symptoms can be prevented, treated or controlled with basic medications and therapies. Non-pharmacological methods are an important adjuvant to symptom management. Efforts to identify the cause of symptoms and pain should be pursued as much as possible, without adversely affecting the quality of the child's life and within the limits of available resources. Symptoms and related pain should be anticipated and prevented to the extent possible.

There are various ways of assessing pain such as by body chart, face scale (as below), numeric scale, color tools, visual analog scale and observation of behavior. Usually, a combination of all these can be done together with information from parents/ caregivers. This may be more difficult in preverbal and developmentally delayed children.

Pain control and analgesia is an essential component in reducing suffering in a child. Various options include using paracetamol, NSAID, codeine etc.

Feeding issues: Inability of nourish the child causes parents (and healthcare providers) distress as it would seem that they are failing to care for the child. Sucking and eating are part of the child's development and provide comfort, pleasure and stimulation. Issues include difficulty with eating (eg. nausea and vomiting), ensuring adequate caloric, nutrient /vitamins and protein intake.



Simplified tool for assessing pain in children

13.4 Supporting family and child

Families need support from the time of diagnosis to treatment and for terminal care (end of life). Each family is unique with different strengths and coping skills. Parents/caregivers go through various emotional difficulties especially for the terminal stage of disease and for issues relating to stopping treatment (ART). Open communication with the dying child is best, with use of play material, support from counselors/psychologist/community-based organizations and other resources.

Sick children need to be given the opportunity to maintain their interests (including education) and have short-term goals as long as possible, before death ensues. Peer group interaction maintains their interests in life and 'normal' living.

13.5 Bereavement

Grief after death of the child is described as most painful and enduring. Parents and caregivers suffer multiple losses. Siblings and peers (friends of the similar age) may have difficulty adjusting with both the death, and of parents who may not have time for them. Support from healthcare providers and community-based organizations and peer groups are crucial during this period.

SECTION B

Management of Opportunistic Infections in Infants and Children

SECTION

B1

Management of Opportunistic Infections in HIV Children

Comprehensive care of HIV-infected children include:

- Early diagnosis of HIV in children
- Early identification and diagnosis of opportunistic infections
- Effective prevention and management of opportunistic infections
- Early initiation of ART to prevent OI
- Cotrimoxazole (CTX) prophylaxis for OI prevention
- Immunization for vaccine preventable diseases
- General prevention advice for caregivers such as handwashing, drinking clean water, washing of raw fruit and vegetables before consumption
- Nutritional counselling and ensuring good diet.
- Psycho-social support and counselling support to ensure adherence
- Involvement of family and gradual disclosure to child as appropriate to maturity and understanding
- Continuum of care and support for children and infants not yet requiring ART

Tables 19-21 summarizes the management of OIs common in HIV-infected children

Table 19: Summary of clinical diagnosis and management of common opportunistic infections in HIV-infected children[i]

Opportunistic infection	Clinical and laboratory manifestations	Diagnosis	Treatment
***Mycobacterium avium* complex (MAC)**	Fever, night sweats, weight loss, fatigue, chronic diarrhoea and abdominal pain. Laboratory findings: neutropenia, elevations in alkaline phosphatase or lactate dehydrogenase.	Definitive diagnosis: isolation of organism from blood or specimens from normally sterile sites. Histology demonstrating macrophages-containing acid-fast bacilli is a suggestive finding.	ART should be provided to restore immune function. **Treatment with at least 2 drugs:** Clarithromycin 7.5-15 mg/kg twice daily (max 500 mg/dose) plus ethambutol 15-25 mg/kg/day once daily (max 1 g/dose). Consider adding a third drug e.g. amikacin or ciprofloxacin in severe cases. Duration of treatment: at least 12 months

[i] Modified from Treating Opportunistic Infections Among HIV-Exposed and Infected Children-CDC, NIH and IDSA recommendations- December 3, 2004 (www.aidsinfo.nih.gov)

Opportunistic infection	Clinical and laboratory manifestations	Diagnosis	Treatment
Pneumocystis jiroveci **pneumonia (PCP)**	Dry cough, tachypnea, dyspnea, cyanosis	**Chest X-ray:** bilateral diffuse parenchymal infiltrates with "ground-glass" or reticulo-granular appearance. Associated with a high level of lactate dehydrogenase (LDH). Microscopy of induced sputum by bronchoalveolar lavage (BAL): GMS stain- stains cyst wall in brown or black, Wright stain: stains the trophozoites and intracystic sporozoites in pale blue.	TMP/SMX 15-20 mg/kg/day of TMP in 3-4 divided dose for 21-day course Steroids eg. prednisolone can be used for severe acute PCP *For alternative regimens: refer to section B2.1 on PCP.*
Candidiasis	**Oral candidiasis:** creamy white curd-like patches that can easily be scraped off with inflamed underlying mucosa. **Esophageal candidiasis:** odynophagia, dysphagia, and/or retrosternal pain.	**Oral candidiasis:** KOH preparation demonstrates budding yeast cells. **Esophageal candidiasis:** Barium swallow show cobblestone appearance. Endoscopy show small white raised plaques to elevated confluent plaques with hyperemia and extensive ulceration.	**Oral candidiasis** Clotrimazole oral 10 g or Nystatin 400,000 600,000 units 5 times daily 7–14 days. *or* Oral fluconazole 3-6 mg/kg once daily 7–14 days. **Esophageal candidiasis** Oral fluconazole 3-6 mg/kg once daily 14–21 days.
Penicilliosis	Persistent fever, anemia, hepatomegaly, generalized lymphadenopathy and translucent umbilicated papules which may resemble molluscum. Laboratory finding: anemia, and/or thrombocytopenia	**Definitive diagnosis:** isolation of organism from blood, bone marrow aspiration or specimens from normally sterile sites. Wright stain of skin scraping shows basophilic, spherical or oval yeast-like organisms with clear central septation (diameter 3-8 μm)	**Induction therapy:** Amphotericin B (0.7-1.5 mg/kg/day) for 2 weeks. **Consolidation therapy:** Itraconazole 5-6 mg/kg/dose twice daily for 8 weeks. **Maintenance therapy:** Itraconazole 3-6 mg/kg/day.
Cryptococcosis	**Meningoencephalitis manifestation:** fever, headache, altered mental status, nuchal rigidity **Disseminated manifestation:** persistent fever with translucent umbilicated papules which may resemble molluscum.	Elevated intracranial pressure and elevated CSF protein and mononuclear pleocytosis. India ink stain of CSF should show budding yeast. Cryptococcal antigen can be detected in CSF or serum by latex agglutination test. Wright stain of skin scraping shows budding yeast.	**Induction therapy:** Amphotericin B (0.7-1.5 mg/kg/day) plus flucytosine (25 mg/kg/dose four times daily) for 2 weeks. **Consolidation therapy:** Fluconazole 5–6 mg/kg/dose twice daily for 8 weeks. **Maintenance therapy**: Fluconazole 3–6 mg/kg/day.

Opportunistic infection	Clinical and laboratory manifestations	Diagnosis	Treatment
Herpes simplex	**HSV gingivostomatitis:** fever, irritability, superficial painful ulcers in the gingival, oral mucosa and perioral area. **HSV encephalitis:** fever, alteration of consciousness, abnormal behavior.	HSV gingivostomatitis is diagnosed by clinical evaluation. HSV encephalitis is diagnosed by detection of HSV DNA in the CSF.	**HSV gingivostomatitis:** oral acyclovir 20 mg/kg/dose three times daily *or* intravenous acycolovir 5-10 mg/kg/dose three times daily for 7-14 days. **Disseminated HSV or encephalitis:** intravenous acyclovir 10 mg/mg/dose or 500 mg/m2/dose three times daily for 21 days.
Herpes zoster virus	**Primary varicella infection:** Generalized pruritic vesicular rash. **Herper zoster:** Painful rash with fluid-filled blisters, dermatomal distribution.	Use clinical diagnosis. If clinical diagnosis is not clear then Giemsa staining (Tzanck preparation) of cell scrapings from lesions can be done. show multinucleated giant cells suggestive of VZV (Note that this is also seen in HSV infection).	**Primary varicella infection:** intravenous acyclovir 10 mg/ mg/dose or 500 mg/m2/dose three times daily for 7 days in children with moderate to severe immuno-suppresion. Oral formulation should be used only in a child with mild immunosuppression. **Herper zoster:** Oral acyclovir 20 mg/kg/dose four times daily (max 800 mg/ dose) for 7 days
Cytomegalovirus infection	**CMV retinitis:** Young HIV-infected children are frequently asymptomatic and discovered on routine examination. Older children present with floaters or loss of vision. Extraocular CMV disease: CMV colitis, CMV esophagitis, CMV pneumonitis, CMV hepatitis.	Diagnosis of CMV retinitis is based on clinical appearance with white and yellow retinal infiltrates and associated retinal hemorrhages. Extraocular CMV disease: recover of virus from tissues or histopathology demonstrates characteristic “owl’s eye” intranuclear inclusion bodies or positive staining with CMV monoclonal antibodies in biopsy specimens.	Ganciclovir intravenous 5 mg/kg/dose twice daily for 14-21 days followed by lifelong maintenance therapy.
Cryptosporidiosis	Subacute or chronic watery diarrhoea often associated with cramps, nausea and vomiting	Modified Kinyoun acid-fast stain of stool: small oocyst (4–6 μm in diameter)	Effective ART is the only treatment that controls persistent cryptosporidiosis. Supportive care with hydration, correction of electrolyte abnormalities, and nutritional supplementation. Nitazoxanide is approved for treatment (age 1–3 years 100 mg twice daily, age 4–11 year 200 mg twice daily)

Table 20: Summary of guidelines for Primary OI prophylaxis in children		
Organism	**When to give treatment**	**Drug regimen**
PCP	**For HIV-exposed children:** CTX prophylaxis is universally indicated, starting at 4-6 weeks after birth and maintained until cessation of risk of HIV transmission (breast-feeding) and exclusion of HIV infection. **For children with confirmed HIV** • Age < 1 year: CTX prophylaxis indicated regardless of CD4 percent or clinical status. • Age 1-5 years: WHO stages 2, 3 & 4 regardless of CD4% • Any WHO stage and CD4 <25% • Age ≥ 6 years: Any WHO clinical stage and CD4< 350 cells/mm^3 • WHO stage 3 or 4 and any CD4 cell level	**Cotrimoxazole** suspension (200mg SMX, 40mg TMP), pediatric tab (100mg SMX, 20mg TMP), single strength adult tab (400mg SMX, 80 TMP) **Recommended** < 6 months: 2.5 ml suspension or 1 paed tab or 1/4 Single Strength adult tab 6 month-5 years: 5 ml suspension or 2 paed tabs or 1/2 Single Strength adult tab 6 -14 years: 10ml suspension or 4 paed tabs or 1 Single Strength adult tab > 14 years: 2 Single Strength adult tab (or 1 double strength adult tab) **Alternative** 1. Dapsone 2 mg/kg once daily *or* 2. Dapsone 4 mg/kg once weekly
TB	All children who are exposed to active TB cases, particularly household contacts, regardless of CD4 cell count/% (Need to exclude clinical disease by physical examination and CXR)	For known INH-sensitive strain or unknown **Recommended by RNTCP programme:** INH prophylaxis for children < 6 yr in close household contact to be given for 6 months; 5mg/kg/daily
MAC	CD4 count<50 in > 6 year-old CD4 count < 75 in 2-6 year-old CD4 count < 500 in 1-2 year-old CD4 count< 750 in < 1 year-old Stop when CD4 count level above threshold for > 3 months	**Recommended** 1. Clarithromycin 7.5 mg/kg/dose (max 500 mg) twice daily *or* 2. Azithromycin 20 mg/kg (max 1200 mg) once weekly **Alternative** Azithromycin 5 mg/kg (max 250 mg) once daily

Table 21: Summary of guidelines for Secondary Prophylaxis to prevent recurrence of opportunistic infections in children		
Opportunistic Infection	**When to give treatment**	**Drug regimen**
PCP	Children who have a history of PCP should be administered prophylaxis for life to prevent recurrence. The safety of discontinuing secondary prophylaxis among HIV-infected children has not been studied extensively.	As for primary prophylaxis
TB	Not recommended	
MAC	Children with a history of disseminated MAC should be administered lifelong prophylaxis to prevent recurrence. The safety of discontinuing secondary prophylaxis among HIV-infected children has not been studied extensively.	**Recommended** Clarithromycin 7.5 mg/kg/dose (max 500 mg) twice daily plus ethambutol 15 mg/kg/dose (max 800 mg) daily **Alternative** Azithromycin 5 mg/kg/dose (max 250 mg) plus ethambutol 15 mg/kg/dose (max 800 mg) daily
Cryptococcus neoformans and Coccidiodes immitis	Children who have a history of cryptococcal meningitis should be administered prophylaxis for life to prevent recurrence. The safety of discontinuing secondary prophylaxis among HIV-infected children has not been studied extensively.	**Recommended** Fluconazole 3-6 mg/kg/once daily **Alternative** Itraconazole 2-5 mg/kg once daily
Histoplasma capsulatum and Penicillum marneffei	Children who have a history of histoplasmosis/peniciliiosis should be administered prophylaxis for life to prevent recurrence. The safety of discontinuing secondary prophylaxis among HIV-infected children has not been studied extensively.	Itraconazole 2-5 mg/kg once daily
Toxoplasma gondii	Children who have a history of cerebral toxoplamosis should be administered prophylaxis for life to prevent recurrence. The safety of discontinuing secondary prophylaxis among HIV-infected children has not been studied extensively.	**Recommended** Sulfadiazine 85–120 mg/kg/day divided into 2-4 times/day plus pyrimethamine 1 mg/kg (max 25 mg) once daily plus leucovorin 5 mg every 3 days **Alternative** Clindamycin 20–30 mg/kg/day in 4 divided doses daily plus pyrimethamine and leucovorin as above Alternative TMP-SMX 8–10 mg/kg to be checked

Details of each condition is as in sections B2–B3

SECTION

B2 Opportunistic Infections – Bacterial, Fungal, Protozoal

B2.1 Pneumocystis pneumonia (PCP)

Suspect PCP if the child is:

- < 12 months old
- Has tachypnea [> 50 breaths/min in children aged 2 – 12 months ; 40 breaths/min in children aged 12 months – 5 years]
- Is dyspneic
- Has cyanosis (in advanced stage)
- Has few crepitations relative to the degree of cyanosis

Most common OI in infants (< 1 year of age) with high mortality rate of 35%. It is caused by **Pneumocystis jiroveci** (for the human strain). P. carinii is now referred to the organism found in rats. PCP is a common AIDS - defining illness.

Pathogenesis

PCP is usually acquired in childhood. Serum antibodies are found in over 80% of children by 4 years of age. In immuno-competent infants, it may lead to mild respiratory symptoms or children are usually asymptomatic. In immuno-deficient individuals it infects the alveoli leads to interstitial edema and results in progressive hypoxemia and respiratory failure. Extrapulmonary manifestation is rare in children and includes ear, eye, thyroid, spleen, GI tract, peritoneum, liver, pancreas, bone marrow, meninges, heart and muscle.

Clinical features

Most of the patients present with acute onset of tetrad of symptoms of fever, tachypnea, dyspnea and cough. On examination, there may be bilateral basal crepts with respiratory distress and hypoxia. Insidious onset of cough and dyspnea may be seen in older children.

Investigations

1. X-ray chest
2. Arterial blood gas
3. Lactic dehydrogenase (Serum LDH)
4. Demonstration of organism by gastric lavage / sputum / bronchoalveolar lavage (BAL) / bronchoscopy with transbronchial biopsy or open lung biopsy.

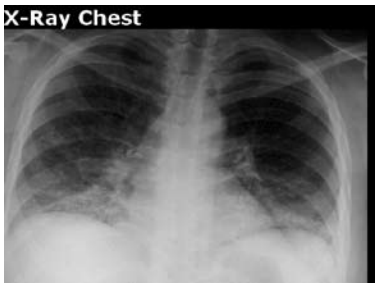
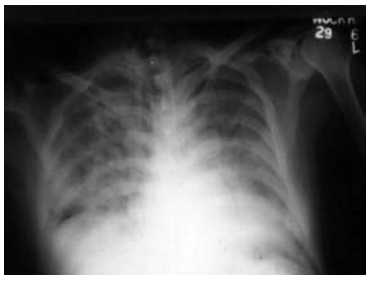
X-Ray Chest  	• Common findings - Bilateral diffuse parenchymal infiltrates with "ground-glass" or reticulo-granular appearance. • Mild parenchymal infiltrates predominantly perihilar and progressing peripherally to reach the apical portion of the lung. • Rarely - Lobar, cavitatory or miliary lesions - Pneumothorax or pneumomediastinum.
Arterial blood gas	Hypoxia with low arterial oxygen pressure.
Lactate dehydrogenase:	LDH is usually increased but not very specific. However it may be of utility when combined with arterial blood gas. In a child with respiratory distress, hypoxia and high LDH, one may strongly suspect PCP.
Demonstration of organism:	• Induced sputum after nebulization with 3% hypertonic saline: -Difficult to induce sputum in children < 2 years and may cause nausea, vomiting and bronchospasm. • Bronchoscopy with bronchoalveolar lavage: Sensitivity is more than that of gastric lavage or sputum examination. Results may be positive even 72 hours after PCP treatment has been initiated. Complications include hemoptysis, pneumothorax, and transient hypoxemia. • Fiberoptic bronchoscopy with transbronchial biopsy: Recommended only if BAL is negative. Cysts can be identified upto 10 days after initiation of treatment. Complications are pneumothorax and hemorrhage. • Open lung biopsy: Requires thoracotomy and chest tube drainage. Not routinely recommended. Complications are Pneumothorax, pneumomediastinum and hemorrhage. It is the most sensitive diagnostic test.
Stains	• Gomori's methenamine – Silver stain: stains the cyst wall brown or black. • Toluidine blue: stains the cyst wall blue or lavender. • Giemsa or Wright stain: stains the trophozoites and intracystic sporozoites pale blue with a punctate red nucleus. Does not stain the cyst wall. • Monoclonal immunoflorescent antibodies: stains the cyst wall. Most specific compared to other methods.

Table 22: Treatment of PCP			
Drugs	**Dosing**	**Side Effects**	**Remarks**
TMP/SMX	15-20 mg/kg of TMP IV/PO in 4 divided doses for 21 days If the acute symptoms resolve and child has no malabsorption, intravenous route may be substituted by oral treatment with same dose of TMP/SMX can be given to complete the 21 day course.	**Adverse effects:** Erythema Multiforme, Stevens Johnson syndrome (SJS), bone marrow suppression, hepatitis and interstitial nephritis. For mild rash, TMP/SMX can be temporarily discontinued and restarted when rash resolves. If SJS occurs, it should be discontinued and not restarted.	Drug of choice Shift to oral administration as soon as clinical improvement occurs
Primaquine/ Clindamycin	Primaquine base 0.3 mg/kg OD PO (max 30 mg/day) + Clindamycin 10 mg/kg IV or PO every 6 hours (max: 600 mg IV, 300-450 mg PO) for 21 days Oral clindamycin can be substituted after 10 days of IV therapy.	Primaquine is contraindicated in patients with G-6-PD deficiency. It can be used as alternative therapy in patients in who TMP/SMX treatment fails or causes adverse effects. **Adverse reactions:** Skin rash, nausea and diarrhoea.	Alternative therapy Data in children not available
Dapsone/ Trimethoprim	Dapsone – 2 mg/kg/day OD PO + Trimethoprim 15 mg/kg/day in 3 divided doses PO for 21 days	Reversible neutropenia, skin rash, elevated liver enzymes, anemia and thrombocytopenia.	Limited data in children Alternative therapy
Steroids (Adjuvant therapy)	Prednisolone Day 1-5 – 2 mg/kg/day PO BD Day 6-10 – 1 mg/kg/day PO Day 11-12 – 0.5 mg/kg/day PO *or* IV/IM Dexamethasone 0.3-0.5 mg/kg 6 hourly for 5 days IV Methyl Prednisolone may be used as an alternative	**Indications for corticosteroids:** Early use of corticosteroids decreases mortality due to acute respiratory failure and decreases need for ventilation. It is indicated if the PaO2 < 70 mm Hg at room air	**Indications** PaO2 <70 mm of Hg at room air

Prophylaxis for PCP in children:

The recommended dose for prophylaxis is trimethoprim 5 mg/kg/day daily as a single dose. Cotrimoxazole prophylaxis is useful to prevent PCP, recurrent bacterial infections, toxoplasmosis, isospora and cyclospora infections

(Refer to section A2 above for Cotrimoxazole Prophylaxis.)

B2.2 Recurrent bacterial infections

Common bacterial infections seen are:

- Pneumonia
- Sepsis
- Abscesses
- Otitis media
- Osteomyelitis and septic arthritis
- Meningitis

Common organisms are:

- Streptococcus pneumoniae
- Hemophilus influenzae type b
- Staphylococcus aureus
- Escherichia coli
- Pneumococcus

Others: Gram negative bacteria such as Pseudomonas aeruginosa, salmonella etc.

<table>
<tr><td colspan="2">Clinical features: Depends upon the site of infection. HIV infected children with bacterial infections usually have a similar clinical presentation as those without HIV infection. However, the severity of the disease may be more and response to standard duration of antibiotics may be poor.</td></tr>
<tr><td>Diagnosis: The methods of diagnosis essentially remain the same as that of an uninfected child. Isolation of organism by culture is essential.</td><td>Treatment: Treatment should be as per the local epidemiologic prevalent strain and sensitivity pattern. If an organism is isolated, then antibiotic susceptibility testing should be performed and therapy based on sensitivity pattern. Longer duration of therapy may be required to cure the infection.</td></tr>
<tr><td colspan="2">Prevention of Bacterial Infections
• TMP-SMX prophylaxis
• Immunization as per Annex 15</td></tr>
</table>

B2.3 Tuberculosis (TB)

If there is any patient with tuberculosis then all exposed family members should be screened for TB.

Suspect TB if the child has:

- Contact with adult who has pulmonary TB
- Fever and/or cough for more than 3 weeks
- With or without weight loss or poor/no weight gain.
- Pneumonia not responding to antibiotics
- Recent glandular enlargement

There is an increased risk of tuberculosis among HIV – infected children with co-infection occurring in up to 48% of children with culture-proven TB. Extra-pulmonary and miliary TB are more common among younger children. **Diagnosis should be based on a combination of clinical presentation, sputum examination wherever possible, Chest XR (PA view), Mantoux test (1 TU PPD RT23 with Tween 80, positive if in duration >5 mm after 48-72 hours) and history of contact.**

Clinical features

Pulmonary TB: May be non-specific symptoms such as fever, weight loss, failure to thrive and cough. Features of presentation in HIV infected children are similar to those among non-HIV infection.

Young children present with localized pulmonary infiltrates with hilar adenopathy. 25% of children may have more than 1 lobe involved. Middle lobe collapse and consolidation may result due to endobronchial tuberculosis. Older children and adolescents may present with cavitatory tuberculosis.

Extrapulmonary TB: Common sites involved are lymph nodes, Disseminated TB, CNS TB, Bone TB and TB of the serosal surfaces. With disease progression of HIV, atypical features of TB are more common

Investigations

- **Mantoux test / MT (Tuberculin test):-** Can be done from 3 months onwards using 5 TU PPD injected intradermally. Induration more than 5 mm is considered positive in HIV infected children. However, negative test may be seen in over 50% of children with tuberculosis. Thus, a negative test does not exclude TB.
- **Gastric lavage/ sputum examination:** Though acid fast stained sputum smears are positive in 50-70% of adults with Pulmonary TB, children with TB disease rarely produce sputum voluntarily and have a low bacterial load. Three consecutive morning gastric aspirates have a better yield than a single sample. Better diagnostic yield is seen on culture.
- **Other fluids and tissues for culture:** Bronchoalveolar lavage (BAL), lung biopsy, lymph node biopsy, serosal fluids and CSF. Specimens should be cultured for 2-6 weeks by radiometric culture methods (Bactec) or culture on L-J medium for 8 weeks. Antimycobacterial drug sensitivity should be done on the initial positive culture if treatment fails or relapse occurs. If no organism is isolated from the specimen of the child, drug sensitivity test can be done on the isolate from the source case.
- **Chest X-ray:**
  - Localized pulmonary infiltrates with hilar adenopathy
  - Middle lobe collapse and consolidation
  - Pleural effusion
  - In older children – cavitatory tuberculosis.
- PCR assays are not useful as primary diagnostic tool because a negative PCR does not rule out TB and a positive result does not absolutely confirm M.tuberculosis infection. Also false positive rates are high with sensitivity ranging from 45-83%. Serological tests for TB are not very specific.

DOTS is the recommended strategy for treatment of TB in all paediatric patients, and should be registered under RTNCP.

Drug resistance TB is increasing and thus a high index of suspicion is necessary especially in HIV-TB children who do not respond well to ATT with good adherence. It is recommended that these cases should be referred to the DOTS Microscopy centre, which is putting in place its MDR-TB programme nationally.

(See annex 10 : diagnostic algorithm for Paediatric pulmonary TB)

Table 23: Drugs used for the treatment of tuberculosis (from RNTCP guidelines for paediatric TB)

Drug	Dosage	Adverse Effects	Remarks
INH	10-15 mg/kg /day PO OD	Hepatotoxicity, peripheral neuritis, mild CNS effects Hypersensitivity reaction	Pyridoxine is recommended in children in all symptomatic HIV disease
Rifampicin	10 mg/kg/day PO OD	Stains urine, tears, sweat, contact lenses and other body fluids orange. GI upset, skin rash, hepatitis, thrombocytopenia, cholestatic jaundice	Rifampicin accelerates clearance of PIs and NNRTIs resulting in sub therapeutic levels of the drug
Pyrazinamide	30 -35 mg/kg/ day PO OD	Hepatotoxicity, hyperuricemia, arthralgia, skin rash, GI intolerance	
Ethambutol	30 mg/kg/day PO OD	Optic neuritis, colour blindness, headache, nausea, peripheral neuropathy, rash, hyperuricemia	Monthly evaluation of vision is recommended
Streptomycin	15 mg/kg/day IM	Ototoxicity and nephrotoxicity	

Table 24: Recommended treatment regimens under RNTCP

Category of treatment	Type of patients	Type of patients	
		Intensive Phase	Continuation Phase
Category I	New sputum smear-positive PTB* New sputum smear- negative PTB, Seriously ill * Extra-pulmonary TB (EPTB), seriously ill*	2 $H_3R_3Z_3E_3$***	4 H_3R_3
Category II	Sputum smear-positive relapse Sputum smear-positive treatment failure Sputum smear-positive treatment after default	2 $S_3H_3R_3Z_3E_3$ + 1 $H_3R_3Z_3E_3$	5 $H_3R_3E_3$
Category III	New sputum smear-negative,not seriously ill ** New extra-pulmonary TB, not seriously ill **	2 $H_3R_3Z_3$	4 H_3R_3

* In seriously ill children, sputum smear negative PTB includes all forms of sputum smear-negative PTB other than primary complex. Seriously ill EPTB includes TB meningitis (TBM), disseminated TB, TB pericarditis, TB peritonitis and intestinal TB, bilateral extensive pleurisy, spinal TB with or without neurological complications, genitor-urinary TB, and bone and joint TB.

** Not seriously ill sputum smear-negative PTB includes primary complex. Not seriously ill EPTB includes lymph node TB and unilateral pleural effusion.

** The number before the letters refers to the number of months of treatment (prefix). The subscript after the letters refers to the number of doses per week.
In patients with TB on Category 1 treatment, 4 drugs used during the intensive phase should be HRZS (instead of HRZE). Continuation phase of treatment in TBM and spinal TB with neurological complications should be given for 6-7 months, thus extending the total duration to 8-9 months. Steroids should be used initially in hospitalized cases of TBM and TB pericarditis and reduced gradually over 6 -8 weeks

Table 25: Induction and continuation phase of ATT			
	Duration	**Drugs**	**Dosage**
Induction phase	2 months	INH Rifampicin Pyrazinamide Ethambutol	10 mg/kg/day (max 300 mg) 10–20 mg/kg/day (max 600 mg) 30 mg/kg/day (max 2 gm) 15 mg/kg/day (max 1 gm)
Continuation phase	7-10 months (7 months for pulmonary TB and 10 months for extra pulmonary TB	INH Rifampicin *or* INH Rifampicin	10 mg/kg/day (max 300 mg) 10–20 mg/kg/day (max 600 mg) 20–30 mg/kg/day 3 times a week (max 900 mg/day) 10–20 mg/kg/day 3 times a week (max 600 mg/day)

Prophylaxis of tuberculosis

- All household contacts of smear-positive TB cases, especially those below 6 years old, must be screened for symptoms of TB. If symptomatic, the diagnostic algorithm for paediatric TB should be followed and child should get full course if TB treatment.
- For asymptomatic children and those found not be positive for TB, chemoprophylaxis with INH should be given. This is regardless of BCG vaccination.
- No secondary prophylaxis for TB.
- Regimen – 6 months of INH - 5 mg/kg daily

(Refer to annex 10 for algorithm for diagnosis of TB in children and for clinical monitoring)

Drug Interactions: ATT and antiretroviral drugs

Rifampicin induces hepatic cytochrome P450 enzymes and accelerates clearance of drugs such as PIs and NNRTIs resulting in sub-therapeutic levels of the drug. Thus, concurrent administration of rifampicin and single PIs excepted boosted PI is not recommended. Also concomitant administration of rifampicin with efavirenz (and also nevirapine) is possible with dose adjustment. Rifabutin can be used as an alternative to Rifampicin for children on ART, but is not available in India.

Refer to annex 5 for drug interactions with ARVs

In children with HIV and TB co-infection, periodic monitoring of liver enzymes is advised. Mild elevations in serum transaminases (e.g. 2–3 times upper limit of normal) does not require discontinuation of the drugs. All patients should be monitored monthly for clinical and bacteriological response. For patients with pulmonary TB, chest X-rays should be obtained after 2-3 months of therapy to evaluate response. Hilar adenopathy might persist for as long as 2-3 years despite successful ATT and is not a criteria for continuation of ATT.

Adjunctive use of steroids is indicated in patients with TB meningitis, serosal TB, miliary TB and endobronchial tuberculosis.

Drug resistant-TB in children

For children who are not responding to treatment and are categorized as treatment failure according to the RNTCP/IAP guidelines, refer these children to paediatricians at medical college/ Regional Pediatric centre, for further management. It is not recommended to treat multi-drug resistant TB (MDR-TB) in private settings or at primary level as the treatment duration is 2 years involving multiple costly drugs and strict supervision is required.

B2.4 Mycobacterium Avium Complex (MAC)

MAC refers to various non-tuberculous mycobacteria such as M. avium, M. intracellulare, and M. paratuberculosis. MAC can appear as isolated lymphadenitis among HIV infected children. Defective cell mediated immunity with CD4 count as low as < 50 cells/cumm is an important risk factor for development of MAC. Lungs, liver, spleen, GI tract, bone marrow and lymph nodes are common sites involved.

Clinical features

Isolated pulmonary disease is rare. Patients present with recurrent fever, weight loss or failure to thrive, night sweats, fatigue, chronic diarrhoea and recurrent abdominal pain. Patients have lymphadenopathy, hepatomegaly and splenomegaly. Associated laboratory findings of neutropenia, anemia and leukopenia are seen.

Diagnosis

Is accomplished by isolation of organism from blood or biopsy sites (bone marrow, lymph node or other tissues). Culture can yield the organisms in 2 weeks. Culture is necessary for species identification. Anemia out of proportion to the stage of the HIV disease and elevated serum alkaline phosphatase may be seen.

Treatment

Combination therapy with a minimum of 2 drugs is recommended. Clarithromycin or Azithromycin plus Ethambutol is recommended. Additional drugs such as Ciprofloxacin, Amikacin or Streptomycin may be considered depending on severity of the disease. For disseminated disease, 3 or 4 drugs are essential. Most patients show improvement within 4-6 weeks. Treatment should then be continued with 2 drugs.

Table 26 : Treatment of Mycobacterium avium complex

Drugs	Dosage	Adverse Effects	Remarks
Clarithromycin	7.5-10 mg/kg/day PO BD (max 1 gm/day)	Nausea, diarrhoea, abdominal pain. Rare - headache, leukopenia, altered taste, elevated transaminases	Clarithromycin inhibits hepatic metabolism of other drugs cleared by the liver, thus potential drug interactions can occur
Azithromycin	10-12 mg/kg/day PO OD (max 500 mg/day)	Nausea, diarrhoea, abdominal pain, ototoxicity. Rare - headache, leukopenia, elevated transaminases	Useful when drug interactions with clarithromycin are a concern
Ethambutol	15-20 mg/kg/day PO OD (max 1 gm/day)	Optic neuritis, colour blindness, headache, nausea, peripheral neuropathy, rash, hyperuricemia	Periodic monitoring for vision is required
Alternative drugs			
Ciprofloxacin	20-30 mg/kg/day IV/PO (max 1.5 mg/day)	GI upset, diarrhoea, rash and headache. Cartilage damage in children	Use with caution in children < 18 years of age due to potential cartilage damage
Amikacin	5-30 mg/kg/day IV / 1 M	Ototoxicity and renal toxicity	

Prophylaxis:

- After initial treatment, secondary prophylaxis is recommended for life time.
- Any child in WHO Stage IV.
- As per CD4 counts, as below

As there is no national data on epidemiology of MAC in India in children, it is currently NOT standard prophylaxis. Pediatricians can decide on individual basis if primary prophylaxis should be started for MAC. Secondary prophylaxis should be given for cases of confirmed laboratory-diagnosed MAC.

Table 27 : Indications for MAC prophylaxis		
Age	**CD4 count (cells/mm^3)**	**WHO Clinical Stage**
< 12 months	< 750	-
1-2 years	< 500	-
2-6 years	< 75	-
> 6 years	< 50	-
Any Age	-	IV

- Prophylaxis may be stopped if CD4% is more than 15% for 6 months, ART has been continued for more than 12 months and child is asymptomatic.

Table 28 : Drugs for MAC prophylaxis	
Drugs	**Dosage**
Clarithromycin	15 mg/kg/day PO BD (max 500 mg/day)
Azithromycin	20 mg/kg/day PO weekly (max 1.25 gm/day
Ethambutol	15-20 mg/kg/day PO OD (max 1.5 gm/day)
Ciprofloxacin	20-30 mg/kg/day PO/IV OD/BD (max 1.5 gm/day)

Notes

- For primary prophylaxis any one of the 3 drugs (Clarithromycin, Azithromycin or Ethambutol) is used for prophylaxis.
- Secondary prophylaxis consists of Clarithromycin or Azithromycin and Ethambutol or Ciprofloxacin.

B2.5 Toxoplasmosis

Very few cases of mother to infant transmission of toxoplasma in HIV infected women have been reported. The risk for congenital infection is low among infants born to women who became infected during first trimester (range: 2-6%) but increases sharply thereafter with a risk as high as 81% for women acquiring infection during the last few weeks of pregnancy. Infection of the fetus in early gestation results in more severe involvement with milder disease with infection late in gestations.

CNS involvement with toxoplasma gondii is uncommon in HIV infected children. In most cases, Toxoplasma encephalitis is considered to be due to congenital infection. Rarely, it may be due to primary acquired toxoplasmosis.

Clinical features

Most children are asymptomatic at birth. Late sequelae such as retinitis, visual impairment and neurological impairment may be seen after several months to years. Symptoms in infants may include maculopapular rash, generalized lymphadenopathy, hepatosplenomegaly, jaundice, hematologic abnormalities, hydrocephalus, microcephaly, intracerebral calcifications and seizures. Acquired toxoplasmosis may lead to malaise, fever, sore throat, myalgia, lymphadenopathy and mononucleosis – like syndrome.

Isolated ocular toxoplasmosis is rare and is usually in association with CNS infection. CNS toxoplasmosis may present as headache, fever, changes in mental status, seizures, psychosis and focal neurological deficits.

Diagnosis

Congenital toxoplasmosis is diagnosed by detection of toxoplasma specific IgM, IgA in neonatal serum within the first 6 months of life or persistence of specific IgG antibody beyond 12 months of age.

A presumptive diagnosis of CNS toxoplasmosis is done with correlating clinical symptoms, presence of Toxoplasma specific IgG and presence of space occupying lesion on imaging studies of the brain especially ring-enhancing lesions in the basal ganglia and cerebral cortico-medullary junction. Definitive diagnosis requires histologic or cytologic confirmation by brain biopsy.

Table 29: Treatment of Toxoplasmosis			
Drugs	**Dosage**	**Adverse Effects**	**Remarks**
Pyrimethamine	**Congenital Toxoplasma** Loading 2 mg/kg/day on Day1 & 2 Continuation 1 mg/kg/day for 2-6 months and then 1mg/kg 3 times a week to complete 12 months **Acquired Toxoplasma** (CNS, ocular or systemic toxoplasmosis) Loading 2 mg/kg/day for 3 days Continuation 1 mg/kg/day for 6 weeks	Rash (including Stevens-Johnson syndrome) nausea, bone marrow suppression.	**Folinic acid (10-25 mg daily)** should be administered with pyrimethamine to prevent bone marrow suppression. It should be continued for 1 week after pyrimethamine has been discontinued
Sulphadiazine	**Congenital Toxoplasma** 50 mg/kg/dose BD for 12 months **Acquired Toxoplasma** 25-50 mg/kg/dose 4 times daily	Rash (including Steven-Johnson syndrome), fever, leukopenia, hepatitis, GI symptoms and crystalluria	
Alternative drugs			
Clindamycin	5–7.5 mg/kg/dose PO 4 times daily (max 600 mg/dose)	Fever rash, GI symptoms, Pseudomembranous colitis, hepatotoxicity	In patients hypersensitive to sulfonamide. Is given along with Pyrimethamine
Azithromycin	–	–	Used in adults with Pyrimethamine in sulfa-allergic patients
TMP/SMX	5 mg/kg TMP + 25 mg/kg SMX IV/PO BD	–	Not used in children. Used as alternative to Pyrimethamine-Sulfadiazine in adults.

Therapy should be continued for 6 weeks and longer courses may be required with extensive disease or poor response.

- For an infant born to a mother with symptomatic toxoplasma during pregnancy, empiric therapy of the newborn should be given.
- Steroids may be indicated in presence of severe chorioretinitis or CNS toxoplasmosis with mass effects. However, they should be discontinued as early as possible.

Table 30 : Prophylaxis for Toxoplasmosis	
Primary prophylaxis	**Secondary prophylaxis**
TMP/SMX prophylaxis also provides prophylaxis against toxoplasmosis.	Life-long suppression is indicated after treatment for toxoplasmosis to prevent recurrence. Sulfadiazine (80–100 mg/kg/day in 2-4 divided doses) + Pyrimethamine (1 mg/kg/day PO) + Folinic Acid (5 mg PO alternate day)

B2.6 Diarrhoea

Chronic diarrhoea: is a major problem in HIV infected children. Organisms responsible for diarrhoea include

Protozoa	Entemoeba histolytica, Giardia lamblia, Cryptosporidium parvum, Isospora belli, Microsporidia, Cyclospora
Bacteria	Salmonella, Campylobacter, Shigella, Clostridium difficile and MAC
Viruses	CMV, Adenovirus, HIV, HSV and Rotavirus

Cryptosporidium:	**Microsporidia:**	**Isospora belli and Cyclospora:**
Cryptosporidium protozoa invade the gut mucosa causing profuse non bloody watery diarrhoea leading to dehydration and malnutrition. Three common species infecting humans are C. hominis, C. parvum, and C. meleagridis. It is transmitted by ingestation of oocysts excreted in the feces of infected humans and animals. The parasite tends to affect the jejunum and terminal ileum. Cryptosporidium can migrate into the bile duct and result in inflammation of the biliary epithelium, cholecystitis and cholangitis.	Microspora are obligate spore forming protozoa that cause moderate to severe diarrhoea with weight loss. They are transmitted by feco-oral route due to contamination of food or water. Diagnosis is established by examination of smear made after formal-ether concentration of stool or duodenal aspirate with modified trichrome stain.	These organisms are rarer causes of chronic diarrhoea in HIV infected children. Diagnosis is established by characteristic oocytes on microscopic examination of the stool with modified acid fast stain.
Diagnosis: Microscopic examination of stool sample with modified acid fast stain for detection of acid-fast positive oocysts. Immuno-florescence and ELISA of stool are more sensitive and specific. At least 3 stool samples should be submitted for oocyst evaluation as oocyst excretion can be intermittent.		
Treatment Immune restoration after HAART frequently results in clearance of Cryptosporidium. No consistently effective therapy exists for cryptosporidiosis in HIV infected children. Agents that can be used are: • Nitazoxanide – In children 1-3 years: 100 mg by mouth twice daily) x 3 days – In children 4 - 11 years: 200 mg by mouth twice daily • Azithromycin: 10 mg/kg on Day 1 and then 5 mg/kg PO OD for 2-10 days	**Treatment** Immune restoration after HAART frequently results in clearance of microsporidia. No consistently effective therapy exists for microsporidia. Agents used: • Albendazole : 7.5 mg/kg/dose BD (max dose : 400 mg BD) • Nitazoxanide – 1-3 years: 100 mg by mouth twice daily x 3 days – 4 - 11 years: 200 mg by mouth twice daily x 3 days	**Treatment for Isospora** • TMP/SMX – 20 mg/kg/day of TMP in 4 divided doses for 10 days and then twice a day for 3 days. • Pyrimethamine with folinic acid can be used in patients allergic to sulfonamide **Treatment of Cyclospora** • TMP/SMX – 10 mg/kg/day of TMP in 2 divided doses for 7 days.

Table 31: Treatment of chronic diarrhoea		
Organism	**Drugs**	**Dosage**
Cryptosporidium	Nitazoxanide	1-3 years 100 mg PO BD x 3 days 4-11 years 200 mg PO BD x 3 days
	Azithromycin	10 mg/kg on Day 1 & then 5 mg/kg PO OD for 2-10 days
Microsporidia	Albendazole	7.5 mg/kg/do BD (max dose : 400 mg BD)
	Nitazoxanide	1-3 years 100 mg PO BD x 3 days 4-11 years 200 mg PO BD x 3 days
Isospora belli	TMP/SMX	20 mg/kg/day of TMP in 4 divided doses for 10 days and then twice a day for 3 days
Cyclospora	TMP/SMX	10 mg/kg/day of TMP in 2 divided doses for 7 days

Prophylaxis

- TMP/SMX prophylaxis also protects against Isospora and cyclospora.
- Secondary prophylaxis with TMP/SMX [5mg/kg/day of TMP] is recommended to prevent relapse.

B2.7 Candidiasis

It is the most common cause of fungal infections in HIV infected children. Oral thrush is the commonest manifestation. Esophageal candidiasis and systemic candidiasis may also be seen.

Clinical features

Oral thrush (oral candidiasis): Recurrent oral candidiasis is one of the clinical indicators of HIV infection in infants beyond 8 weeks of age. Patients may have creamy white curd like patches with inflamed underlying mucosa in the oropharynx, palate and tonsils. It may also present as erythematous lesions (atrophic), hyperplastic (hypertrophic) and angular cheilitis.

Esophageal candidiasis: Esophageal candidiasis is seen in patients with low CD4 cell count (< 100/cumm), high viral load and neutropenia (< 500/cumm) and those with concomitant oropharyngeal candidiasis. It is an AIDS defining condition. Patients present with odynophagia (pain during swallowing), dysphagia, retrosternal pain, nausea and vomiting.

Systemic candidiasis may be seen in patients especially on prolonged antibiotics and can cause endophthalmitis, hepatic, splenic, renal and bone involvement. Patients may present in shock and with sepsis.

Diagnosis: Oral thrush can be diagnosed clinically by its characteristic appearance and bleeding of the mucosa on scraping. KOH /Lactophenol cotton blue preparation with demonstration of budding yeast cells, hyphae/ pseudohyphae in wet mounts and culture or biopsy specimen under microscope can be used for confirming the diagnosis.

Esophageal candidiasis has classic cobblestoning appearance on barium swallow. It should be suspected in a child with oral candidiasis who has refusal to feeds, swallowing difficulty especially to solids, drooling, hoarse voice or stridor. Endoscopy shows white raised plaques with extensive ulceration and biopsy will prove candida on KOH preparation. Endoscopy is required in resistant cases to rule out other infections such as HSV, CMV, MAC and azole resistant candida.

Systemic candidiasis is diagnosed on isolation of candida from blood culture.

Treatment

Oral candidiasis:

Early oral thrush can be treated with topical application of clotrimazole applied 4-6 hourly to oral mucosa for 7-14 days. Alternatively nystatin suspension administered as 4,00,000 – 6,00,000 U/ml (4-6 mL 4 times daily after feed for 1-10 days) may be given. Only if nystatin or clotrimazole troches/mouth paint is not available, then gentian violet may be used. In patients who fail topical therapy, oral fluconazole (3-6 mg/kg/day OD) for 7-14 days or itraconazole (2-5 mg/kg/dose OC BD) for 7 days may be given. Ketoconazole also can be used as a second-line therapy in dose of 5-10 mg/kg/day in BD doses for 14 days but is less effective than fluconazole or itraconazole. Intravenous amphotericin B (0.3-0.5 mg/kg/day) may be used in resistant cases.

Esophageal candidiasis

For esophageal candidiasis, fluconazole is the drug of choice. It is given at dose of 3 -6 mg/kg/day IV for 21 days changing to oral route once the child starts tolerating food. Itraconazole capsule is not useful for treatment of esophageal candidiasis, however oral solution may be given for 14-21 days.

Systemic candidiasis

Amphotericin B is the drug of choice in dose of 0.5-1.5 mg/kg OD IV over 1-2 hours for 14 to 21 days after the last positive blood culture and signs and symptoms have resolved. Flucytosine (100-1560 mg/kg/day in 4 doses) may be used in combination with amphotericin B in patients with severe invasive disease. Fluconazole may be used as an alternative to amphotericin B in stable patients who have not recently received azole therapy. Lipid amphotericin B can be used in patients who are intolerant to conventional Amphotericin B or have a pre-existing renal disease.

Table 32 : Treatment of candida infection			
Drugs	**Dosage**	**Adverse Effects**	**Remarks**
Clotrimazole mouth paint/ trouche	10 mg orally 4 times daily for 14 days for oral thrush	-	Treatment of choice for oral thrush
Nystatin suspension	4,00,000-6,00,000 U 4 times daily for 7-14 days for treatment of oral thrush	Bitter taste	Alternative drug for oral thrush
Fluconazole	3-6 mg/kg/ OD PO for 7-14 days (max: 400 mg/ dose) for oral thrush. 3-6 mg/kg/day IV/PO for 14-21 days (max: 400 mg/dose) for esophageal candidiasis 10-12 mg/kg/day IV/PO BD (max: 800 mg/day) for 4 weeks for systemic candidiasis.	Skin rash, pruritis, Stevens Johnson syndrome, Hepatitis, alopecia in scalp and pubic area.	Fluconazole is the drug of choice for esophageal candidiasis. In uncomplicated systemic candidiasis, fluconazole may be used for initial therapy or an initial course of amphotericin B may be followed by fluconazole to complete treatment. Oral fluconazole is used for oral candidiasis if topical therapy fails.
Itraconazole	Oral solution: 5 mg/kg/ day PO BD (max: 200-400 mg/day for 7-14 days for oral candidiasis and for 14-21 days for esophageal candidiasis.	GI upset, hepatitis, skin rash, pruritis, thrombocytopenia, leukopenia.	Itraconazole solution is absorbed in presence of gastric acid and should be given without food whereas capsules should be given with food. Itraconazole capsule is ineffective for treatment of esophageal disease. Itraconazole is a second line drug for esophageal candidiasis.
Ketoconazole	5-10 mg/kg/day PO BD x 14 days for oral thrush	Nausea, vomiting, hepatitis, hemolytic, anemia, adrenal insufficiency, gynaecomastia	Inhibits P-450 cytochrome enzyme and this has drug interaction with antiretroviral drugs. Absorption is variable and thus is less effective than fluconazole or itraconazole. Used as second line drug for oral thrush
Amphotericin B	0.3-0.5 mg/kg/IV OD for 7 days for esophageal candidiasis 0.5-1.5 mg/kg/ day IV OD for 2-3 weeks after last positive blood culture and signs and symptoms have resolved for systemic candidiasis.	Nephrotoxicity, fever, nausea, vomiting hepatotoxicity, anemia, neurotoxicity, hyperkalemia	Amphotericin should be initiated at doses of 0.25-0.5 mg/kg/day & then increased to 0.5-1.5 mg/kg/day if tolerated. For severe disease it can be started at regular doses. Once patients with systemic candidiasis stabilize, it can be administered as 1.5 mg/kg alternate day.
Lipid complex Amphotericin B	5 mg/kg/day IV OD for 2-4 weeks for systemic candidiasis	Acute infusion related reactions such as chest pain, dyspnea, abdominal pain and urticaria.	Useful in patients intolerant to conventional amphotericin B or have nephrotoxicity.
Liposomal Amphotericin B	3-5 mg/kg/day IV OD for 2-4 weeks for systemic candidiasis	Acute infusion related reactions such as chest pain, dyspnea, hypoxia, abdominal pain, flushing and urticaria.	Useful in patients intolerant to conventional amphotericin B or have nephrotoxicity
Flucytosine	100-150 mg/kg/day PO in 4 divided doses as an adjunct to Amphotericin B in patients with severe systemic candidiasis	Bone marrow suppression, Hepatotoxicity, GI upset, renal and skin toxicity	Should be avoided in children with severe renal involvement. TDM levels should be between 40-60 μg/ml.

Table 33: Prophylaxis for candidiasis	
Primary prophylaxis	**Secondary prophylaxis**
Routine primary prophylaxis is not recommended because of effectiveness of therapy for acute disease, low mortality with candidiasis, potential for resistant candida to develop and possibility of drug interactions.	Fluconazole (3-6 mg/kg OD PO) or Itraconazole (5 mg/kg PO OD) may be considered for infants who have severe recurrent mucocutanenous candidiasis and for those who have esophageal candidiasis. If the child is started on ART, prophylaxis may be stopped if CD4 % is >15% on more than 2 occasions (at least 3 months apart)

B2.8 Cryptococcal meningitis

Cryptococcal meningitis occurs less frequently among HIV infected children (1%) than adults.

Clinical features

Patients present with fever, headache and altered mental status. HIV infected children between 6-12 years of age with severe immunosuppression are prone.

Neck stiffness and focal neurological deficit is rare.

Diagnosis

In cryptococcal meningitis, CSF pressure should be measured as CSF cell count, glucose and protein may be virtually normal but opening pressure may be elevated. CSF analysis with India ink preparation is a must.

Cryptococcal antigen on CSF should be sent in centers where facilities are available. SF antigen detection may be negative in culture positive cryptococcal meningitis; high titers of antigen (prozone effect), low levels of antigen or non-encapsulated organisms.

However, cryptococcal antigen titers in CSF is helpful in evaluation response to therapy. A CSF titer of > 1:8 after completion of therapy indicates treatment failure or relapse.

Fungal cultures from CSF or blood may be useful especially for susceptibility testing in patients with refractory disease.

Treatment

Cryptococcal meningitis is a severe infection and initial treatment consists of a combination of amphotericin B (0.7-1.5 mg/kg/day) plus flucytosine (100 mg/kg/day in 4 divided doses) for a minimum of 2 weeks. In India, flucytosine is not available and amphotericin B alone can be used. Liposomal Amphotericin B (3-5 mg/kg/day) is found to be useful. After successful initial therapy, consolidation therapy with fluconazole (5-6 mg/kg/do IV or orally BD) for a minimum of 8-10 weeks is recommended. If fluconazole cannot be given, itraconazole can be used as an alternative (2-5 mg/kg/dose BD). In refractory cryptococcal meningitis, intrathecal or intraventricular amphotericin B can be used.

For elevated intracranial pressure, serial lumbar punctures to relieve CSF pressure may be required.

Table 34: Treatment of cryptococcal meningitis			
Drugs	**Dosage**	**Adverse Effects**	**Remarks**
Amphotericin B	0.7-1.5 mg/kg/day IV OD for acute therapy (2 weeks of induction phase)	Nephrotoxicity, fever, nausea, vomiting, hepatotoxicity, anemia, neurotoxicity, hyperkalemia	Nephrotoxicity is related to cumulative dose
Flucytosine	100 mg/kg/day PO in 4 divided doses (2 weeks of induction phase)	Bone marrow suppression, Hepatotoxicity, GI upset, renal and skin toxicity	Should be avoided in hildren with severe renal involvement. TDM levels should be between 40-60 μg/ml.
Fluconazole	10-12 mg/kg/day PO/IV BD (max: 800 mg/day) [8-10 weeks of consolidation phase]. 3-6 mg/kg/day PO (max:200 mg) [Secondary prophylaxis].	Skin rash, pruritis, Stevens-Johnson syndrome, hepatitis, alopecia in scalp and pubic area	Inhibits P-450 cytochrome and thus adjustment with anti-retroviral therapy is required.
Itraconazole	2-5 mg/kg/day PO BD [Consolidation phase – 8 weeks]	Skin rash, pruritis, thrombocytopenia, leukopenia, hepatitis, GI upset	Inhibits P450 cytochrome enzyme and thus has drug interactions with anti-retroviral agents.
Liposomal Amphotericin B	3-5 mg/kg/day IV OD [Induction phase – 2 weeks]	Acute infusion related reactions such as chest pain, dyspnea, hypoxia, abdominal pain, flushing and urticaria.	Can be used instead of Amphotericin B in patients with renal insufficiency or infusion related toxicity to Amphotericin B.

Induction phase

Amphotericin B + Flucytosine for 2 weeks

or

Amphotericin B for 2 weeks

or

Liposomal Amphotericin B + Flucytosine for 2 weeks

or

Liposomal Amphotericin B.

Alternative

Fluconazole + Flucytosine [Not enough data in children]

Consolidation phase

Fluconazole for 8-10 weeks.

or

Itraconazole for 2 weeks

Table 35 : Prophylaxis for cryptococcal meningitis	
Primary prophylaxis	**Secondary prophylaxis**
Antifungal prophylaxis is not to be used routinely to prevent cryptococcosis because of rarity of the disease, lack of survival benefit, possibility of drug interaction and potential development of antifungal drug resistance.	After successful treatment of cryptococcal meningitis, secondary prophylaxis should be given life-long, Fluconazole (3-6 mg/kg/day, max: 200 mg) may be effective. For adolescents receiving ART, maintenance fluconazole may be stopped if improvement occurs and CD4 count increases to between 100-200 cells.

SECTION

B3 Opportunistic Infections – Viral

B3.1 Cytomegalovirus

CMV infection in humans is common and usually asymptomatic. CMV is usually acquired during infancy or early childhood. Transmission can occur congenitally or acquired post-natally through contact with saliva or urine or through transfusion, sexual contact or transplantation with infected organs. CMV can also be transmitted through breast milk. CMV causes 8-10% of pediatric AIDS defining illness.

Clinical features

Symptomatic congenital CMV syndrome is not very common at birth but 10-15% develop late developmental abnormalities, sensori-neural hearing loss, chorioretinitis or neurological disease.

CMV retinitis

CMV retinitis is the most common CMV disease among HIV-infected children. It is usually asymptomatic and discovered on routine examination. Older children with CMV retinitis usually present with floaters, loss of peripheral or central vision. Funduscopy reveals white and yellow retinal infiltrates and retinal hemorrhages.

CMV disease can also occurs in lungs, liver, GI tract, pancreas, sinuses and CNS (55 – 58). Pulmonary CMV is often difficult to assess due to presence of other organisms such as PCP. CMV pneumonia is usually an interstitial pneumonia with dry cough and hypoxemia.

CMV encephalopathy is rare in children and is difficult to distinguish from HIV induced encephalopathy. Disseminated disease can present with hepatosplenomegaly generalized lymphadenopathy, fever and respiratory symptoms. CMV may also manifest as part of IRIS.

Diagnosis

Diagnosis of CMV is difficult as presence of antibodies to CMV does not necessary imply infection.

Histological diagnosis is the most useful test demonstrating characteristic "owl's eye" intra-nuclear and smaller intracytoplasmic inclusion bodies. Staining with CMV monoclonal antibodies can also be done.

Hence, children with HIV infection should have a fundoscopy done by an ophthalmologist every 6 monthly to identify CMV retinitis.

Treatment

All children with CMV infection should be treated as inpatients. Ganciclovir in dose of 5 mg/kg/dose IV twice daily administered over 1-2 hours for 14-21 days followed by life-long maintenance therapy is required for treatment of disseminated CMV and CMV retinitis. Alternatively, in ganciclovir resistant CMV infections, foscarnet may be used as 60 mg/kg/dose every 8 hours for 14-21 days followed by life-long maintenance therapy.

Valganciclovir is used in adults with CMV retinitis as induction dose of 900 mg PO BD for 21 days followed by 900 mg OD daily as maintenance but appropriate dose of this drug in children is not known.

Oral ganciclovir in dose of 30 mg/kg administered every 8 hours is effective for maintenance treatment of CMV retinitis.

Table 36 : Treatment of cytomegalovirus			
Drugs	**Dosage**	**Adverse Effects**	**Remarks**
Ganciclovir	Induction phase 5 mg/kg every 12 hours IV for 14-21 days [in disseminated disease & CMV retinitis] 6 mg/kg every 12 hours IV for 6 weeks [in symptomatic congenital infection] Prophylaxis 30 mg/kg tid PO *or* 5 mg/kg/day IV x 5 days/week	Neutropenia, myelo-suppression, renal toxicity, CNS effects, GI dysfunction, thrombophlebitis and elevated liver enzymes	Combination therapy with Ganciclovir and Foscarnet can be used in children with sight threatening disease.
Foscarnet	60 mg/kg tid IV for 14-21 days, then 90-120 mg/kg once a day for chronic suppression.	Renal dysfunction, electrolyte imbalance (especially in calcium, phosphorus, magnesium and potassium levels), seizures, cardiac arrhythmias, elevated liver enzymes and CNS symptoms	Used in induction phase as alternative in case of ganciclovir resistant CMV

Table 37: Prophylaxis for CMV	
Primary prophylaxis	**Secondary prophylaxis**
All HIV infected children with severe immunosuppression (CD4 count < 50 cells/mm^3) may be considered for primary prophylaxis against CMV.	Life-long maintenance therapy following treatment for CMV disease is recommended. Maintenance therapy may be discontinued in patients on HAART who have an increase in CD4 count to > 100-150 cells/mm^3 after 6 months of therapy. All patients who have had maintenance therapy discontinued should undergo 6 monthly ophthalmologic evaluation as data for children is inadequate.
Drug of choice – Oral ganciclovir : 30 mg/kg po tid.	

B3.2 Herpes simplex

HSV is transmitted as vertical transmission and horizontal transmission through direct contact infected oral secretions or lesions. Vertical transmission occurs predominantly intra-partum when the fetus passes through the birth canal and is exposed to genital ulcer. Caesarean section lowers the risk of transmission. Neonatal infections are usually caused by HSV type 2.	
Clinical features:- Recurrent or persistent HSV infection is an AIDS indicating condition. Neonatal HSV leads to CNS involvement or involves skin, eyes and mouth. Vesicular rash is seen. Outside the neo-natal period, the most common manifestation is extensive ulcers in and around the mouth which are painful 4-5 mm in diameter and can be seen on tongue, lips and all mucosal surfaces (Gingivostomatitis). Other sites such as esophagus, CNS, genitals and systemic disease may occur.	**Diagnosis:** Typical ulcers lead to a clinical diagnosis. The virus can be isolated in culture and detected in tissue culture cells with 1-3 days. Giemsa staining (Tzanck smear) of lesion cell scraping may show multinucleated giant cells and eosinophilic intra-nuclear inclusion, but this does not differentiate HSV from varicella zoster infection and is not routinely recommended. Detection of HSV 1 and 2 antigens from skin or mucosal scrapings by immuno-florescent techniques aids in diagnosis. In patients with suspected HSV encephalitis, detection of HSV DNA by PCR is the diagnosis of choice. Rising antibody titres of HSV 1 and 2 IgG is also useful.

Table 38 : Treatment of Herpes simplex			
Drugs	**Dosage**	**Adverse Effects**	**Remarks**
Acyclovir	Neonatal CNS disease 20 mg/kg/dose IV tds x 21 days Neonatal skin, eye or oral disease 20 mg/kg/dose IV tds x 14 days Outside neo-natal period – CNS disease 10 mg/kg/dose IV tds x 14 days Severe gingivostomatitis 5-10 mg/kg/dose IV tds x 14 days Mild gingivostomatitis and genital herpes 20 mg/kg/dose PO tds x 7-14 days (max: 400 mg/dose)	Phlebitis, renal toxicity, nausea, vomiting, rash, neutropenia	Drug of choice for Herpes simplex 1 and 2
Foscarnet	120 mg/kg/d IV in 2-3 divided doses till infection resolves	Renal toxicity, electrolyte abnormalities in calcium, phosphorus, magnesium, potassium, seizures, cardiac arrhythmias, elevated liver transaminases	Used for acyclovir resistant HSV infection

Prophylaxis: Antiviral prophylaxis after exposure to HSV or to prevent initial episodes of HSV disease in patients with latent infection is not recommended.

B3.3 Varicella infections

Chickenpox in immuno-competent children is usually inconsequential but in HIV infected children, it can cause severe disease.

Clinical features

Patients present with vesicles which start as papules and eventually become crusted with distribution over face, trunks and limbs. With immunosuppression, vesicles may be large and extensive. New vesicles may also appear in crops over several days. Mucosal surfaces may also be involved. Systemic involvement in form of pneumonia, hepatitis and encephalitis may be seen with immunosuppression.

Diagnosis

Chickenpox is a clinical diagnosis. Tzanck smear of cell scrapings from lesions may show multinucleated giant cells but is non-specific. Laboratory tests such as demonstration of VZV antigen in skin lesion, isolation of virus in culture from vesicle contents and a significant rise in VZV IgG antibody during convalescence of presence of VZV IgM antibody can help to confirm diagnosis.

Treatment

A child with chickenpox is infectious till all the lesions have crusted. Hence, they should be isolated to avoid infecting other HIV infected children or adults. In the HIV-infected child with chickenpox, intravenous acyclovir (10 mg/kg/do IV tds) should be started as soon as initial lesions appear and continued till crusting of all lesions occur or till 7 days.

Oral acyclovir (20 mg/kg/do PO qds) can be given in patients with a mild disease. Children who continue to develop lesions or whose lesions fail to heal may have acyclovir-resistant VZV and can be treated with IV Foscarnet (120 mg/kg/day in 3 divided doses) for 7 days.

Table 39 : Treatment of chickenpox			
Drugs	**Dosage**	**Adverse Effects**	**Remarks**
Acyclovir	Moderate to severe disease 10 mg/kg/dose IV tds for 7 days Mild disease 20 mg/kg/dose PO qds for 7 days	Renal toxicity, phlebitis, nausea, vomiting, rash, neutropenia	Drug of choice for chickenpox
Foscarnet	120 mg/kg/day IV in 3 divided doses for 7 days	Renal toxicity, electrolyte imbalances including abnormalities in calcium, phosphorus, magnesium and potassium, seizures, cardiac arrhythmias, elevated liver enzymes, CNS symptoms	Useful in acyclovir resistant chickenpox

Table 40 : Prophylaxis for chicken pox	
Primary prophylaxis	**Secondary prophylaxis**
See annex 15	No suppressive treatment is required post therapy. HIV infected children who have been exposed to chickenpox should be given varicella immunoglobulin within 96 hours of exposure.

B3.4 Herpes zoster

Herpes zoster occurs in children previously exposed to varicella zoster virus. It is reactivation of previous varicella infection.

Clinical features

In immuno-competent adults, vesicular lesions usually occur in the region of a dermatome unilaterally and are associated with pain and fever. Herpes zoster is rare in immuno-competent children and if it occurs in a child, then HIV infection should be suspected. In HIV infected children usually vesicles occur in multiple dermatomes and can occur bilaterally. Patients may have associated retinitis, pneumonitis, hepatitis and even encephalitis.

Diagnosis

Clinical presentation leads to the diagnosis. Laboratory tests in form of viral isolation or detection of viral antigens in the skin lesions is confirmatory.

Treatment

Acyclovir is the treatment of choice in herpes zoster. IV Acyclovir (10 mg/kg/do IV tds) for 7-14 days may be given in children with severe immunosuppression, trigeminal nerve involvement, multi-dermatomal zoster. Oral acyclovir (20 mg/kg/do PO tds) for 7 days should be given for mild disease. Patients who fail to respond to acyclovir may be treated with foscarnet (120 mg/kg/day IV in 3 divided doses).

Table 41 : Treatment of herpes zoster			
Drugs	**Dosage**	**Adverse Effects**	**Remarks**
Acyclovir	Severe immuno-suppression, Trigeminal nerve involvement or Multidermatomal zoster: 10 mg/kg/dose IV tds for 7-14 days Mild disease: 20 mg/kg/dose tds PO for 7-10 days	Renal toxicity, phlebitis, nausea, vomiting, rash, neutropenia	Drug of choice for chickenpox
Foscarnet	120 mg/kg/day IV in 3 divided doses for 7 days	Renal toxicity, electrolyte imbalance including abnormalities in calcium, phosphorus, magnesium and potassium, seizures, cardiac arrhythmias, elevated liver enzymes, CNS symptoms	Useful in acyclovir resistant chickenpox

Prophylaxis: Same as that for chickenpox.

B3.5 Penicilliosis

Penicilliosis is endemic in North-eastern part (Manipur) of India. It is one of the AIDS defining opportunistic infections (WHO stage 4)	
Penicilliosis is caused by the dimorphic fungus *Penicillium marneffei.* This commonly manifests with fever, weight loss, skin lesions as well as bone marrow, lymphnode and hepatic involvement. Skin lesions consist of a generalized papular rash; some of the papules may have central umbilication resembling molluscum contagiosum. Skin lesions commonly appear on the face, ears, extremities and occasionally the genitalia. Patients with hepatic penicilliosis have fever, abdominal pain, hepatomegaly and marked increase in serum alkaline phosphatase levels.	**Diagnosis** An early presumptive diagnosis can be made several days before the results of fungal culture are available by microscopic examination of Wright stained sample (skin scrapings, bone marrow aspirate or lymph node biopsy specimen). Many intra and extra cellular basophilic spherical, oval and elliptical yeast like organisms can be seen, some with clear central septation, which is a characteristic feature of P marneffei. Isolation of fungus can be done from blood and other clinical specimens. Fungal cultures demonstrate characteristic features that include a flat green surface and underlying deep red coloring. On HPE the organism can be demonstrated in the biopsy material.
Treatment: Recommended treatment: Amphotericin B in dose of 0.6 mg /kg/day IV for 2 weeks followed by oral Itraconazole 2-5mg/kg/ day for a subsequent duration of 10 weeks.	

Secondary prophylaxis: Relapse is common. Itraconazole is given orally in a dose of 2-5 mg/kg/ day.

SECTION C

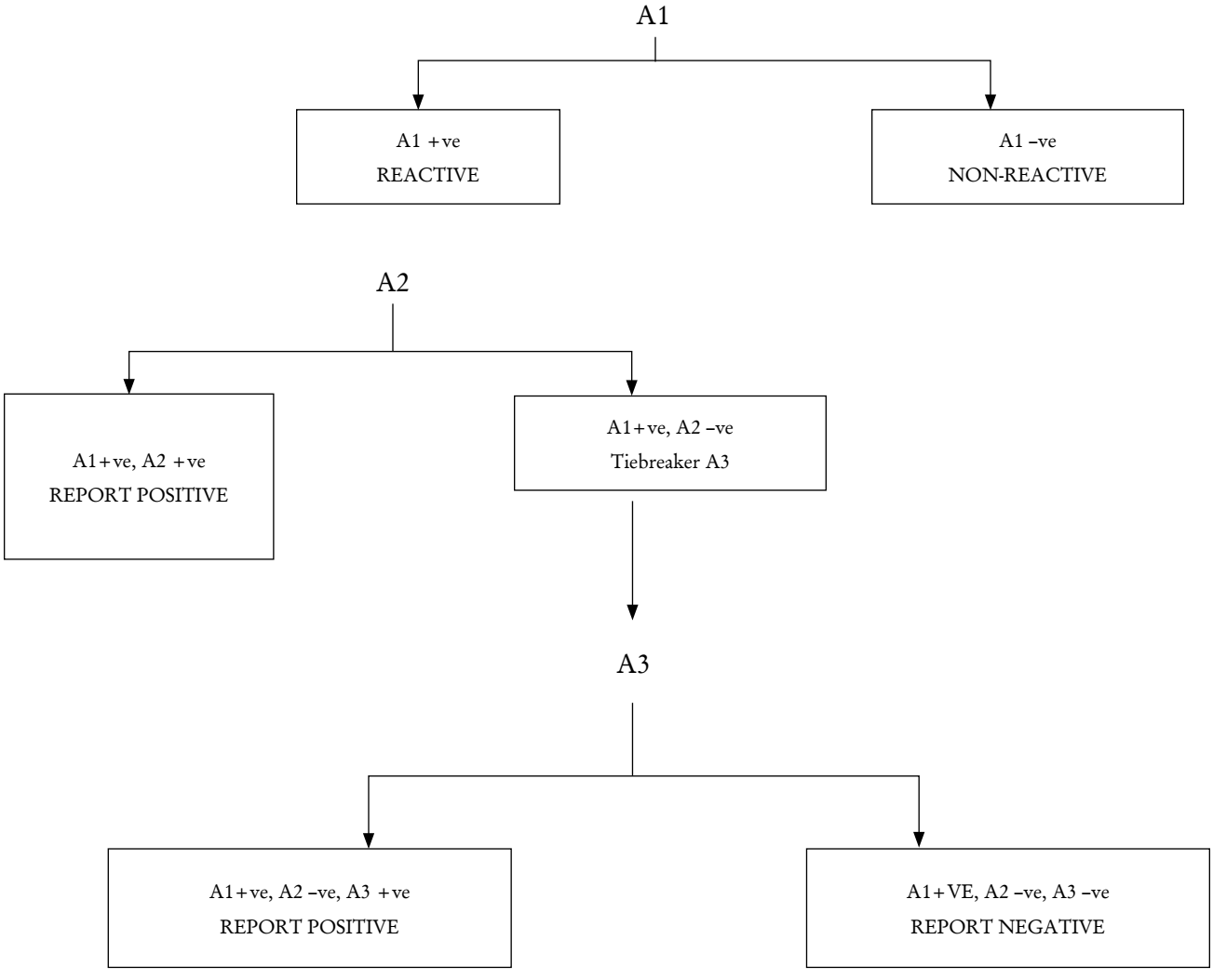
Annexes

ANNEX

1

Diagnosis in Children > 18 months

A. HIV TESTING STRATEGY II B (BLOOD/ PLASMA/SERUM): (For symptomatic children)



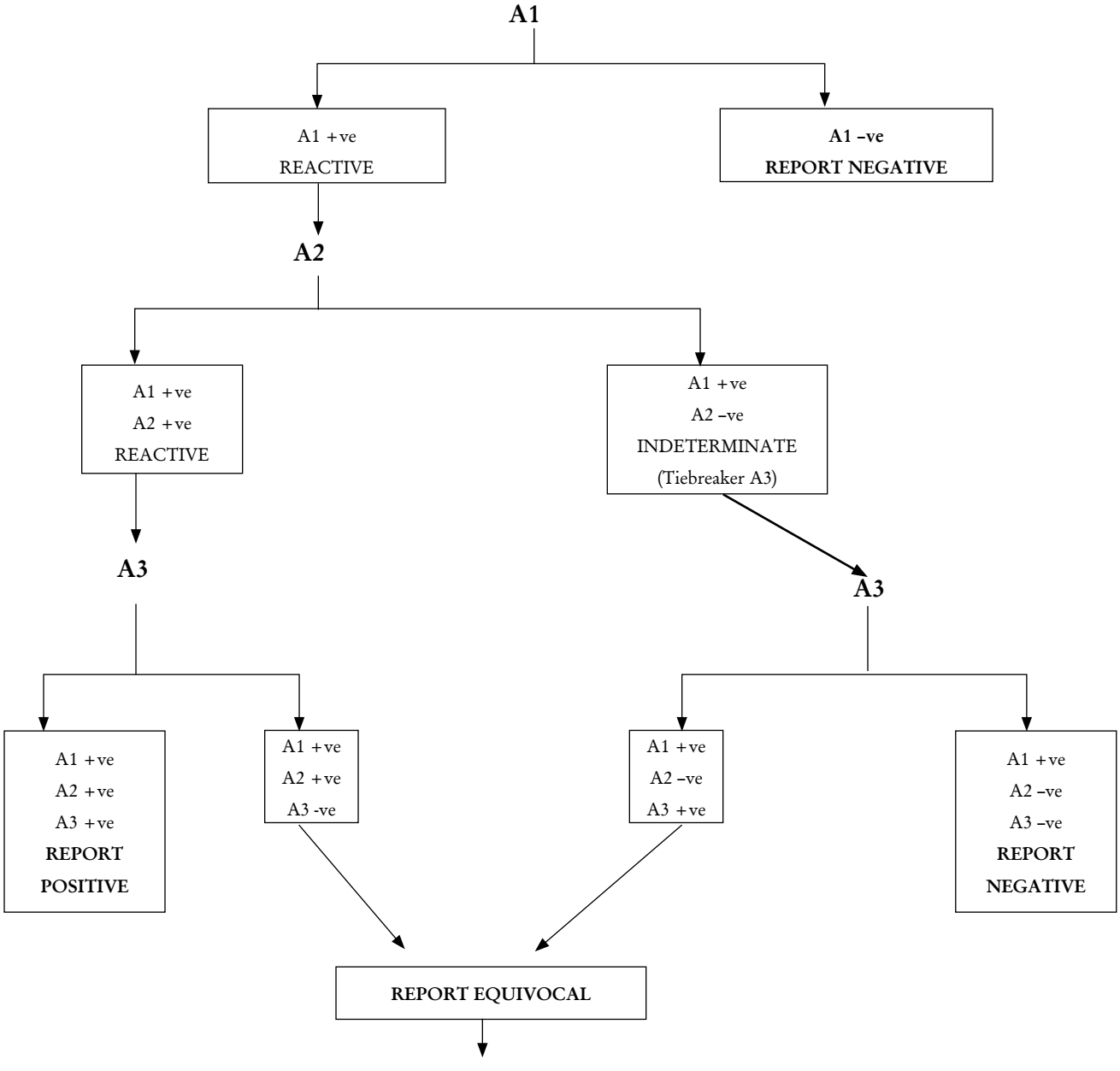
(In breastfed child, test 3 months after stopping breast-feeding)

Source: National adult guidelines on HIV testing.

Notes:

- For symptomatic children: the sample should be reactive with two different kits.
- For asymptomatic children : the sample should be reactive with three different kits
- The blood sample collected at one time is tested with the 1st kit, and if reactive, retested sequentially with the 2nd and 3rd kits depending on the clinical status of the child.

B. HIV TESTING STRATEGY III : (For asymptomatic children)



Source: National adult guidelines on HIV testing.

ANNEX 2

WHO Clinical Staging of HIV for Infants and Children with Confirmed HIV Infection

Clinical Stage 1

Asymptomatic
Persistent generalized lymphadenopathy

Clinical Stage 2

Unexplained persistent hepatosplenomegaly
Papular pruritic eruptions
Extensive wart virus infection
Extensive molluscum contagiosum
Recurrent oral ulcerations
Unexplained persistent parotid enlargement
Lineal gingival erythema
Herpes zoster
Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis)
Fungal nail infections

Clinical Stage 3

Unexplained[i] moderate malnutrition not adequately responding to standard therapy
Unexplained persistent diarrhoea (14 days or more)
Unexplained persistent fever (above 37.5°C intermittent or constant, for longer than one month)
Persistent oral candidiasis (after first 6-8 weeks of life)
Oral hairy leukoplakia
Acute necrotizing ulcerative gingivitis/periodontitis
Lymph node TB
Pulmonary TB
Severe recurrent bacterial pneumonia
Symptomatic lymphoid interstitial pneumonitis
Chronic HIV-associated lung disease including bronchiectasis
Unexplained anaemia (< 8g/dl), neutropenia (< 0.5X $10^9/L^3$) or chronic thrombocytopenia (< 50 x $10^9/L^3$)

Clinical Stage 4[ii]

Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy
Pneumocystis pneumonia
Recurrent severe bacterial infections (e.g. 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)
Extrapulmonary TB
Kaposi sarcoma
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Central nervous system toxoplasmosis (after one month of life)
HIV encephalopathy
Cytomegalovirus infection: retinitis or CMV infection affecting another organ, with onset at age over 1 month.
Extrapulmonary cryptococcosis (including meningitis)
Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis)
Chronic cryptosporidiosis
Chronic isosporiasis
Disseminated non-tuberculous mycobacteria infection
Cerebral or B cell non-Hodgkin lymphoma
Progressive multifocal leukoencephalopathy
Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

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[i] Unexplained refers to where the condition is not explained by other conditions.

[ii] Some additional specific conditions can also be included in regional classifications (e.g. reactivation of American trypanosomiasis [meningoencephalitis and/or myocarditis] in Americas region, Penicilliosis in Asia and HIV associated rectovaginal fistula in Africa).

ANNEX 3

Presumptive and Definitive Criteria for Recognizing HIV/AIDS-Related Clinical Events in Infants and Children with Confirmed HIV Infection

	Presumptive	Definitive
Primary HIV infection		
Asymptomatic infection Acute retroviral syndrome	Acute febrile illness 2–4 weeks post-exposure, often with lymphadenopathy, pharyngitis and skin rashes	In children 18 months or over sero-conversion from HIV antibody negative to antibody-positive. A positive virological test for HIV virus or its components (RNA or DNA or ICD HIV p 24 antigen) confirmed by a second virological test obtained from a separate determination. Profound temporary lymphopaenia and other transient blood abnormalities may occur.
Clinical Stage 1		
Asymptomatic	No HIV related symptoms reported and no signs on examination.	Not required.
Persistent generalized lymphadenopathy (PGL)	Swollen or enlarged lymph nodes >1 cm at two or more non-contiguous sites, without known cause.	Not required.
Clinical Stage 2		
Unexplained persistent hepatosplenomegaly	Enlarged liver and spleen without obvious cause.	Not required.
Papular pruritic eruptions	Papular pruritic vesicular lesions. Also common in uninfected children: scabies and insect bites should be excluded.	Not required.
Fungal nail infections	Fungal paronychia (painful, red and swollen nail bed) or onycholysis (painless separation of the nail from the nail bed). Proximal white subungual onchomycosis is uncommon without immuno-deficiency.	Not required
Angular cheilitis	Splits or cracks on lips at the angle of the mouth with depigmentation, usually responding to antifungal treatment but may recur.	Not required.
Lineal Gingival Erythema (LGE)	Erythematous band that follows the contour of the free gingival line; may be associated with spontaneous bleeding.	Not required.
Extensive wart virus infection	Characteristic warty skin lesions; small fleshy grainy bumps, often rough, flat on sole of feet (plantar warts); facial, more than 5% of body area or disfiguring.	Not required.
Extensive molluscum contagiosum infection	Characteristic skin lesions: small flesh-coloured, pearly or pink, dome-shaped or umbilicated growths, may be inflamed or red; facial, more than 5% of body area or disfiguring.	Not required.

	Presumptive	Definitive
Recurrent oral ulcerations (two or more in six months)	Aphthous ulceration, typically with a halo of inflammation & yellow-grey pseudo-membrane.	Not required.
Unexplained parotid enlargement	Asymptomatic bilateral swelling that may spontaneously resolve and recur, in absence of other known cause, usually painless.	Not required.
Herpes zoster	Painful rash with fluid-filled blisters, dermatomal distribution, can be haemorrhagic on erythematous background, and can become large and confluent. Does not cross the midlines.	Not required
Recurrent upper respiratory tract infection (URTI)	Current event with at least one episode in past 6 months. Symptom complex; fever with unilateral face pain and nasal discharge (sinusitis) or painful swollen eardrum (otitis media), sore throat with productive cough (bronchitis), sore throat (pharyngitis) and barking croup-like cough (LTB). Persistent or recurrent ear discharge.	Not required.
Clinical stage 3		
Unexplained moderate malnutrition	Weight loss: low weight-for-age, up to 2 standard deviations (SDs), not explained by poor or inadequate feeding and or other infections, and not adequately responding to standard management.	Confirmed by documented loss of body weight of –2SD, failure to gain weight on standard management and no other cause identified during investigation.
Unexplained persistent diarrhoea	Unexplained persistent (14 days or more) diarrhoea (loose or watery stool, three or more times daily), not responding to standard treatment.	Confirmed by stools observed and documented as unformed. Culture and microscopy reveal no pathogens.
Unexplained persistent fever (intermittent or constant, for longer than one month)	Reports of fever or night sweats for longer than one month, either intermittent or constant, with reported lack of response to antibiotics or anti-malarials. No other obvious foci of disease reported or found on examination. Malaria must be excluded in malarious areas.	Confirmed by documented fever of >37.5 °C with negative blood culture, negative malaria slide and normal or unchanged CXR, and no other obvious foci of disease.
Oral candidia (outside first 6–8 weeks of life)	Persistent or recurring creamy white to yellow soft small plaques which can be scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender (erythematous form).	Confirmed by microscopy or culture.
Oral hairy leukoplakia	Fine small linear patches on lateral borders of tongue, generally bilaterally, which do not scrape off.	None
Lymph node TB	Non acute, painless “cold” enlargement of lymph nodes, usually matted, localized to one region. May have draining sinuses. Response to standard anti-TB treatment in one month.	Confirmed by histology or fine needle aspirate for Ziehl Neelsen stain. Culture.

	Presumptive	Definitive
Pulmonary TB	Nonspecific symptoms, e.g. chronic cough, fever, night sweats, anorexia and weight loss. In the older child also productive cough and haemoptysis. Abnormal CXR. Response to standard anti-TB treatment in one month.	Confirmed by positive sputum smear or culture.
Severe recurrent presumed bacterial pneumonia	Cough with fast breathing, chest indrawing, nasal flaring, wheezing, and grunting. Crackles or consolidation on auscultation. Responds to course of antibiotics. Current episode plus one or more in previous 6 months.	Confirmed by isolation of bacteria from appropriate clinical specimens (induced sputum, BAL, lung aspirate).
Acute necrotizing ulcerative gingivitis or stomatitis, or acute necrotizing ulcerative periodontitis	Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odour, and rapid loss of bone and/or soft tissue.	None
Symptomatic LIP	No presumptive diagnosis.	Diagnosed by CXR: bilateral reticulo-nodular interstitial pulmonary infiltrates present for more than two months with no response to antibiotic treatment and no other pathogen found. Oxygen saturation persistently <90%. May present with cor pulmonale and may have increased exercise-induced fatigue. Characteristic histology.
Chronic HIV-associated lung disease (including bronchiectasis)	History of cough productive of copious amounts of purulent sputum (bronchiectasis only), with or without clubbing, halitosis, and crepitations and/or wheezes on auscultation;	Confirmed by CXR may show honeycomb appearance (small cysts) and/or persistent areas of opacification and/or widespread lung destruction, with fibrosis and loss of volume.
Unexplained anaemia (<8g/dl), or neutropenia (<1000/mm^3) or chronic thrombocytopenia (<50 000/ mm^3)	No presumptive diagnosis.	Diagnosed on laboratory testing, not explained by other non-HIV conditions, or not responding to standard therapy with haematinics, antimalarials or anthelmintics as outlined in IMCI.
Clinical stage 4		
Unexplained severe wasting, stunting or severe malnutrition not adequately responding to standard therapy	Persistent weight loss not explained by poor or inadequate feeding, other infections and not adequately responding in two weeks to standard therapy. Characterized by: visible severe wasting of muscles, with or without oedema of both feet, and/or weight-for-height of –3 SDs, as defined by WHO IMCI guidelines.	Confirmed by documented weight loss of >-3 SD +/- oedema
Pneumocystis pneumonia (PCP)	Dry cough, progressive difficulty in breathing, cyanosis, tachypnoea and fever; chest indrawing or stridor. (Severe or very severe pneumonia as in IMCI). Usually of rapid onset especially in infants under six months of age. Response to high-dose co-trimoxazole +/- prednisolone.	Confirmed by: CXR typical bilateral perihilar diffuse infiltrates; microscopy of induced sputum or BAL or NPA, or histology of lung tissue.

	Presumptive	Definitive
Recurrent severe presumed bacterial infection, e.g. empyema, pyomyositis, bone or joint infection, meningitis but excluding pneumonia	Fever accompanied by specific symptoms or signs that localize infection. Responds to antibiotics. Current episode plus one or more in previous 6 months.	Confirmed by culture of appropriate clinical specimen.
Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration or visceral at any site)	Severe and progressive painful orolabial, genital, or anorectal lesions caused by HSV infection present for more than one month.	Confirmed by culture and/or histology
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs).	Chest pain and dysphagia (difficulty in swallowing), odynophagia (pain on swallowing food and fluids), or retrosternal pain worse on swallowing (food and fluids) responds to specific treatment. In young children, suspect particularly if oral candida observed and food refusal occurs and/or difficulties/ crying when feeding.	Confirmed by macroscopic appearance at endoscopy, microscopy of specimen from tissue or macroscopic appearance at bronchoscopy or histology.
Extrapulmonary/ disseminated TB	Systemic illness usually with prolonged fever, night sweats, weight loss. Clinical features of organs involved, e.g. sterile pyuria, pericarditis, ascites, pleural effusion, meningitis, arthritis, orchitis. Responds to standard anti-TB therapy.	Confirmed by positive microscopy showing AFB or culture of Mycobacterium tuberculosis from blood or other relevant specimen except sputum or BAL, biopsy and histology.

ANNEX

4

Pros and Cons of Various Antiretroviral Drugs in Children

Nucleoside RTI (NRTI)

NRTI	Pros	Cons
AZT (Preferred NRTI if Hb ≥ 8g/dl)	– AZT causes less lipodystrophy and lactic acidosis than d4T.	– AZT has more initial gastrointestinal (GI) side effects. – Large volume of AZT liquid formulation is often poorly tolerated. – Severe anemia and neutropenia can occur. FBC monitoring before and after treatment is recommended.
ABC	– ABC is less likely to cause lipodystrophy and lactic acidosis. – ABC has little hematologic toxicity and is well tolerated. – ABC does not need refrigeration. – ABC has good efficacy.	– ABC is associated with potentially fatal hypersensitivity in 3% of children. – ABC is more expensive and is not available in paediatric formulation in India.
D4T	– d4T causes less GI side effects and anemia than AZT.	– d4T causes more lipodystrophy, lactic acidosis and peripheral neuropathy than AZT. – d4T liquid formulation needs refrigeration.
Note: 3TC is also an NRTI, and is generally well tolerated		

Non-nucleoside RTI (NNRTI)

NRTI	Pros	Cons
NVP[a]	– NVP can be given to children at any age. – NVP does not have teratogenic effect. – NVP is available in both pill and liquid formulation, and neither requires refrigeration. – NVP is part of several three-drug fixed dose combinations that can be used in older children.	– NVP has higher incidence of rash than EFV. NVP rash may be severe and life-threatening. – NVP is associated with rare but potentially life-threatening risk of hepatotoxicity. – For adolescent girls, the risk of NVP associated hepatotoxicity or serious rash increases with CD4 > 250 cells/mm3. – Rifampicin lowers NVP level more than EFV.
EFV[b]	– EFV causes less rash and hepatotoxicity than NVP. The rash is generally mild. – EFV levels are less affected by rifampicin and can be considered the NNRTI of choice in children receiving rifampicin-based anti-TB treatment. – For children EFV is avaliable in dispersable tablets and syrup form.	– EFV can only be used in children age ≥ 3 years old – Transient CNS disturbance can occur in 26-36% of children; therefore, EFV should be avoided in children with a history of severe psychiatric illness. – EFV has teratogenic effect and should be avoided in adolescent girls with potential for pregnancy. – EFV is not available in liquid formulation. – EFV is more expensive than NVP

[a] NNRTI may lower the drug levels of estrogen-based contraceptives;

[b] Barrier methods should always be used to prevent HIV transmission regardless of HIV sero-status. Adolescent girls in reproductive age taking efavirenz should prevent pregnancy.

Protease-Inhibitors (PI) - for reference.

Preferred PI	Pros	Cons
LPV/r	– Excellent efficacy especially in PI-naïve children. – High threshold for drug resistance development due to its high drug level from boosting with ritonavir. – The only available liquid ritonavir-boosted PI. – Pediatric dosing is available at all ages.	– Both liquid and gel capsule formulations require refrigeration. – Gel capsule is large in size. – Tablet form is now available in some countries but cannot be split. – Expensive.
SQV/r	– Can be used with ritonavir boosting. – Good efficacy.	– Can only be used in children who weigh > 25 kg and can swallow capsules. – The soft-gel capsule formulation is large in size and requires refrigeration. – High pill load. – Frequent gastrointestinal side effects.

Alternative PI	Pros	Cons
NFV	– Long term data showed good efficacy and safety profile. – Cause less hyperlipidemia and lipodystrophy than ritonavir-boosted PI.	– Data in adults shown to be **inferior in efficacy** compared to boosted PI and EFV. – High pill burden. – Frequent GI side effects.

ARV	NVP	EFV	LPV/r	NFV	SQV
Antimycobacterium					
Rifampicin	↓NVP level by 20-58%. Virologic consequences are uncertain, the potential of additive hepatotoxicity exists. Co-administration is not recommended and should only be done with careful monitoring	↓EFV level by 25%	↓LPV AUC by 75% Should not co-administer	↓NFV level by 82% Should not co-administer	↓SQV level by 84% Severe liver impairment with co-administer reported Should not co-administer
Clarithromycin	none	↓Clarithromycin by 39% Monitor for efficacy or use alternative drugs	↑Clarithromycin AUC by 75%, adjust clarithro dose if renal impairment	No data	Without RTV, ↑clarithromycin level by 45%, ↑SQV level 177% RTV can ↑ Clarithromycin level by 75% No clarithromycin dose adjustment needed for unboosted SQV. For boosted SQV if renal impairment – no data
Antifungal					
Ketoconazole	↑Ketoconazole level by 63% ↑NVP level by 15-30% Do not recommend co-administer	No significant changes in ketoconazole or EFV levels	↑LPV AUC ↑Ketoconazole level 3-fold Do not exceed 200mg/day ketoconazole	No dose adjustment necessary	↑SQV level by 3 fold No dose adjustment necessary if given unboosted. For RTV-boosted SQV – no data (RTV treatment dose can increase ketoconazole level 3-fold)
Fluconazole	↑NVP Cmax, AUC, Cmin by 100% No change in fluconazole level Possible increase hepatotoxicity with co-administer requiring monitoring of NVP toxicity	No data	No data	No data	No data

ARV	NVP	EFV	LPV/r	NFV	SQV
Intraconazole	No data	No data	↑Itraconazole level Do not exceed 200mg/ day itraconazole	No data but potential for bidirectional inhibition, monitor toxicities	Bidirectional interaction has been observed. May need to decrease intraconazole dose. Consider monitor SQV level (especially if given unboosted with RTV)
Oral contraceptives					
	↓Ethinyl estradiol by 20%. Use alternative or additional methods	↑Ethinyl estradiol by 37%. Use alternative or additional methods	↓Ethinyl estradiol level by 42% Use alternative or additional methods	↓levels of norethindrone by 18% and ethinyl estradiol by 47%	No data for unboosted SQV. RTV treatment dose can ↓ level of ethinyl estridiol by 41%
Lipid lowering agents					
Simvastatin, Lovastatin	No data	↓Simvastatin level by 58% EFV level unchanged Adjust simvastatin dose according to lipid response, not to exceed the maximum recommended dose	Potential large ↑ statin level Avoid concomitant use	↑ Simvastatin AUC by 505% Potential large ↑ lovastatin AUC Avoid concomitant use	Potential large ↑ statin level Avoid concomitant use
Atorvastatin	No data	↓Atorvastatin AUC by 43% EFV level unchanged Adjust atorvastatin dose according to lipid response, not to exceed maximum recommended dose	↑Atorvastatin AUC 5.88 fold Use lowest possible starting dose with careful monitoring	↑Atorvastatin AUC 74% Use lowest possible starting dose with careful monitoring	↑Atorvastatin level by 450% when use as SQV/RTV Use lowest possible starting dose with careful monitoring

ARV	NVP	EFV	LPV/r	NFV	SQV
Pravastatin	No data	No data	↑Pravastatin AUC 33% No dose adjustment needed	No data	↓Pravastatin level by 50% No dose adjustment needed
Anticonvulsants					
Carbamazapine, Phenobarbital, phenytoin	Unknown. Use with caution Monitor anticonvulsant levels	Use with caution. One case report showed low EFV levels with phenytoin Monitor anticonvulsant and EFV levels	↑Carbamazapine from RTV Both phenytoin and LPV/r levels ↓ For all, avoid concomitant use or monitor LPV/ anticonvulsant levels	Unknown but may decrease NFV level substantially Monitor NFV/ anticonvulsant levels	Unknown for unboosted SQV but may markedly↓ SQV level Monitor SQV/anticonvulsant levels

Abbreviations

AUC: area under the curve,
C_{max}: maximum concentration,
C_{min}: minimum concentration.

Note:

- Concomitant use of fluticasone with RTV results in significant reduced serum cortisol concentrations. Coadministration of fluticasone with RTV or any RTV-boosted PI regimen is not recommended unless the potential benefit outweighs the risk of systemic corticosteroid side effects.
- The following combinations are not recommended as they are either virologically not desirable or they have overlapping toxicities: d4T and AZT, ddC and ddI, ddC and d4T, ddC and 3TC

(Adapted from the Guidelines for the use of anti-retroviral agents in pediatric HIV infection, Nov 3, 2005, www.aidsinfo.nih.gov.)

ANNEX

6

Doses of the Common Antiretroviral Drugs for Children

ARV Drugs	Age (Weight)	Dose	Frequency
Stavudine (d4T/STV)	< 30 kg 30 kg to 60 kg Maximum dose: > 60kg	1 mg / kg / dose 30 mg /dose 40 mg/dose	Twice daily Twice daily Twice daily
Zidovudine (ZDV/AZT)	< 4 weeks 4 week - 13 yrs > 13 yrs	4 mg / kg / dose 240 mg/m2/dose maximum dose ≥ 13 yrs : 300mg/dose	Twice daily Twice daily Twice daily
Lamivudine (LMV)	< 30 days > 30 days or < 60 kg > 60 kg	2 mg/kg/dose 4 mg/kg/dose Maximum dose: 150 mg/dose	Twice daily Twice daily Twice daily
Nevirapine (NVP)	15 -30 days > 30 days to 13 years > 13 years	5 mg/kg/dose and 120 – 200 mg/m²/dose 120 – 200 mg/m²/dose 200 mg/dose	Once daily for 2 weeks, then 120 mg/m²/dose twice daily for 2 weeks, then 200mg/ m²/dose twice daily 120 mg/m²/dose once daily for 2 weeks, then 120-200 mg/m²/dose twice daily Once daily for 2 weeks, then twice daily
Abacavir (ABC)	Only prescribed for > 3 months of age < 16 yrs or < 37.5 kg wt > 16 yrs or > 37.5 kg wt	 8 mg/kg/dose 300 mg/dose	 Twice daily Twice daily
Efavirenz (EFV)	Only for children over 3 yrs of age or weight > 10 kg 10 to 15 kg 15 to < 20 kg 20 to < 25 kg 25 to < 33 kg 33 to < 40 kg > 40 kg	 200 mg/dose 250 mg/dose 300 mg/dose 350 mg/dose 400 mg/dose Maximum dose : 600 mg/ dose	 Once daily Once daily Once daily Once daily Once daily Once daily

ARV Drugs	Age (Weight)	Dose	Frequency
Nelfinavir (NFV)	< 1 yr	50 mg/kg/dose *or* 75 mg/kg/dose	Three times daily Twice daily
	> 1 yr to 13 yrs	55 to 65 mg/kg/dose	Twice daily
	> 13 yrs	Maximum dose : 1250 mg/dose	Twice daily
Lopinavir/ritonavir (LPV/r)	6 months of age or older:		
	> 6 mths to 12 yrs	225 mg/m^2 LPV with 57.5 mg/m^2 ritonavir/ dose	Twice daily
	or		
Without NVP/ EFV	Weight based dosing		
	7 to < 15 kg wt.	12 mg/kg LPV and 3 mg/kg ritonavir/dose	Twice daily
	15 to 40 kg wt.	10 mg/kg LPV and 5 mg/kg ritonavir/dose	Twice daily
	> 40 kg wt.	Maximum dose : 400 mg LPV/100 mg ritonavir	Twice daily Twice daily
With NVP/EFV			
	7 to < 15 kg wt	13 mg/kg LPV and 3.25 mg/kg ritonavir/dose	Twice daily
	15 to 40 kg wt	11 mg/kg LPV and 2.75 mg/kg ritonavir/dose	Twice daily
	> 40 kg wt	533 mg LPV and 133 mg ritonavir /dose	Twice daily
Saquinavir/r (SQV/r)	Use only in weight > 25 kg	Approved dosage in adults: SQV 1000 mg/RTV 100 mg There is no data in children. For children weighing >25 kg, the approved adult dose can be used If possible, monitoring of SQV	Twice daily

ANNEX 7

Serious Acute and Chronic Toxicities due to ARV Drugs that may require Therapy Modification: Clinical Presentation, Laboratory Abnormalities and Implications for ART Management [a]

Possible clinical manifestations (Most common ARV drug(s) associated with the toxicity)	Possible laboratory abnormalities	Implications for antiretroviral drug treatment
Acute Serious Adverse Reactions		
Acute Symptomatic Hepatitis (NNRTI class, particularly NVP, more rarely EFV; NRTIs or PI class)		
• Jaundice • Liver enlargement • Gastrointestinal symptoms • Fatigue, anorexia • May have hypersensitivity component (rash, fever, systemic symptoms), usually occurs within 6-8 weeks • May have accompanying lactic acidosis (see below) if secondary to NRTI drug	• Elevated transaminases • Elevated bilirubin	• Discontinue all ARV until symptoms resolve • If possible, monitor transaminases, bilirubin • If receiving NVP, NVP should NOT be readministered to the patient in future • Once symptoms resolve, either – restart ART with change to alternative ARV (if on NVP regimen, this is required); or – restart current ART regimen with close observation; if symptoms recur, substitute an alternative ARV[c]
Acute Pancreatitis (NRTI class, particularly d4T, ddI; more rarely 3TC)		
• Severe nausea and vomiting • Severe abdominal pain • May have accompanying lactic acidosis (see below)	• Elevated pancreatic amylase • Elevated lipase	• Discontinue all ARVs until symptoms resolve • If possible, monitor serum pancreatic amylase, lipase • Once symptoms resolve, restart ART with substitution of an alternative NRTI, preferably one without pancreatic toxicity[c]
Hypersensitivity Reaction (ABC or NVP)		
• ABC: Combination of acute onset of both respiratory and gastrointestinal symptoms after starting ABC, including fever, fatigue, myalgia, nausea, vomiting, diarrhoea, abdominal pain, pharyngitis, cough, dyspnea; rash (usually mild) may or may not occur; progressive worsening of symptoms soon after receives ABC dose, usually occurs within 6-8 weeks • NVP: Systemic symptoms of fever, myalgia, arthralgia, hepatitis, with or without rash	• Elevated transaminases • Elevated eosinophil count	• Immediately discontinue all ARVs until symptoms resolve • NVP or ABC should NOT be readministered to the patient in future • Once symptoms resolve, restart ART with substitution of an alternative ARV for ABC or NVP[c]

Possible clinical manifestations (Most common ARV drug(s) associated with the toxicity)	Possible laboratory abnormalities	Implications for antiretroviral drug treatment
Lactic Acidosis (NRTI class, particularly d4T)		
• Generalized fatigue and weakness • Gastrointestinal features (nausea, vomiting, diarrhoea, abdominal pain, hepatomegaly, anorexia, poor weight gain and/or sudden unexplained weight loss) • May have hepatitis or pancreatitis (see above) • Respiratory features (tachypnea and dyspnea) • Neurological symptoms (including motor weakness).	• Increased anion gap • Lactic acidosis • Elevated aminotransferase • Elevated CPK • Elevated LDH	• Discontinue all ARVs until symptoms resolve • Symptoms associated with lactic acidosis may continue or worsen despite discontinuation of ART • Once symptoms resolve, restart ART with substitution of an alternative NRTI with lower mitochondrial toxicity risk (eg. ABC or AZT)[c]
Severe Rash/Stevens Johnson Syndrome (NNRTI class, particularly NVP, less common EFV)		
• Rash usually occurs during first 6-8 weeks of treatment • *Mild to moderate rash*: erythematous, maculopapular, confluent, most often on the body and arms, with no systemic symptoms • *Severe rash*: extensive rash with moist desquamation, angioedema, or serum sickness-like reaction; or a rash with constitutional findings such as fever, oral lesions, blistering, facial edema, conjunctivitis • Life-threatening Stevens Johnson Syndrome or toxic epidermal necrolysis	• Elevated aminotransferases	• If mild or moderate rash, can continue ART without interruption but close observation • For severe or life-threatening rash, discontinue all ARVs until symptoms resolve • NVP should NOT be re-administered to the patient in the future • Once symptoms resolve, restart ART with substitution of an alternative ARV for NVP (note: most experts would not change to another NNRTI drug if patient had severe or life-threatening Stevens Johnson Syndrome with NVP)[c]
Severe, Life-Threatening Anemia (AZT)		
• Severe pallor, tachycardia • Significant fatigue • Congestive heart failure	• Low haemoglobin	• If refractory to symptomatic treatment (e.g. transfusion), discontinue AZT only and substitute an alternative NRTI[c]
Severe neutropaenia (AZT)		
• Sepsis/infection	• Low neutrophil count	• If refractory to symptomatic treatment (e.g. transfusion), discontinue AZT only and substitute an alternative NRTI[c]
Chronic Late Serious Adverse Reactions		
Lipodystrophy/Metabolic Syndrome (d4T; PIs)		
• Fat loss and/or fat accumulation in distinct regions of the body: – Increased fat around the abdomen, buffalo hump, breast hypertrophy – Fat loss from limbs, buttocks, and face occurs to a variable extent • Insulin resistance, including diabetes mellitus • Potential risk for later coronary artery disease	• Hypertriglyceridaemia; • Hypercholesterolaemia; • Low HDL levels • Hyperglycaemia	• Substitution of ABC or AZT for d4T may prevent progression of lipoatrophy • Substitution of an NNRTI for a PI may decrease serum lipid abnormalities

Possible clinical manifestations (Most common ARV drug(s) associated with the toxicity)	Possible laboratory abnormalities	Implications for antiretroviral drug treatment
Severe Peripheral Neuropathy (d4T, ddI; more rarely 3TC)		
• Pain, tingling, numbness of hands or feet; refusal to walk • Distal sensory loss • Mild muscle weakness and areflexia can occur	• None	• Stop suspect NRTI only and substitute a different NRTI that is not associated with neurotoxicity[c] • Symptoms may take several weeks to resolve

Notes:

[a] Alternative explanations for the toxicity must be excluded before it is concluded it is secondary to the ARV drug. Note: This table does not describe detailed clinical toxicity management, only management of the ART regimen.

[b] All laboratory abnormalities may not be observed.

[c] See Table 14 for recommended antiretroviral drugs substitutions.

ARV – antiretroviral drug; ART – antiretroviral therapy; CPK - creatinine phosphate kinase; LDH - lactate dehydrogenase; HDL - high-density lipoprotein; NRTI – nucleoside analogue reverse transcriptase inhibitor; NNRTI – non-nucleoside reverse transcriptase inhibitor; PI – protease inhibitor

ANNEX 8

Severity Grading of Selected Clinical and Laboratory Toxicities most commonly seen with Recommended Antiretroviral Drugs for Children

Parameter	Mild	Moderate	Severe	Severe, potentially life-threatening
General guidance to 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[c]: Requires medical or operative intervention to prevent permanent impairment, persistent disability, or death
HAEMATOLOGY *Standard International Units are listed in italics*				
Absolute neutrophil count	750 – < 1,000/mm^3 *0.75 x10^9 – < 1x10^9/L*	500 – 749/mm^3 *0.5 x10^9 – 0.749x10^9/L*	250 – 500/mm^3 *0.25 x10^9 – 0.5x10^9/L*	< 250/mm^3 *< 0.250x10^9/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 due to anaemia (e.g., cardiac failure) refractory to supportive therapy
Platelets	100,000- < 125,000/mm^3 *100x10^9 – 125x10^9/L*	50,000- < 100,000/mm^3 *50x10^9 – < 100x10^9/L*	25,000- < 50,000/mm^3 *25x10^9 – < 50x10^9/L*	< 25,000/mm^3 *< 25x10^9/L* Or bleeding
GASTROINTESTINAL				
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

Parameter	Mild	Moderate	Severe	Severe, potentially life-threatening
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 IV 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., IV fluids)	Persistent nausea with no or minimal oral intake resulting in dehydration with aggressive rehydration indicated
Pancreatitis	NA	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., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
ALLERGIC/DERMATOLOGIC				
Acute systemic allergic reaction	Localized urticaria (wheals) lasting a few hours	Localized urticaria with medical intervention indicated OR mild angioedema	Generalized urticaria OR angiooedema with medical intervention indicated OR symptomatic mild bronchospasm	Acute anaphylaxis OR life-threatening bronchospasm or laryngeal oedema

Parameter	Mild	Moderate	Severe	Severe, potentially life-threatening
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR target lesions	Diffuse macular, maculo-papular, 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)
NEUROLOGIC				
Alteration in personality-behaviour or in moodb	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 exam 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 exam 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]

Parameter	Mild	Moderate	Severe	Severe, potentially life-threatening
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*	NA
Glucose, serum, high: Nonfasting	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)	NA	500 – < 751 mg/dL *5.65 – < 8.49 mmol/L*	751 – 1,200 mg/dL *8.49 – 13.56 mmol/L*	> 1,200 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 paediatric adverse events, Bethesda, Maryland, USA; December 2004.

ULN - upper limit of normal

Notes:

[a] Values are provided for children in general except where age groups are specifically noted.

[b] Usual social and functional activities in young children include those that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc).

[c] Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement, walking or using hands).

ANNEX 9

Weight Bands in Kilograms with Dosing of Various Formulations

Weight Band in kgs	Zidovudine Syrup (50 mg /5 ml) 12 mg/m sq twice daily	Lamivudine syrup (50 mg /5 ml) 4 mg /kg twice daily	Stavudine Syrup (1 mg /ml) 1 mg /kg twice daily	Nevirapine syrup (50 mg /5ml) <8 yrs 7 mg /kg	Nevirapine syrup (50mg/5ml) > 8 yrs 4 mg /kg	FDC-10 d4T-10 3TC-40 NVP-70	FDC-6 d4T-6 3TC-30 NVP-50	FDC-30 d4T-30 3TC-150 NVP-200	Efavirenz Syrup 30 mg /ml	Efavirenz tab 200 mg	NVP Lead in-50 mg /ml
5 - 6.9	7 ml	2 ml	5 ml	4 ml	-	1	1	_			2 ml
7 - 9.9	9 ml	3ml	8 ml	6 ml	-	1.5	1.5	_			3 ml
10 - 11.9	12 ml	4 ml	11 ml	8 ml	-	1 1/2	1.5		3 ml	0.5	4 ml
12 - 14.9	14 ml	5ml	13.5 ml	9 ml		1.5	2	0.5	4ml	1	5 ml
15 - 16.9	15 ml	6ml	15.5 ml	10 ml	10 ml	2	2	0.5	5ml	1	6 ml
17 - 19.9	17 ml	7ml	18 ml		11 ml	2.5	2.5	1	5 ml	1	7 ml
20 - 24.9	20 ml	9ml	22 ml		13 ml	2.5	2.5	1	8 ml	1.5	9 ml
25 - 30	25 ml	11 ml	25 ml		15 ml	3	3	1	10 ml	1.5	11ml

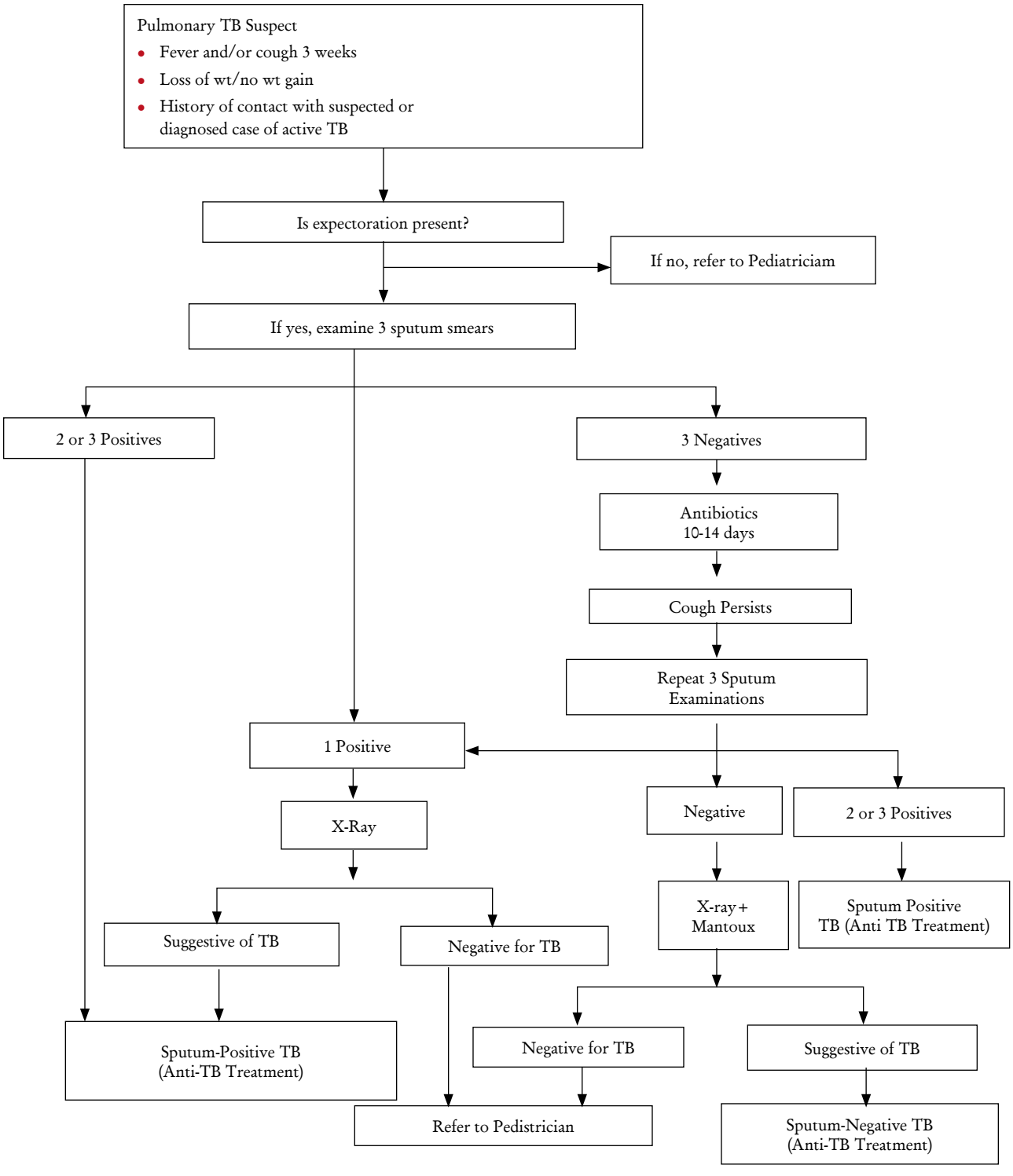
NACO provides fixed dosed combinations FDC-6, 10 (both stavudine-based combinations) and 30 (stavudine and zidovudine-based regimens). Single ARV drug formulations are recommended for children < 5 kg ; otherwise any child > 5 kg can use FDCs as above.

ANNEX

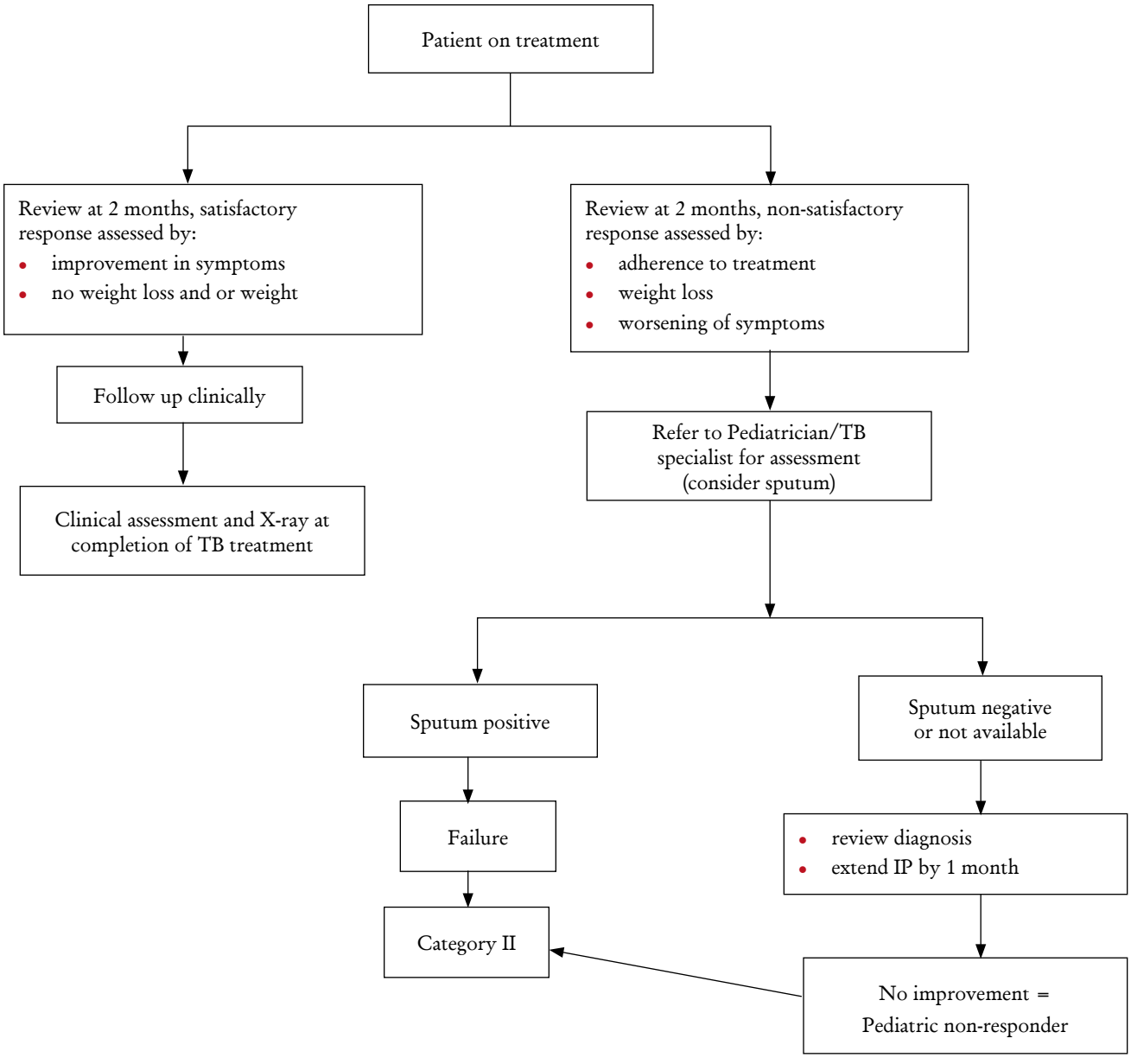
10

Algorithms for Paediatric Pulmonary TB

10.1 Diagnostic algorithm



10.2 Clinical monitoring algorithm for children with TB



Source: RNTCP - IAP guidelines for TB in children.

ANNEX

11

Developmental Milestones

Age	Gross Motor	Visual Motor	Language	Social/Adaptive
2mth	Holds head in midline, Lifts chest off table	No longer clenches fist tightly, Follows object past midline	Smiles socially (after being stroked or talked to)	Recognizes parent
6mth	Sits with a little support, no head lag when pulled to sit, Puts feet in mouth in supine position	Unilateral reach Uses raking grasp	Babbles, imitates speech sounds, turns toward voice	Recognizes strangers
9mth	Pivots when sitting, sits without support, pulls to stand, Stands holding on, Cruises	Uses pincer (thumb-finger) grasp Probes with forefinger Holds bottle Throws objects	"Mama" Indiscriminately Gestures Waves bye-bye Understands " No"	Starts to explore environment, plays gesture games (pat-a-cake, peek-a-boo)
12mth	Stands alone for 2 seconds, walks with help	Uses mature pincer grasp Releases voluntarily Marks paper with pencil	Uses 2 words other than "mama/dada Immature jargoning (runs several unintelligible words together)	Imitates actions, Comes when called, Cooperates with dressing
18mth	Runs, walks backwards, Throws objects from standing without falling	Scribbles spontaneously, Builds tower of 2-3 blocks, Turns 2-3 pages at a time	Uses 2 word combinations	Copies parent roles, Plays in company of other children
24mth	Walks up and down steps without help	Imitates stroke with pencil, Builds tower of 7 blocks, Turns pages one at a time, Removes shoes, pants, etc.	Uses pronouns (I, you, me inappropriately) Follows 2 step commands	Parallel play
30mth	Jumps with both feet off floor Throws ball overhand	Holds pencil in adult fashion Performs horizontal and vertical strokes Unbuttons	Uses pronouns appropriately Understands concept of '1'	Tells first and last names when asked, Gets self drink without help
3yr	Can alternate feet when going up steps Pedals tricycle	Copies a circle Undresses completely Dresses partially Dries hands if reminded	Uses minimum 250 words 3 word sentences Uses plurals Past tense Knows all pronouns Understands concept of "2"	Group play, Shares toys Takes turns, Plays well with others Knows full name, age, sex
4yr	Hops, skips, alternates feet going down steps	Copies a square Buttons clothing Dresses self completely Catches ball	Knows colors Says song or poem from memory Asks questions	Tells " tall tales" Plays cooperatively with a group of children
5yr	Skips alternating feet Jumps over low obstacles	Copies triangle Ties shoes Spreads with knife	Prints first name Asks what a word means	Plays competitive games Abides by rules, likes to help in household task

* Please note that each child has a different developmental pace: this list represents when the child ' begins' some of the milestones.

ANNEX 12

Tanner Staging (Sexual Maturity Rating)

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-dolescent 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
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

Contd. next page...

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
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

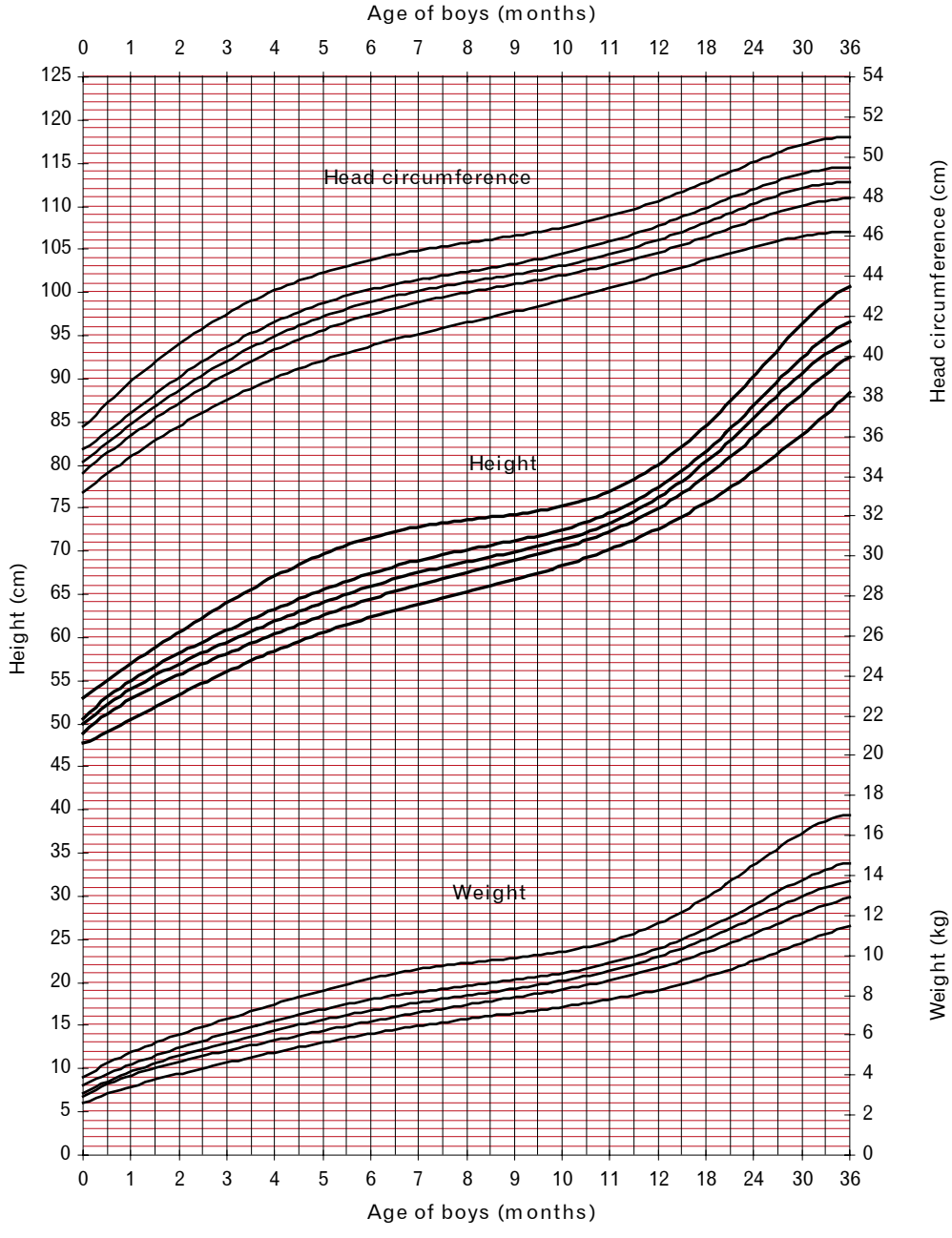
Source: Adapted from Arpadi SM, Cuff PA, Kotler DP, Wang J, Bamji M, Lange M, et al. Growth velocity, fat-free mass and energy intake are inversely related to viral load in HIV-infected children. J Nutr. 2000 Oct;130(10):2498-502

ANNEX

13

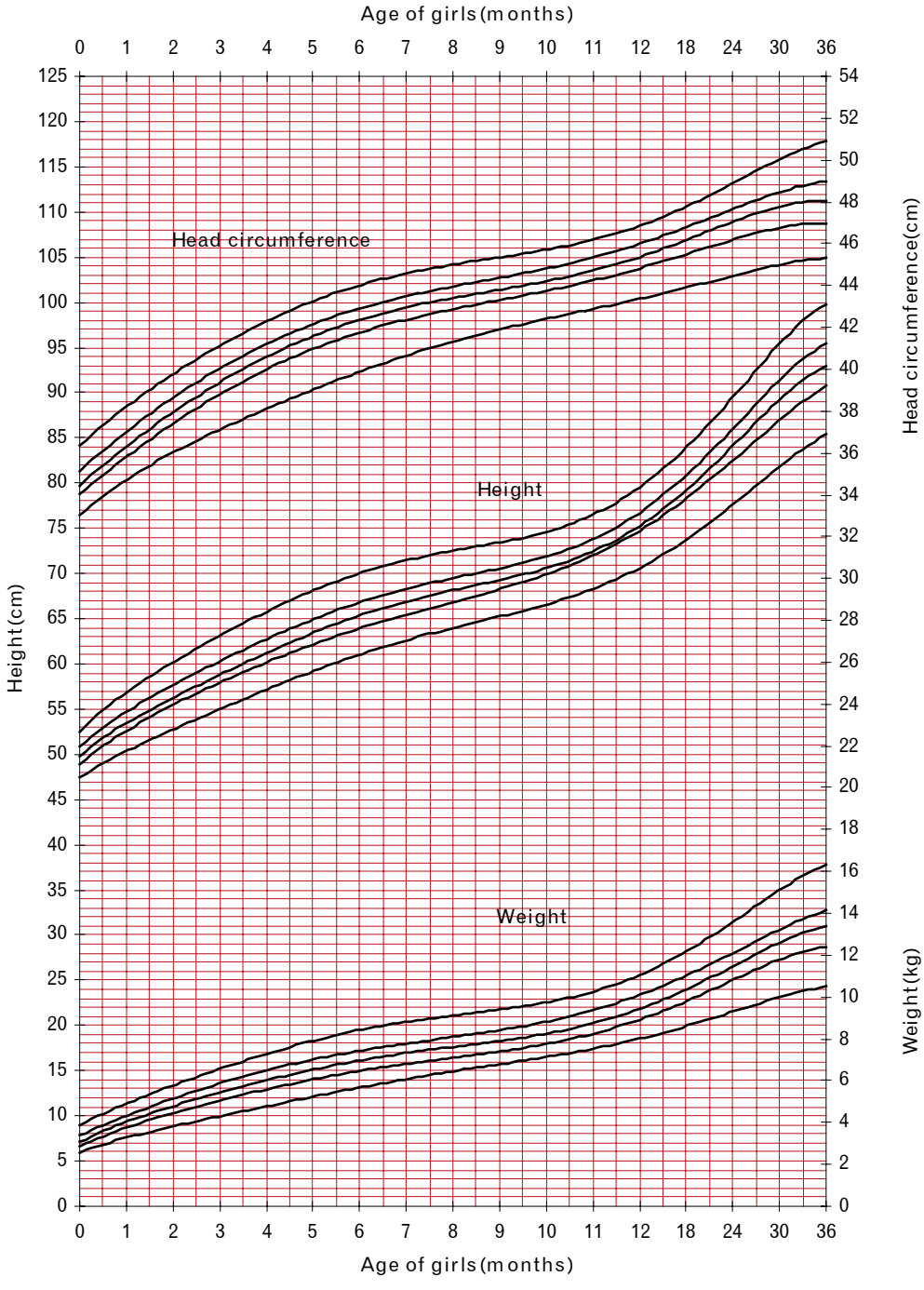
Growth Monitoring Chart

i. Height, weight and head circumference for boys from 0-36 months



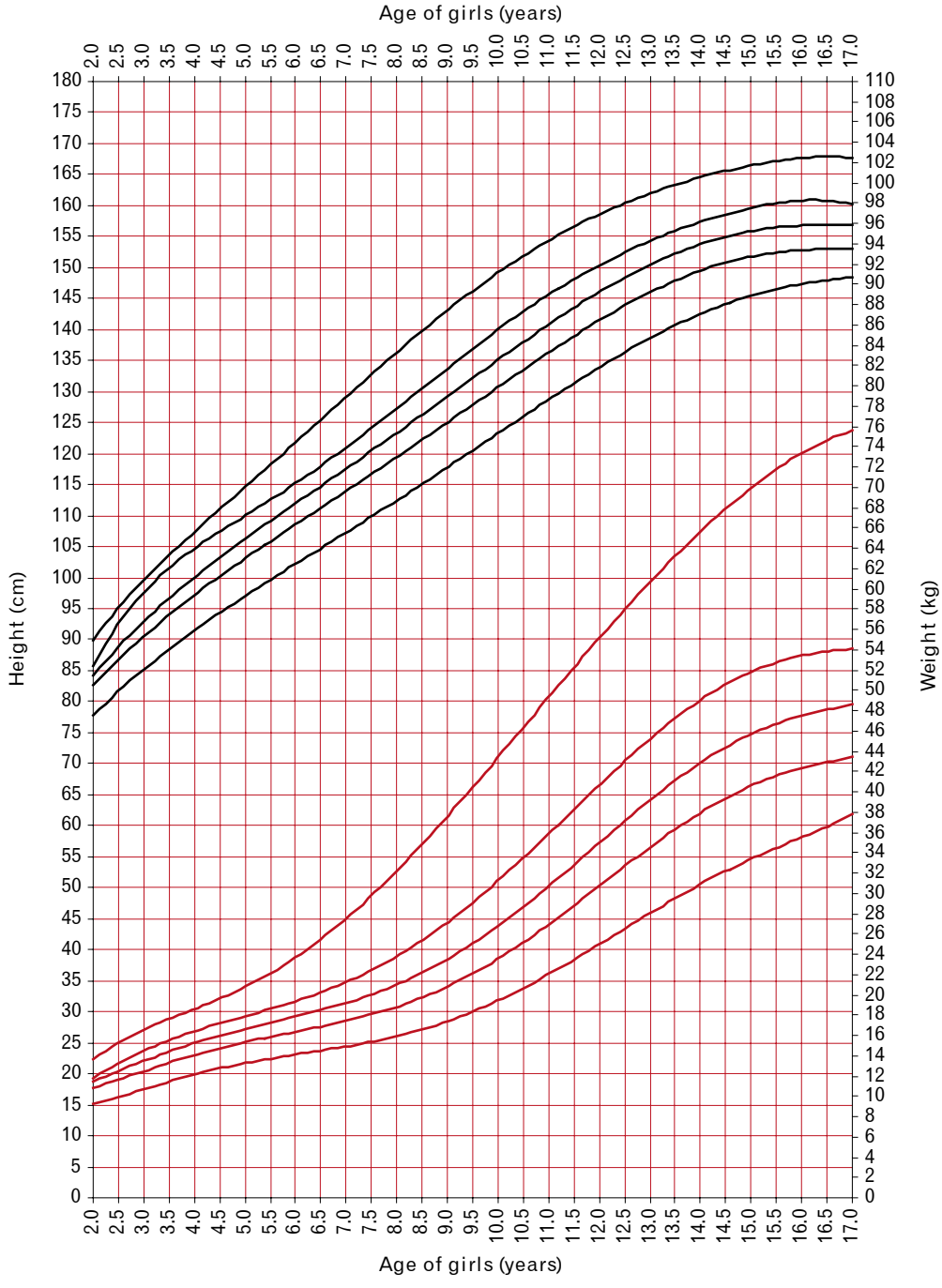
Source: **IAP growth charts.**

ii. Height, weight and head circumference for girls from 0-36 months



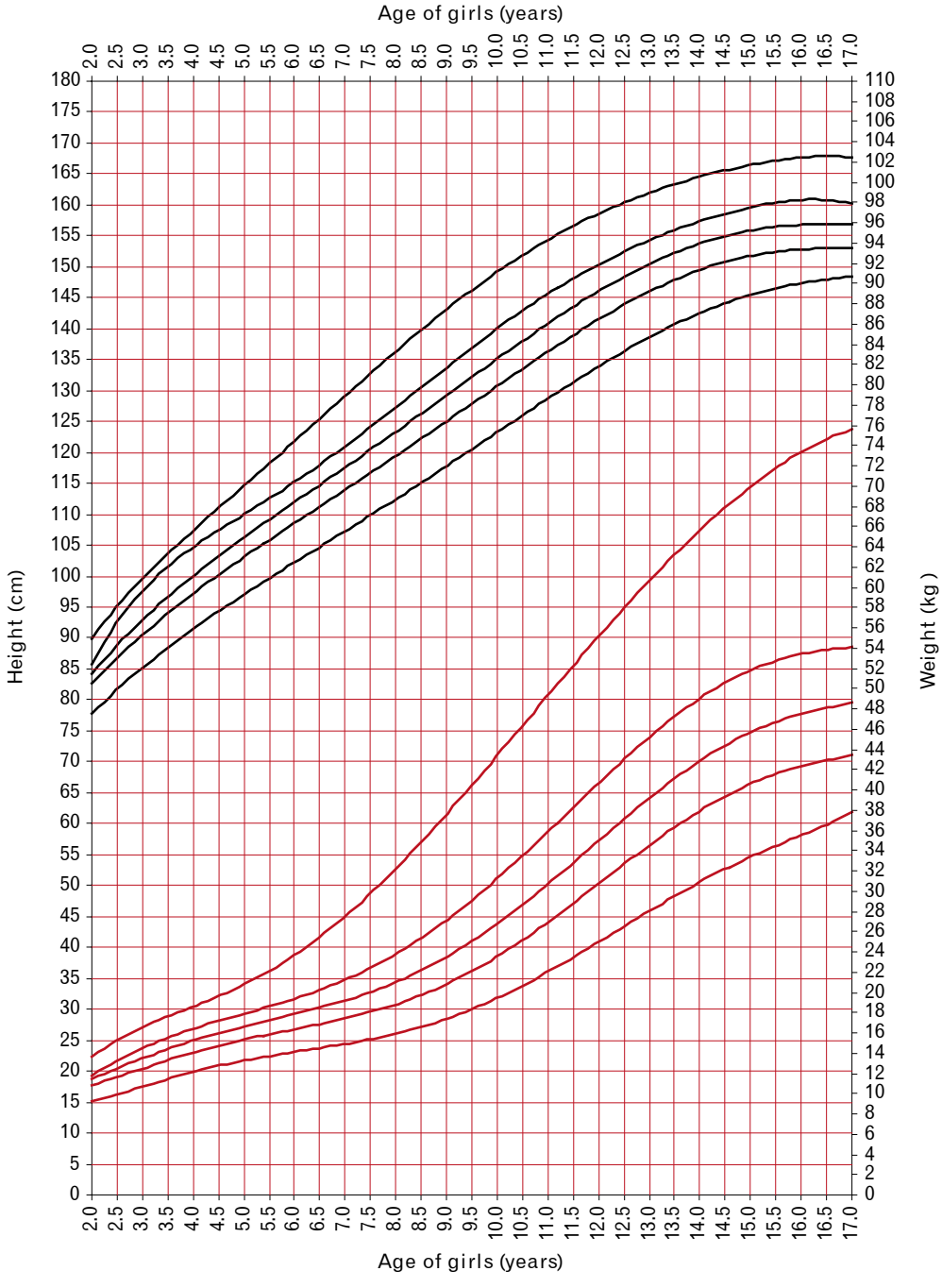
Source: **IAP growth charts.**

(iii) Height and weight for boys from 2-18 years:



Source: **IAP growth charts.**

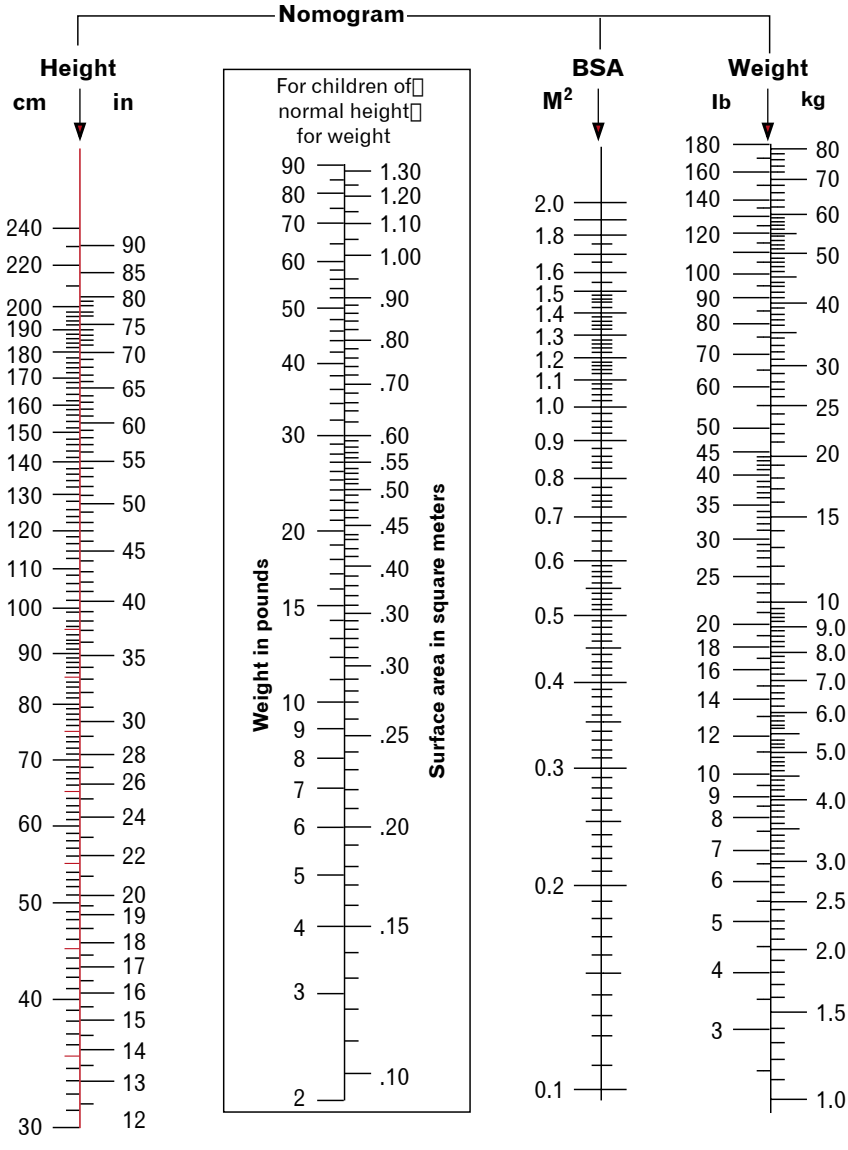
(iv) Height and weight for girls from 2-17



Source: **IAP growth charts.**

ANNEX

14 Estimation of Body Surface Area



West Nomogram (for Estimation of BSA). The BSA is indicated where a straight line connecting the height and weight intersects the BSA column or, if the patient is roughly of normal proportion, from the weight alone (enclosed area). (Nomogram modified from data of E. Boyd by C.D. West; from voughan, V.C., and R. J. Mckay, eds., *Nelson Textbook of Pediatrics*, 12th ed., Philadelphia:saunders, 1983.)

ANNEX

15

Immunization Chart for Children Living with HIV

(From: GOI and IAP recommendations on immunization)

Age	Vaccine	Remarks
Birth	BCG + OPV 1 + HBV 1	
6 weeks	DPT 1 + OPV2 + HBV 2	
10 weeks	DPT2 + OPV 3	
14 weeks	DPT 3 + OPV 4	
6-9 months	OPV 5 + HBV 3	Assess clinical status of child before giving live vaccines
9 months	Measles Vitamin A	Assess clinical status of child before giving live vaccines
15-18 mo	MMR DPT1 booster OPV 6	Assess clinical status of child before giving live vaccines
5 years	DPT2 booster OPV 7	Assess clinical status of child before giving live vaccines
10 years	TT3	
15-16 years	TT4	

Notes:

- Inactivated Polio vaccine (IPV) is now registered in India, and will be available soon.
- Generally, if the HIV-infected child is asymptomatic or mildly symptomatic – vaccinations should be given.
- Withold vaccine (live vaccines) for HIV-infected children who are symptomatic and severely immuno-compromised.
- Other vaccines not within the normal EPI schedule include: Japanese B encephalitis, chickenpox vaccine, Haemophilus influenza B, etc

Instructions for use of the Pediatric ART dosing disc for FDCs:

The pediatric ART drug dosing discs provides dosing information for 2 ART regimen:

a. Stavudine + Lamivudine + Nevirapine (for children > 5 kg)
b. Stavudine + Lamivudine + Efavirenz (for children > 10 kg, older than 3 years)

Instructions:

1. First select the regimen.
2. Thereafter, select the weight band in which the child's weight fits.

Nevirapine based regimen

1. The window in the bottom half of the disc will show the formulation to be used and the AM (morning) and PM (evening) doses.
2. For the first 2 weeks of the treatment, nevirapine has to be administered once a day. This can be achieved by administering the AM dose using the 2 drug FDC (Stavudine + Lamivudine) and the PM dose using 3 drug FDC (Stavudine + Lamivudine + Nevirapine). After this 2 week period, only 3 drug FDC has to be used for both AM and PM doses.

Example: The child's weight is 12.5 kg.This lies in 12- 13.9 kg weight band. Once we select this weight band, the window in the bottom half will show the following

Medicine	FDC-10
AM	1.5
PM	1.0

So, the prescription for the first 2 weeks will be:

i. Tab FDC 10 (2-drug) 1.5 tab in morning
ii. Tab FDC 10 (3-drug) 1 tab in evening

For 2 weeks

After 15 days, the prescription should read:

Tab FDC-10 (3-drug) 1.5 tab in morning & 1 tab in evening.

Please ensure that the interval between the AM and PM doses is approximately 12 hours.

Efavirenz based regimen

The window in the bottom half will show the dose of 2- drug FDC to be administered in morning and evening (AM and PM). In addition, efavirenz has to be administered in evening (PM) only. The required dose is to be delivered using a tablet (EFV T) with/ without syrup (EFV S).

Example: The child's weight is 16 kg. This lies in 15- 16.9 kg weight band. Once we select this weight band, the window in the bottom half will show the following

Medicine	FDC-10
AM	1.5
PM	1.5
EFV T	1.0
EFV S	2.5 ml

So, the prescription should read:

i. Tab FDC-10 (2-drug) 1.5 tab in morning & 1.5 tab in evening
ii. Tab EFV (200 mg) 1 tab in evening
iii. Syrup EFV 2.5 ml in evening

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