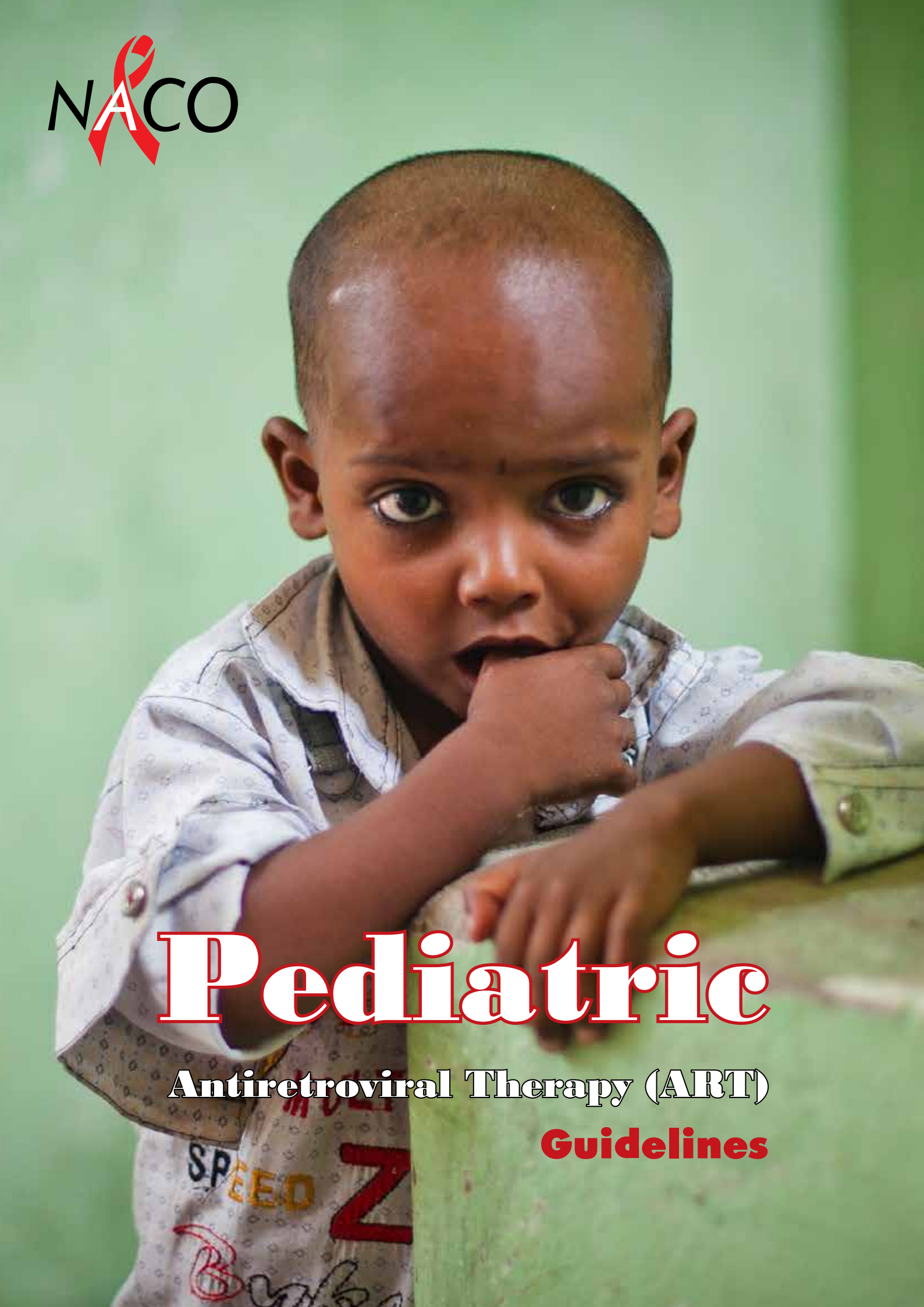

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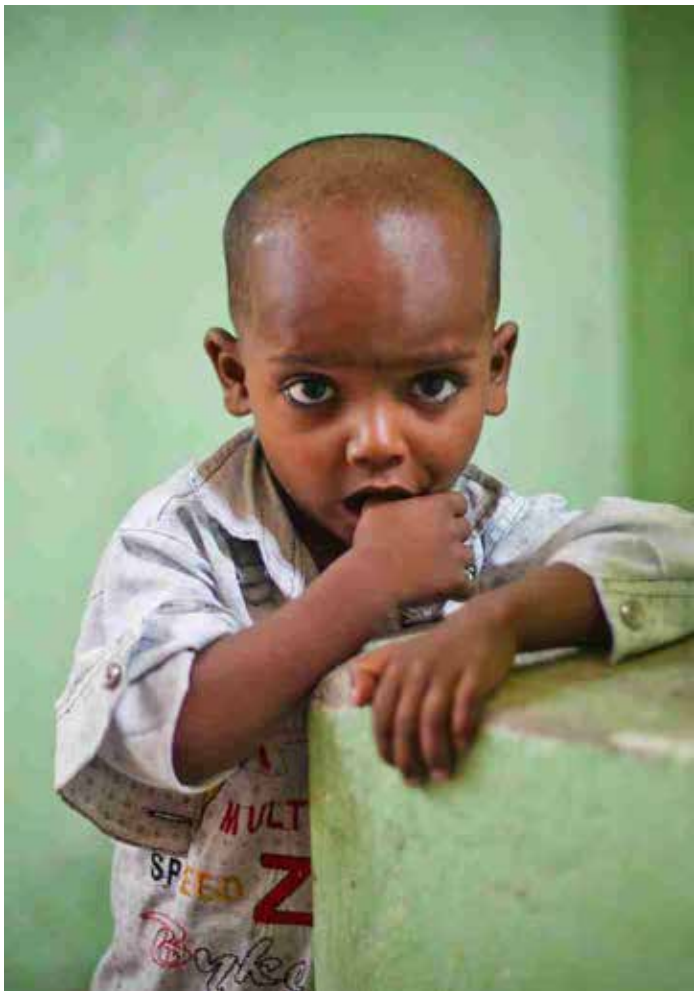

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Contributions

Writing group :

Guidance group :

Mentors :

Foreword

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	Bron Choalveolar Lavage
CD4	CD4+ T-lymphocyte
CMV	Cytomegalovirus
CNS	Central Nervous System
CSF	Cerebro Spinal Fluid
d4T	Stavudine
ddI	Didanosine
DNA	Deoxyribonucleic Acid
EFV	Efavirenz
EID	Early Infant Diagnosis
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 ITnhibitor
NVP	Nevirapine
OHP	Oral Hairy Leukoplakia
OI	Opportunistic Infection
PCP	Pneumocystis jiroveci pneumonia (previously Pneumocystis cariniip 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	RTitonavir
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

Objectives of the Guidelines

Children of today are the youth of tomorrow. HIV infects this very precious generation and bear gave 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 the nations .

Although , children represent only 6 percent of all people infected with HIV/AIDS as of December 2005, they account for 18 represent of the 3.1 million AIDS deaths in 2005. Only 40,000 or 4 percent of the one million people who are 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 estimate 202,000 children infected by HIV/AIDS (UNAIDS 2004). Using a conservative vertical transmission rate of 30 percent 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 reas on for this lack of access for treatment of children with HIV/AIDS are manifold and include,

- 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 the 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 , the 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 at the ART centers, on the practical issues regarding care and treatment of HIV among 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-exposure 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.

These guidelines are based on the WHO 2006 guidelines on ART in infants and children in limited resource 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 and more evidences become available .

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SECTION

A

Care of HIV exposed Infants and children

A1: HIV exposure in infants and young children

A2: Care of Exposed Infant/Child

A1: HIV exposure in infants and young children

A1.1 HIV exposure in infants and young children

A1.1.1 Burden of Pediatric HIV

Globally, the number of children younger than 15 years living with HIV infection has increased from 1.6 million in 2001 to 2.5 million in 2009. In 2009 alone, globally, 370,000 children under the age of 15 years were newly infected, i.e. approximately1,000 a day; and 260,000 children died, the majority under the age of five.

However, the number of newly infected children has been declining since 2003 due to increasing access to prevention of parent to child transmission (PPTCT) services. According to the UNAIDS report on the global AIDS epidemic 2010, in Asia, in 1999, 26,000 children were newly infected with HIV whereas in 2009, number of HIV infected children declined to 22,000. AIDS related deaths among children less than 15 years of age has also declined by 15 percent since 2004.

It is estimated that currently about 115,000 children are living with HIV in our country. Access to HIV testing and counseling is available at 5,069 ICTCs nationwide, enabling more and more children to be diagnosed and included into care, support and treatment services. As on March 2013 (NACO), 35,345 children less than 15 years were provided with ART by the national programme at 400 ART centers and 810 LACs. Most of these are older children, above 5 years of age. Asymptomatic children under 18 months were not getting diagnosed earlier and were missing out on prevention, care, support and treatment. However, with early infant diagnosis with DNA PCR becoming available in the national programm e, more infants and children are now being brought into the fold of care, support and treatment.

A1.1.2 Modes of transmission

90 percent of the children living with HIV are infected through mother-to-child transmission during pregnancy, around the time of birth or through breast feeding.

Table 1: Estimated risk and timing of Mother to child transmission(MTCT) in the absence of interventions

Timing of HIV Infection	% of Chidlren at risk
During pregnancy	5–10
During labour and delivery	10–15%
During breast feeding	5–20%
Overall risk without breast feeding	15–25%
Overall risk with breast feeding to 6 months	20–35%
Overall risk with breast feeding to 18 to 24 months	30–45%

Source: De Cook KM, et al. JAMA.2000; 283(9):1175-82

Other routes of transmission include

- transfusion with blood products from HIV-infected donor,
- injections with contaminated needles and
- sexual transmission either through sexual abuse or among children/adolescents with early sexual contact (Table 1).

India, has an estimate of 29 million pregnancies annually and a overall HIV prevalence of 0.40 percent in antenatal women,

It is estimated that there are 38,200 (using Spectrum modeling) HIV–infected pregnant women annually. If no intervention is done, this would mean adding 11, 460 infants with HIV infection, using a conservative vertical transmission rate of 30 percent. However, with the present national PPTCT program me (sdNevirapine), this figure should be estimated at approximately 3,800 infants with HIV infection through vertical transmission, and this would rather decline to 1,900 or less, if the revised more efficacious PPTCTprogramme is (Option B) rolled out across the country.

In the absence of any intervention, a substantial proportion of children born to women living with HIV infection will acquire the virus from their mother during pregnancy, labour, delivery and through breastfeeding. Without any intervention, the risk of transmission from parent-to-child is estimated to be 20-45 percent The use of antiretroviral (ARV) drugs for the prevention of parent-to-child transmission of HIV (PPTCT) has been shown to be effective for over a decade.

The use of single dose Nevirapine (sd-NVP) at the onset of labour significantly reduces peri-partum HIV transmission. However, this approach is less effective than other ARV prophylactic regimen and may be associated with acquisition of viral resistance to non-nucleoside reverse transcriptase inhibitor (NNRTI) drugs. Additionally, the use of sd-NVP does not reduce HIV transmission risk during the breastfeeding period.

- In the last few years, new evidence on ARV prophylaxis to prevent HIV transmission from parent-to-child and optimal timing of ART initiation has been accumulated, it includes:
- Early initiation of ART is associated with improved survival and reduced HIV-related morbidity. In pregnant women, the early initiation of ART will not only benefit maternal health, but can also have a significant impact on MTCT. Women with more advanced HIV infection (CD4 < 350 cells/mm3) account for more than 75 percent of the HIV transmission to their child.
- Longer the ARV prophylactic regimen for PPTCT, started earlier during pregnancy has , more benefit in preventing HIV transmission
- Extended ARV prophylaxis to mothers and/or infants during the breastfeeding period will significantly prevent transmission through breastfeeding.

With the rapid and significant expansion in the National AIDS Control Program including. the PPTCT, ICTC, ART (for adults and children) programs, including access to early diagnosis for HIV testing of infants and children below 18 months of age, it is now possible to ensure that HIV exposed and infected infants and children receive the required essential package of care.

Care of the HIV exposed infant starts in pregnancy itself. In the new guidelines, there has been a paradigm shift linking PMTCT to pediatric care and support. PMTCT, care of the HIV exposed infant/ child and ART in children should be the continuum of care. The mission of PMTCT services should be elimination of HIV of mother to child transmission.

A2: Care of Exposed Infant/Child

HIV disease progresses very rapidly in most young children, especially in the first few months of life, often leading to death. HIV infected infants frequently present with clinical symptoms in the first year of life. Without care and treatment, about one third of infants living with HIV will die in their first year of life and almost half of the children with HIV will die the second year of life.

A2.1 Definition of HIV-exposed Infant/Child

Infant and child born to HIV infected woman, are reliably excluded or confimed with HIV status and the infant or child is no longer exposed to HIV through breast feeding.

A2.2 Components of Care

Components of Care of HIV-Exposed Infant/Child

2.2.1 Immediate Care at Birth

2.2.2 Infant feeding

2.2.3 ARV prophylaxis

2.2.4 Cotrimoxazole prophylaxis (CPT)

2.2.5 Immunization and Vitamin A Supplementation

2.2.6 Growth and Development

2.2.7 Early infant diagnosis

2.2.8 Follow up

A2.2.1 Immediate Care at Birth

The immediate care of the newborn infant at birth should follow standard neonatal care guidelines including resuscitation guidelines.

However , the following should be adhered to:

- Follow universal precautions.
- Do not milk the cord.
- The cord should be clamped soon after birth.
- Cover the cord with gloved hand and gauze before cutting to avoid blood splattering.
- Initiate breast feeding within the first hour of birth in accordance with the preferred and informed choice of the mother.

A2.2.2 Infant Feeding

Counseling for infant feeding should begin in the antenatal period.

- All HIV infected pregnant women should be informed about infant feeding options, viz. exclusive breast feeding or exclusive replacement feeding. Breast feeding is the preferred choice in developing countries as it maximizes the chances of survival of the infant. Breast-feeding provides the infant with all required nutrients and immunological factors that help to protect against common infections.
- Mixed feeding i.e. breast milk and replacement feeds combined increases the risk of transmission of HIV and should be avoided at all cost.

The health care providers and counselors should be trained to help the pregnant women in reaching the right decision and to support them in implementing breast feeding.

The 10 principles of infant feeding for HIV-infected women are:

1. All HIV positive pregnant women should have PPTCT interventions provided early in pregnancy as far as possible. The interventions include either maternal or infant ARV prophylaxis during the duration of breast feeding.
2. Exclusive breast feeding is the recommended infant feeding choice in the first 6 months, irrespective of whether mother or infant is provided with ARV drugs for the duration of breastfeeding.
3. Only in situations where breastfeeding cannot be done or on individual parents' informed decision, then replacement feeding may be considered only if all the 6 criteria for replacement feeding are met (Table 2).
4. Mixed feeding should not be practiced for the first six months as it enhances the risk of transmission of HIV to the infant.
5. Exclusive breast feeding should be done for first 6 months, after which complementary feeding should be introduced gradually, irrespective of whether the infant is diagnosed
6. With HIV infection or is uninfected by early infant diagnosis.
7. Mother should receive ARV prophylaxis or ART during the whole duration of breast feeding . ARV prophylaxis should continue for one week after the breast feeding has completely stopped.
8. Breast feeding should be stopped once a nutritionally adequate and safe diet without breast milk can be provided.
9. For breast feeding infants who are diagnosed HIV uninfected, breast feeding should be continued till 12 months of age.
10. For breast feeding infants diagnosed HIV infected, ART should be started and breast feeding should be continued till 2 years of age (Table 3).
11. Abrupt stopping of breast feeding should NOT be done. Mothers who decide to stop breast feeding should stop gradually over one month..

Table 2 : Infant feeding options for HIV exposed infants < 6 months of age.

The 2011 National Guidelines on Feeding for HIV-exposed and infected infants < 6 months old recommends: Exclusive breastfeeding for first 6 months and continue breast feeding till 12 months where possible.

Only in situations where breast feeding is not possible (maternal death, severe maternal sickness etc.) or individual mother's informed choice, then replacement feeding may be considered and only if ALL the 6 criteria for replacement feeding are met.

1. Safe water and sanitation are assured at the household level and in the community.
2. The mother or other caregiver can reliably afford to provide sufficient replacement feeding (milk), to support normal growth and development of the infant.
3. The mother or caregiver can prepare replacement feeding frequently enough in a clean manner, so that it is safe and carries a low risk of Diarrhoea and malnutrition.
4. The mother or caregiver can, in the first six months exclusively give replacement feeding.
5. The family is supportive of this practice, and
6. The mother or caregiver can access health care that offers comprehensive child health services.

Table 3 : Summary table of feeding guidelines in HIV for infants and children < 2 years of age.

Situations	Until first 6 Months	Beyond 6 months
Situation 1 **Mother on ART for her own health**	EBF ¥ Mother on ART ensures safer breast feeding	Continue Breast Feeding till 12 months.*
Situation 2 **Mother and infant on ARV Prophylaxis for PPTCT**	EBF ¥ Mother on triple ARV prophylaxis during breastfeeding will make breast feeding safer	Introduce complementary feeding from 6 months onwards**
Situation 3 **No access to ARV during breast feeding**	EBF ¥ (unless conditions suitable for RF@)	Introduce complementary feeding from 6 months onwards. ▪ If nutritionally adequate and safe diet ensured, stop BF gradually. ▪ If not feasible, continue BF until safe diet ensured.§
Situation 4 **Infant detected HIV infected, and initiated on ART**	EBF ¥	Introduce complementary feeding from 6 months onwards Continue breast feeding up to two years or beyond. Stop breast feeding gradually as per mother's choice §

* *If child found to be HIV negative through EID, continue breast feeding till 12 months. If found to be HIV positive through EID, continue breast feeding till 2 years.*

** *All children more than 6 months of age should be started on complementary feeding as per usual practice .*

¥ *EBF means that infants are given only breast milk and nothing else – no other milk, food, drinks and water.*

The infant receives only breast milk and no other liquids, or solids; with the exception of drops or syrups consisting of vitamins, mineral supplements or medicines.

§ *Do not stop breast feeding abruptly. Stop breast feeding gradually according to comfort level of mother and infant.*

@ *In situations where women opt for replacement feeding or where breastfeeding is not possible (maternal death or sickness), two options are available:*

1. Locally available animal milk (unmodified)

2. Commercial infant feeding formula.

(See section on nutritional guidelines for details)

A2.2.3 ARV Prophylaxis

ARV prophylaxis to the infant must be given in accordance with the current National PPTCT Guidelines. For all the exposed infants, Syp. NVP has to be given for 6 weeks and these children have to be linked to the EID programme. The ART provision shall depend on the result of EID.

In the revised PPTCT guidelines (NACO, 2012), there is provision for ARV to mother during pregnancy, intra partum and through post partum period and also to the infant.

All Infants born to women who are receiving ART / maternal triple ARV prophylaxis / who present directly-in-labor and receive intra partum ARV prophylaxis should be started on daily NVP prophylaxis at birth and continue for a minimum of 6 weeks (i.e., till the first immunization visit for the infant).This regardless of whether the infant is exclusively breastfed or receives replacement feeding it helps in reducing the risk of postpartum HIV transmission.

In situations, where infants born to women who present directly-in-labor and receive intra partum ARV prophylaxis, the daily NVP prophylaxis for the infant should not be stopped at 6 weeks of life. These infants should be continued on NVP prophylaxis until the mother initiated on ART/ARV prophylaxis and complete a minimum of six weeks of therapy (Table 4).

Table 4 : Dose and Duration of Infant Daily NVP Prophylaxis

Birth Weight	NVP daily dose(in mg)	NVP daily dose(in ml)*	Duration
Infants with birth weight < 2000 gm	2 mg/kg once daily	0.2 ml/kg once daily	Upto 6 weeks** irrespective of exclusively breast fed or exclusive Replacement fed
Birth weight 2000 – 2500 gm 10 mg	10 mg once daily	1 ml once daily	
Birth weight more than 2500 gm	15 mg once daily	1.5 ml once daily	

* *Considering the content of 10 mg Nevirapine in 1ml suspension*

** *In situations, where infants born to women who present directly-in-labour and receive intra partum ARV prophylaxis, the daily NVP prophylaxis for the infant should not be stopped at 6 weeks of life. These infants should be continued on NVP prophylaxis until the mother initiated on ART/ARV prophylaxis and complete a minimum of six weeks of therapy.*

A2.2.4 Cotrimoxazole Preventive Therapy (CPT) for HIV-Exposed/Infected infants and Children

Cotrimoxazole Preventive Therapy (CPT) protects the infant from Pneumocystis jiroveci pneumonia (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 receive CPT from the age of 6 weeks until HIV is reliably excluded. In all those confirmed to be HIV-infected, it should be continued till 5 years of age (Table 5). The recommended dose is 5 mg/kg/day of TMP once daily (Table 6).

Children with the history of severe adverse reaction (grade 4 reaction) to Cotrimoxazole or other sulfa drugs and children with G6PD (glucose-6-phosphate dehydrogenase deficiency) should not be initiated on CPT. The alternative drug is Dapsone 2 mg/kg once daily (not to exceed 100 mg/day) orally. Aerolised pentamidine for children > 5 years administered via respigard II inhaler in the dose of 300 mg once a month is another alternative.

Table 5: Indications for CPT prophylaxis

Group	When to start Cotrimoxazole?	When to discontinue CPT prophylaxis?
All HIV-exposed infants/ children	From 6 weeks of age (or at first encounter with health services)	HIV infection has been reliably excluded by a negative antibody test at 18 months, regardless of ARV initiation
All HIV-infected infants and children upto 5 year of age	Irrespective of WHO stage or CD4 counts or CD4%	At 5 yrs of age, 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 WHO T - stage 1 or 2 and CD4 count of > 350 cell/mm3 on two occasions not less than 3 months apart
All HIV-infected children > 5 years of age	WHO Stage 3 and 4 irrespective of CD4 OR CD4 < 350 cells/mm3 irrespective of WHO staging	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 WHO T- stage 1 or 2 and CD4 count of > 350 cell/mm3 on two occasions not less than 3 months apart
As secondary prophylaxis	After completion of treatment for PCP	— < 5 years old: do not stop — > 5 years old: may consider stopping as per the adult guidelines

A2.2.4.2 Co-trimoxazole desensitization

Co-trimoxazole desensitization has been shown to be successful and safe in approximately 70 per cent of patients with previous mild to moderate hypersensitivity. If the patient reports a history of hypersensitivity to sulpha-containing drugs, desensitization regimen should be attempted only in a hospital setting.

Desensitization should not be attempted in individuals with a history of severe co-trimoxazole or other sulphonamide reaction. Desensitization can be attempted two weeks after a non-severe (grade 3 or less) co-trimoxazole reaction which has resulted in a temporary interruption in the use of the drug. If any reaction occurs, the desensitization regimen should be stopped. Once the patient recovers fully, dapsone at a dosage of 100 mg per day shall be tried. Some patients may be allergic to both co-trimoxazole and dapsone. There are no other drug options for prophylaxis available in resource-limited settings.

	Step	Dosage
Day 1	80 mg SMX + 16 mg TMP	2 ml oral suspension
Day 2	160 mg SMX + 32 mg	4 ml oral suspension
Day 3	TMP 240 mg SMX + 48 mg	6 ml oral suspension
Day 4	TMP 320 mg SMX + 64 mg TMP	8 ml oral suspension
Day 5	400 mg SMX + 80 mg TMP	One single-strength SMX-TMP tablet
Day 6	800 mg SMZ + 160 mg TMP	Two single-strength SMX or One double-strength SMX-TMP tablet

A2.2.4.2 Dose of Cotrimoxazole for PCP Prophylaxis

Table 6: Weight and Age based dosing for TMP/SMX (CTX) prophylaxis

Weight (kg)	Approx. Age	CTX once a day			
		Syrup 5 ml (40 TMP / 200 SMX)	Child tablet (20 TMP, 100 SMX)	Single strength adult (80 TMP/400 SMX)	Double strength adult tablet (160 TMP/800 SMX)
< 5	6 wk -2 months	2.5 ml	1 tablets	-	-
5-10	2-12 months	5 ml	2 tablets	½ tablet	-
10-15	1-2 years	7.5 ml	3 tablets	½ tablet	-
15-22	2-5 years	10 ml	4 tablets	1 tablets	½ tablet
>22	> 5 years	15 ml	-	1 ½ tablet	½ to 1 tablet depending on weight

*Dosage: 5mg/kg of TMP/day orally once daily *splitting of tablets into quarters is not recommended, unless there is no syrup available.*

- *Patients and families should be emphasized upon the fact that Cotrimoxazole does not treat and cure HIV Infection.*
- *Counsel caregivers well for side-effects to CPT (although these are not common).*
- *Discontinue CPT if: Stevens - Johnson syndrome, severe liver disease, severe anemia, severe pancytopenia or completely excluded HIV Infection.*

A2.2.5 Immunization And Vitamin A Supplementation

HIV-exposed /infected children should be immunized according to the following schedule:

- Live vaccines should be avoided in all severely immune compromised infants (CD4 %< 25% or WHO stage 3 and 4).
- Vitamin A supplementation should be as per the national immunization schedule.
- National Immunization schedule is as follows:

Table 7 : Immunization chart for children living with HIV

Age	Vaccines	Age	Vaccines
Birth	OPV	9 months	Measles
	BCG		
	Hepatitis B		
6 weeks	OPV	15 months	MMR
	DPT		
	Hepatitis B		
	Hib*		
10 weeks	OPV	18 months	OPV DPT Hib*
	DPT		
	Hepatitis B		
	Hib*		
14 weeks	OPV	4.5- 5 years	OPV DPT
	DPT		
	Hepatitis B		
	Hib*		

*Available only at few states

Additional vaccines like varicella, MMR, IPV, Pneumococcal, Hepatitis A – as per IAP schedule. Live vaccines should be avoided in symptomatic children till such a time when there CD4 improves as a response to ART.

A2.2.6 Growth and Development

Growth monitoring:

Growth monitoring should be done using MCP growth charts in all HIV exposed infants and children as per scheduled visits (refer 2.2.8) (For further details, refer to section on Nutrition). If the child's growth curve is falling down, flattening or faltering, reinforce nutrition and work up for urgent assessment for nutrition status, 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. For the children on ART with growth flattering or decline, look for treatment failure.

Developmental Assessment:

All children require a routine development milestone screening to detect delays or regression of milestones. Early detection allows

for early interventions which is a key to successful management. For most busy clinicians, it is suggested that One should keep in mind the "Red Flags" for referral and a basic table of milestones up to 24 months of age for rapid routine assessments (Table 8). Only then it shall be necessary to refer to a Pediatrician and Child Psychologist.

Delayed development or loss of milestones after attaining them (Regression of Milestones), may be the first sign of HIV infection suggesting HIV encephalopathy, if other common causes are ruled out. Even in these circumstances, early identification of developmental delay and neurologic abnormalities, confirmation of HIV and initiation of ART can facilitate intervention and suitable remedial actions. Therefore it is crucial to assess the development in an HIV-exposed /HIV-infected infant and child (Table 8).

Table 8 : Developmental Red Flags.

Age	Red Flag
4-6 months	• Poor head control • Failure to smile • Failure to reach for objects by 5 months
6-12 months	• No baby sounds or babbling • Inability to localize sounds by 10 months
12-24 months	• Lack of consonant production • Hand dominance prior to 18 months (indicates contralateral weakness) • No imitation of speech and activities by 16 months
Any age	• Loss of previously attained milestones

(Baylor College of Medicine's HIV curriculum for the Health Professional, 2006)

Table 9: Development Milestones.

Age (months)	Gross Motor	Fine Motor	Social Skills	Language
3	Supports weight on forearms	Opens hands spontaneously	Smiles appropriately	Coos, laughs
6	Sits momentarily	Transfers objects	Shows likes and dislikes	Babbles
9	Pulls to stand	Pincer grasp	Plays pat-a-cake, peek-a-boo	Imitates sounds
12	Walks with one hand held	Releases an object on command	Comes when Called	1-2 meaningful words
18	Walks upstairs with assistance	Feeds from a spoon	Mimics actions of others	At least 6 words
24	Runs	Builds a tower of six blocks	Plays with Others	2-3 word sentences

(From Nelson's Textbook of Pediatrics)

A2.2.7 Diagnosis of HIV infection in Infants and Children

A. Early Infant Diagnosis

Maternal HIV antibody transferred passively during pregnancy can persist for as long as 18 months in children born to HIV-infected mothers. Hence, positive HIV antibody test does not necessarily indicate HIV infection in the infant/child. In children who are breastfed, since they have ongoing risk for HIV transmission, HIV infection can only be excluded after 6 weeks of complete cessation of breast-feeding.

In the current Early Infant Diagnosis (EID) program, virological tests i.e. HIV-1 DNA PCR by Dried Blood Spot (DBS) and on Whole Blood Sample (WBS) are being done for infants and children below

18 months of age, as per the algorithm (Below). Antibody tests, using rapid test method can be used for children > 18 months of age for diagnosis of HIV infection as in adults.

A2.2.8 Follow-up of HIV exposed infants and children

In view of ARV prophylaxis to all exposed babies for at least 6 weeks of age, the first follow up visit should be at 2 weeks of age. During the first follow up visit at 2 weeks of life, child should be looked for any adverse reaction to NVP. The subsequent visits should be according to the immunization schedule starting at 6 weeks of age.

The road to health card for HIV-exposed children will include information on maternal HIV status, Co-trimoxazole prophylaxis, infant HIV diagnosis and infant feeding information.

The exposed infants and children should be followed up at ICTCs at 6, 10, 14 weeks of age and then at 6, 9, 12 and 18 months of age. If they test positive by DBS-DNA PCR test done at ICTC, they should be referred to ART centre for confirmation of the diagnosis by WBS-DNA PCR.

Table 10 : Activities at each follow up visit.

Activities at each follow up visit								
Visit	**Birth**	**6 Weeks**	**10 Weeks**	**14 Weeks**	**6 months**	**9 months**	**12 months**	**18 months**
Cotrimoxazole prophylaxis therapy (CPT)		• Start from 6 weeks (or first immunisation visit) for all HIV-exposed infants and children • Continue CPT: for those tested to be HIV infected • Stop cotrimoxazole: for those tested to be HIV un-infected						
NVP prophylaxis	✓	• Stop at 6 weeks of life or at least6 weeks of ART to mother whichever is later						
Counselling for Infant feeding	✓	✓		✓	✓	✓	✓	✓
Start complementary feeds					6 months onwards irrespective of HIV status.			
Growth monitoring	✓	✓		✓	✓	✓	✓	✓
Developmental assessment	✓	✓		✓	✓	✓	✓	✓
Immunisation & Vitamin A supplements	BCG OPV 0 HBV0*	OPV 1 DPT 1 HBV 1 Hib1		OPV 2 DPT 2 HBV2 Hib 2	OPV 3 DPT 3 HBV 3* Hib 3		OPV 4 Measles Vit. A		OPV DPT (B) Vit. A
Clinical assessment	✓	✓		✓	✓	✓	✓	✓
HIV testing (✓-if required)		✓			✓		✓	✓
Follow the National and State Immunisation Protocols								

At every visit, give information and address to the mother or caregiver on common HIV related conditions, availability of EID, psycho-social concerns, reinforce the importance of Co-trimoxazole prophylaxis, infant feeding and the importance of follow up and adherence to ARV prophylaxis/ART.

A2.2.9 Counselling and Psychosocial support

Appropriate counselling is ultimately the responsibility of the team providing care to the HIV exposed infant and child. This would include.

- counseling on PPTCT, ARV prophylaxis,
- infant feeding,
- nutrition,
- EID,
- CPT initiation,
- vaccination,
- opportunistic infections,
- ART therapy and adherence

Counsellors must make sure that the psychosocial issues have been dealt appropriately. If the child is infected, the parent or the care giver must be explained what to expect with regard to the health of the child, starting of ART, prophylaxis for various OIs, 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 more details on Counselling support in Children)

SECTION

B

Pre-ART Care in Children

B1: Assessment and management after confirmed HIV infection in the child

Pre-ART care is the comprehensive care and regular monitoring of HIV infected children who are not yet eligible for ART (as per the national guidelines). It is essential in order to maintain a healthy positive living status until, these children require anti-retroviral therapy.

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

B1. Assessment and management after confirmed HIV infection in the child includes:

- Assess growth, development and nutritional status using standard techniques and scales, and assess the intervention needs. WHO growth charts should be used for assessment of growth . (refer to section on nutrition)
- Assess immunization status and provide appropriate immunization as per the National Immunization Schedule.
- Assess for signs and symptoms of opportunistic infections including tuberculosis (TB). If opportunistic infection is suspected, then diagnosis and treatment of OIs take priority over ART initiation. Screening for TB is strongly recommended in all HIV infected children as it is an important aspect of pre-ART care. (Refer to Section On Tuberculosis and HIV)
- Assign WHO clinical stage (Refer to Annexure -II WHO Clinical staging for infants and children with established HIV infection)
- A baseline and annual fundoscopic examination for evidence of CMV retinitis is recommended.
- Ensure that the child is on cotrimoxazole prophylaxis as per guidelines .
- Identify any concomitant medication use that may have drug interactions with ART.
- Perform baseline and six monthly follow up CD4 count or CD4%.
- Assess whether the child fits the criteria for starting ART according to clinical stage and/or CD4 counts or CD4%.
- Cascade screening - Screen the family for HIV and other OIs .
- Following Assessment to be done by the counsellor Psychosocial and family background assessment by the counsellor
- to identify primary caregiver for the child and his/her ability and willingness to adhere to follow up and administer medications, especially ART;
- to assess family members' understanding of HIV disease and treatment and
- family's 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.
- Assess disclosure of HIV status within the family (whether the child knows his/her status and whether anyone else knows, and also if the child knows the parent/s' HIV status)

Item	Baseline	Month 1	Month 2	Month 3	Month 6	Every 6 months
Item	✓		✓	✓	✓	✓
Clinical evaluation[a]	✓	✓	✓	✓	✓	✓
Weight, height	✓	✓	✓	✓	✓	✓
Nutritional status and needs	✓	✓	✓	✓	✓	✓
Cotrimoxazole needs and adherence[b]	✓				✓	✓
Counseling for prevention of STI and pregnancy in adolescents[c]	✓	✓	✓	✓	✓	✓
OI prevention and treatment needs[d]	✓	✓	✓	✓	✓	✓
Clinical Screening for TB	✓					✓
CD4 % or countse	✓					✓

Notes

a. *Includes history taking and physical exam and assessment of neurodevelopment. Children below 2 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. *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 .*

d. *Assessing TB exposure is important .*

e. *Children not yet eligible for ART should be monitored with CD4 every six months. For children who become symptomatic or whose CD4 approaches the threshold values, the CD4 can be repeated even before six months. CD4% is preferred in children below years of age for determining ART initiation and monitoring.*

SECTION

C

Antiretroviral Therapy (ART)

Pediatric formulations of Anti-Retro Viral (ARV) drugs have greatly improved the care of HIV infected children. Initiation of Antiretroviral Therapy (ART) at the earliest is crucial in reducing mortality and morbidity of infants and children. Recommendations for the care of those who are HIV-infected will change over time, but the challenges of providing this care are the major hurdles in managing both acute and chronic conditions. ART is a life-long therapy, and HIV-infected infants and children are surviving till adolescence and adulthood today.

C1 When to start ART for infants and children?

The decision to start ART, depends on, the age of the child, clinical and immunological staging.

C1.1 When to initiate ART in HIV-infected Infants and children less than 24 months?

- As per the newer recommendations, all HIV-infected children under 24 months of age should receive ART, regardless of their clinical or immunological status.

> **All children < 24 months of age** with confirmed HIV infection should be started on ART, irrespective of clinical or immunological stage.

C1.2 When to initiate ART in HIV-infected children 24 months of age and older?

In children aged above to 24 months, ART is initiated on the basis of clinical stage and /or CD4 %. Children older than 24 months, in clinical stages 3 and 4 should be initiated on ART irrespective of the CD4 counts or percent whereas in Clinical Stage 1 and 2, ART should be started when the CD4 value falls close to the threshold values set for each age group. A drop below the threshold value should always be avoided as it is associated with higher mortality.

> **For children ages 24 - 59 months, initiate ART for all children with**
>
> -Clinical Stage 3 and Stage 4 disease
>
> *and/or*
>
> -CD4 < 25% or CD4 count < 750/ mm^3
>
> For children aged > 60 months, initiate ART for all children with
>
> -Clinical Stage 3 and Stage 4 disease
>
> *and/or*
>
> CD4 count < 350/ mm^3

ART should generally be deferred until acute infections have been treated, whenever possible.

In the case of confirmed or presumptive TB disease, initiating TB treatment is the priority. Any child with active TB disease should be started on TB treatment immediately and ART should be started between 2 to 8 weeks of TB treatment, preferably as early as possible, irrespective of the CD4 count and clinical stage.

When decided to start ART, one should also consider the child's social environment, including identification of a clearly defined caregiver who understands the prognosis of HIV and the requirements of ART.

C1.2.1 Immunologic criteria for initiation of ART

- CD4 levels in children are considerably higher than in adults, however, the CD4 levels slowly decline to match adult values by the age of about 6 years. Therefore, immunologic criteria in HIV infected children below 6 years of age are different from those in HIV infected adults.
- In comparison to absolute CD4 counts, the CD4 percentage in young children vary less within age groups. Therefore, in children < 5 years of age, CD4% is considered for initiating ART.
- Serial CD4 measurements are more informative than individual values, as they reflect trends over time. Where ever possible, these assessments should compare the same parameter.

Table 12: Recommendations for initiating ART in HIV-infected infants and children according to clinical stage and immunological markers

	Clinical stage	Immunological
< 24 months	Treat all[a,b]	
≥ 24 months	WHO Stage 4[b]	Treat all[b]
	WHO Stage 3[b]	Treat all[b]
	WHO Stage 2	Treat when CD4 below /close to the age-adjusted threshold: 2-5 years:CD4% < 25% or absolute CD4 counts <750/mm^3 >5years: absolute CD4counts <350/mm^3
	WHO Stage 1	

a Baseline CD4 should be done for all children. This will be useful for monitoring even if it is not required for decision to initiate ART.

b Stabilize any opportunistic infection before initiation of ART

C1.3 Assessing the family's psychosocial readiness for ART

When deciding to start ART, one should also consider the child's social environment, including identifying a clearly-defined caregiver who understands the prognosis of HIV and the implications of ART (i.e. lifelong therapy, importance of adherence and also administration, toxicities and storage of drugs). Identifying a second (back-up) informed caregiver is also advised. Disclosure of HIV status to older children and their family members improves adherence and should be encouraged with the support from trusted health professionals. A family's access to adequate nutrition and support is equally important.

Figure 1: Initiating ART in Infants and Children

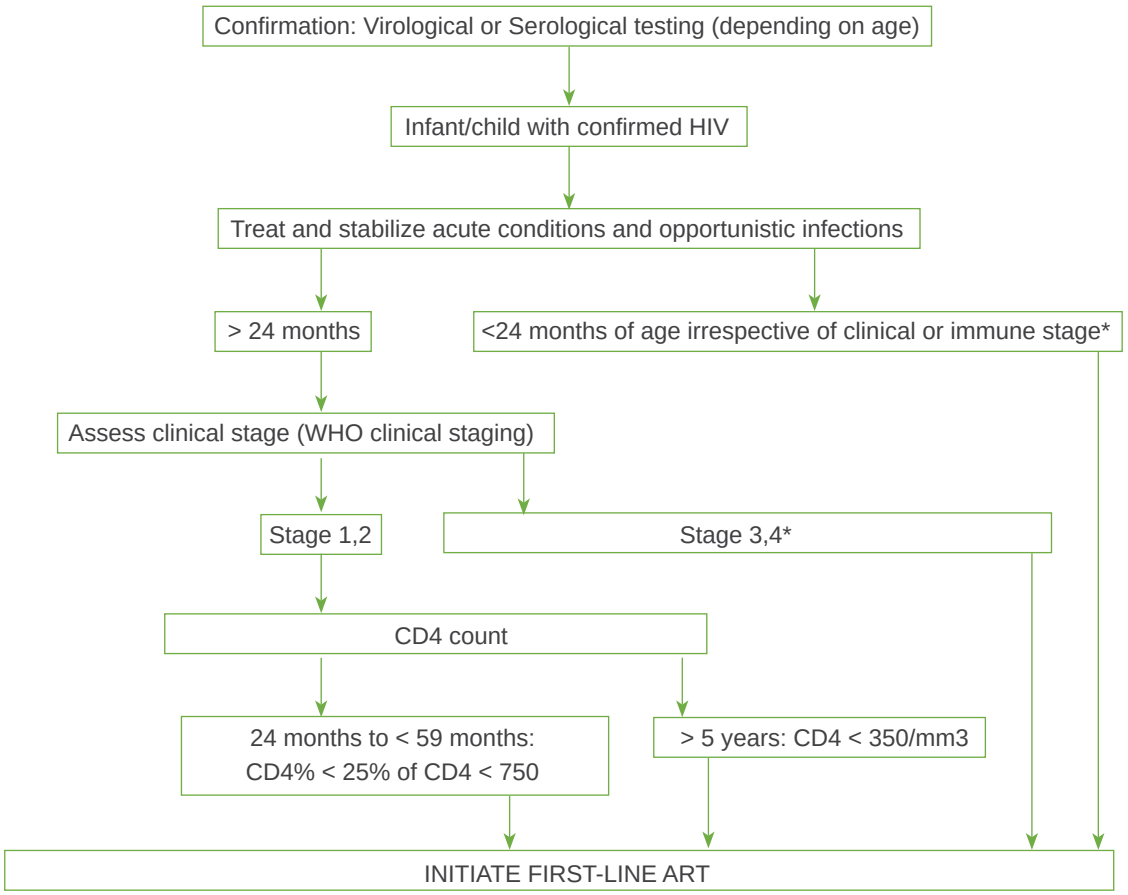
Baseline Clinical and Laboratory Assessment

Following confirmation of HIV infection, a baseline clinical assessment for children should include:

- Clinical staging of HIV disease
- Identification of active OI's, tuberculosis, concomitant medical conditions, pregnancy in adolescent girls
- Details of concomitant medications, including co-trimoxazole and traditional or herbal therapies
- Growth and nutritional (quality and quantity of intake) assessment including weight, height, head circumference and mid upper arm circumference.
- Developmental Assessment
- Sexual maturity (Tanner Staging) in adolescents

Laboratory assessment should include:

- Hemoglobin
- White blood cell count(Total and differential count)
- ALT/AST (if available)
- BUN/ S.Creatinine(if available)
- Pregnancy test for sexually active adolescent girls
- Screening for TB and other major treatable HIV co-infections and HIV-related `Opportunistic diseases as clinically indicated
- CD4 Count/Percentage
- Additional tests(as clinically indicated)



** Baseline CD4 should be done for all children. This will be useful for monitoring even if it is not required for decision to initiate ART .*

C2: Recommended first-line antiretroviral regimens for infants and children

Antiretroviral drugs are not a cure for HIV - but they reduce mortality and morbidity, and help to improve quality of life for HIV-infected infants, children, and their families. The current standard treatment for HIV infection uses three ARV medications (triple drug therapy) in order to suppress viral replication as much as possible, and to arrest the progression of HIV disease. It is important to actively support first-line adherence in order to maximize the durability and efficacy of the regimen- as first-line therapy is cheaper, relatively less toxic, and more easily administered than second line therapy.

C2.1 Drug formulations and doses for infants and children

Important considerations for ART regimens for infants and children include: the availability of a suitable formulation that can be taken in appropriate doses; simplicity of the dosage schedule; and the taste and palatability, and thus the potential for compliance in young children.

Fixed-dose combinations (FDCs) are increasingly available for younger children, and are preferred to syrups and single drugs because they promote and support treatment adherence and reduce the cost of treatment. Adult tablets that require cutting up can result in under dosing or overdosing when given to children, and this may lead to an increased risk of resistance or toxicity. In view of the availability of pediatric formulations, use of adult dose solid formulations is usually not resorted to.

Dosing of antiretroviral drugs in children is usually based on either body surface area, or weight, or more conveniently by weight band (as in the National programme). As these change with growth, drug doses must be adjusted for weight in order to avoid under-dosing.

C2.2 ART drugs

Antiretroviral comprise three main classes of drugs:

1. Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTIs)

Zidovudine	AZT/ZDV
Lamivudine	3TC
Stavudine	d4T
Didanosine	ddI
Abacavir	ABC
Emtricitabine	FTC

Nucleotide Analogue Reverse Transcriptase Inhibitors (NtRTIs)

Tenofovir	TDF

2. Non-Nucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)

Nevirapine	NVP
Efavirenz	EFV

3. Protease Inhibitors (PIs)

Lopinavir/ritonavir	LPV/r
Ritonavir	RTV
Nelfinavir	N FV
Atazanavir	ATV

C2.3 Pediatric ART regimens

The standard regimen for first-line ART consists of 2 NRTIs + 1 NNRTI.

NRTIs include a thymidine analogue Zidovudine [AZT] or Stavudine [d4T]

a guanosine analogue Abacavir [ABC] (Alternative First line drug)

Combined with a cytidine analogue Lamivudine [3TC]

NNRTIs include: Nevirapine [NVP] or Efavirenz* [EFV]

Zidovudine is the preferred NRTI in children, Stavudine is to be used only in children with Hb<9 gm%.
*Efavirenz should only be used in children over 3 years of age with weight > 10 kgs.

C2.4 Choice of a first-line regimen for infants and children < 24 mths

C2.4.1 No exposure to NNRTIs

Standard Nevirapine-containing triple therapy is the preferred option when choosing a first-line regimen for infants and children (< 24 months) without exposure to maternal or infant NNRTIs, or whose exposure to maternal or infant NNRTI is not known.

Standard Nevirapine-containing Regimen

2 NRTIs + NVP

C2.4.2 With exposure to Nevirapine

HIV-infected infants and children < 24 months exposed to nevirapine through infant prophylaxis, maternal treatment, or prophylaxis exhibit viral resistance and their response to nevirapine-containing first line treatment regimens may be compromised.

Therefore, HIV-infected infants and children with a history of exposure to single dose nevirapine or NNRTI-containing maternal ART or preventive ARV regimens, should start on a protease inhibitor-based triple ART regimen. Only where protease inhibitors are not available, affordable, or feasible, nevirapine ¬based therapy should be used.

Protease Inhibitor-based Regimen

Lopinavir/ritonavir + 2 NRTIs

C2.5 Choice of a first-line regimen for children > 24 mths

The recommended first line regimen for HIV-infected children > 24 months of age is two NRTIs plus one NNRTI.

Preferred NNRTI is Nevirapine (NVP), but should be used with close monitoring of liver function tests in adolescent girls with CD4 count > 250 due to the risk of hepatotoxicity

Efavirenz (EFV) should not be used in:

- Adolescent girls who are sexually active or pregnant adolescent girls due to the teratogenic potential of EFV in the first trimester of pregnancy.
- In children < 3 years of age or < 10 kgs due to lack of appropriate dosing information in this age group

*For those exposed to NVP (Infant or Maternal) provide a boosted PI + 2 NRTIs regimen irrespective of duration of exposure to NVP/EFV

C2.6 Alternative regimen restricted to special circumstances

The use of a triple NRTI regimen is currently restricted only to special circumstances:

Infants and children less than 3 years receiving TB treatment, where NVP may not be an optimal choice because of drug interactions with rifampicin and non-availability of pediatric formulations of Rifabutin. Here also it is preferred to give higher dose of NVP plus 2 NRTI rather than triple NRTI.

Regimen of triple NRTI

AZT/d4T + 3TC + ABC

Regimens recommended in the national program

National Paediatric ART Regimen	Type of Regimen	Regimen	Remarks	Available at
Regimen P I	First line regimen	Zidovudine + Lamivudine + Nevirapine	Preferred pediatric first line regimen for patients initiated on ART , who are not anemic (Hb > 9 g/dL) and not on concomitant ATT	All ART centers
Regimen P I (a)		Stavudine + Lamivudine + Nevirapine	For children with Hb ≤ 9 g/dL, not on concomitant ATT	
Regimen P II		Zidovudine + Lamivudine + Efavirenz	Preferred regimen for children on concomitant ATT; Hb > 9 g/dL and age > 3 yr with weight > 10 kg	
Regimen P II (a)		Stavudine + Lamivudine + Efavirenz	For children on concomitant ATT; Hb ≤ 9 g/dL and age > 3 yrs with weight > 10 kg	
Regimen P III	Alternative first-line regimen	Abacavir + Lamivudine + Nevirapine	For patients with dual toxicity to AZT & d4T already on a NVP-based regimen	Centers of Excellence, Pediatric Centre of Excellence and ART Plus Centres
Regimen P III (a)		Abacavir + Lamivudine + Efavirenz	For patients with dual toxicity to AZT & d4T already on a EFV-based regimen	
Regimen P IV		Zidovudine + Lamivudine + Lopinavir/ Ritonavir	For patients with dual toxicity to NVP & EFV and Infants and young children exposed to Sd NVP perinatally or to maternal ART/ARV prophylaxis containing NVP if Hb > 9 g/dL	
Regimen P IV (a)		Stavudine + Lamivudine + Lopinavir/ Ritonavir	For patients with dual toxicity to NVP and EFV and Infants and young children exposed to Sd NVP perinatally or to maternal ART/ARV prophylaxis containing NVP or ARV if Hb ≤ 9 g/dL	
Regimen P V	Second-Line regimen	Abacavir +Lamivudine + Lopinavir/ Ritonavir	Preferred pediatric second line regimen in the event of First line Treatment Failure for those who were on AZT/d4T containing regimen	Centers of Excellence, Pediatric Centre of Excellence and ART Plus Centres

To summarize, following are the recommendations in various situations

- AZT based regimen is preferred for children with Hb more than 9 g/dl
- d4T based regimen is recommended for those with Hb less than9 g/dl
- Children on d4T based regimen should be evaluated after 6 months and shifted to AZT based regimen if Hb found to be more than 9 g/dl
- If patient is still anemic at 6 months, shift to AZT based regimen any time thereafter when Hb is more than 9 g/dl.
- Patients shifted to AZT therapy at 6 months, who develop anemia later on, may be re-shifted to d4T based therapy. However, those children who had evidence of d4T toxicity before being shifted to AZT would be shifted to ABC instead.
- All children who have been on Stavudine based treatment for more than 3 years to be shifted to AZT based regimen if Hb> 9 gm%. If Hb persists to be below 9 gm%, shift to ABC or TDF (TDF- only if age>12 years and weight>35kgs). These children who develop anemia later on after shifting to AZT would be

C2.7 Alternative ARV Drugs for Intolerance To AZT/d4T and NVP/EFV: Substitution ARV Adverse Events

Adverse Events is the term used to describe side effects due to normal dose of medications as well as toxicities due to abnormal dose of medications. It is however not uncommon to use side effects to describe both types of events.

Substitute versus Switch?

- The general rule to follow is that when one has identified an adverse event or side effect due to a particular drug then the rule is to substitute the identified drug with another.
- When features and evidence suggests treatment failure then the rule is to switch i.e. entire regimen to avoid the risk of developing resistance.

General Issues

- Clinical features suggestive of ARV related adverse events or side effects will have to be distinguished from HIV associated conditions, Opportunistic Infections, or other common childhood diseases. Complications of HIV infection itself may present with organ dysfunction that also has to be differentiated from ARV adverse events or side effects. There remains limited data in children when it comes to drug adverse events and much is extrapolated from adult studies.
- It is important to recognize that the onset of events in relation to the initiation of the potential drug ,when suspecting a side effect. They may be described as follows:
  * Acute, immediately after drug use
  * Sub acute, 1-2 days after drug use
  * Late, prolonged drug use
- Another aspect in side effects is the determination of Severity that determines management of side effects and is described as follows:
  * Mild
  * Moderate to severe
  * Severe life threatening
- Whenever one deals with a chronic care patient requiring support for adherence to drugs with potential side effects, one need to have a ‘proactive’ approach to limit non-adherence. Explaining common side effects of drugs prescribed and simple home remedies during initiation and early visits will go a long way in allowing the patient to self-manage towards an improved adherence to medications.
- The majority of common ARV related side effects is time limited and resolve on continued ARVs with simple supportive measures.
- Types of side effects may be classified into the following broad categories:
  * Hematological
    - Bone marrow suppression
    - Anemia
    - Neutropenia
    - Thrombocytopenia, rarely
  * Mitochondrial - Especially NRTIs
    - Lactic acidosis
    - Hepatic toxicity
    - Pancreatitis
    - Peripheral neuropathy

* Metabolic - Especially PIs and Some NRTIs (d4T)
  - Fat (Lipodystrophy, hyperlipidemia)
  - Glucose (Hyperglycemia, Insulin resistance, diabetes)
  - Bone (osteopenia, osteoporosis, osteonecrosis)
* Allergic
  - Skin rash
  - Hypersensitivity

ARV	Most Common Side Effects	Most Significant Side Effects
Zidovudine ZDV/ AZT	Headache Gastrointestinal Disturbances Nausea Anorexia Vomiting	Hematologic toxicity Red blood cells Granulocytes Myopathy Lactic acidosis
Stavudine d4T	Diarrhea Nausea Vomiting Headache	Peripheral neuropathy Pancreatitis Lactic acidosis
Lamivudine 3TC	Headache Nausea Diarrhea Abdominal pain Insomnia	Pancreatitis
Efavirenz EFV	CNS Dizziness Insomnia Somnolence Impaired concentration Psychiatric s/s Abnormal dreams Rash	Serious neuropsychiatric Severe depression Suicidal AST/ALT elevation Teratogenicity
Nevirapine NVP	Rash Rash Rash Rash Rash Rash Mucosa Rash Rash Mucosa Systemic	Severe life-threatening skin reactions SJ Syndrome TEN Hypersensitivity Life-threatening hepatotoxicity
Abacavir ABC	Nausea Vomiting Malaise Headache Diarrhea Anorexia	Hypersensitivity Reaction (Fever, rash, fatigue, malaise, GI symptoms, arthralgia, cough, dyspnea with HLA-B5701 India)
Lopinavir/Ritonavir Lpv/r	Diarrhea Abdominal pain Nausea Elevated liver enzymes	Insulin Resistance Fat accumulation Hyperlipidemia
Tenofovir TDF	Flatulence	Nephrotoxicity Fanconi syndrome

Management of Adverse Events

Adverse Event	Palliative Measures	Specific Measures
Headache	▪ Rest ▪ Hydration	▪ Step 1: Non-opioid +/- adjuvants Paracetamol ▪ Step 2: Weak opioid +/- adjuvants Paracetamol + Codeine ▪ Step 3: Strong opioid +/- adjuvants Morphine
Peripheral Neuropathy	▪ Rest ▪ Warmth ▪ Causes Consider Pyridoxine	▪ Step 1: Non-opioid +/- adjuvants Paracetamol ▪ Step 2: Weak opioid +/- adjuvants Paracetamol + Codeine ▪ Step 3: Strong opioid +/- adjuvants +/- Anticonvulsants
Nausea and Vomiting	Causes? ▪ Environment ▪ Smell ▪ Food ▪ Calm ▪ Small frequent feeds	▪ Step 1: Select narrow Domperidone/ Metaclopramide Haloperidol ▪ Step 2: Select narrow or combination Ondansetron, Cyclizine + Haloperidol
Insomnia	Causes? ▪ Review day activity ▪ Environment ▪ Warm milk ▪ Restrict frightening TV ▪ Story telling ▪ Parent/Guardian's presence	Sedatives ▪ Benzodiazepine ▪ Chloral hydrate

Principles of Management of Adverse Events

- Determine Severity of adverse events
- Establish cause –ARV related side effects or due to other concurrent drugs
- Consider other diseases (hepatitis, viral, IRIS)
- In severe life threatening events,
  - * Immediate drug withdrawal is the safest option while considering "covering the NNRTI tail"
  - * Symptomatic/supportive
  - * Once stable, reintroduce modified regimen
- In severe event,
  - * Substitute without stopping ART
- In moderate event,
  - * Continue ART
  - * Symptomatic
  - * If non-resolving, substitute
- In mild event,
  - * Symptomatic

Table 2: Toxicities in infants and children associated with specific ARV drugs and potential substitutions

ARV drug[a]	Most frequent significant toxicity For the ARV drug	Suggested first line ARV drug substitution
AZT	Severe anemia[b] or neutropenia[c]	d4T or ABC
	Lactic acidosis	ABC
	Severe gastrointestinal intolerance[d]	d4T or ABC
d4T	Lactic acidosis	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 PI (disadvantage, premature start of 2nd line ARV drug)[k]
	Severe or life-threatning rash (Stevens-Johnson Syndrome)[j]	
TDF	Renal tubular Dysfunction[l] (Fanconi's syndrome)	AZT/ABC
	Bone Mineral Density loss[m]	
ABC	Fatal hypersensitivity reaction[n]	AZT
DDI	Peripheral neuropathy Pancreatitis	AZT

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 gastrointestinal intolerance that prevents ingestion of ARV drug regimen (e.g., persistent nausea and vomiting).

e. ABC is preferred in this situation as it is the least likely of the NRTIs to cause lactic acidosis; however, where ABC is not available AZT may be used.

f. Substitution of d4T may not reverse lipoatrophy, but may prevent further 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. In most cases of non life-threatening NVP-associated rash, EFV may be re-introduced with caution and monitored for adverse events. 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

l. Regular monitoring of proximal tubular dysfunction and serum creatinine in high-risk patients is required to minimize nephrotoxicity.

m. Careful monitoring of BMD (e.g., DXA at baseline and every 6–12 months) is indicated.

*n. Hypersensitivity is strongly associated with presence of HLA-B*5701 allele .Any patient with a positive test for HLA-B*5701 should not receive abacavir.*

Table 3: Substituting with alternative first line ARV drugs

<table>
<tr><th>First line ARV causing the toxicity</th><th>Alternative substitute</th><th>Remarks</th></tr>
<tr><td colspan="3">▪ Intolerance to both AZT and d4T
Patient should have been tried on AZT and d4T with documented intolerance to both: ABC+3TC will be provided.</td></tr>
<tr><td>d4T + 3TC</td><td rowspan="2">ABC + 3TC</td><td rowspan="2">Continue the same NNRTI
(either NVP or EFV)</td></tr>
<tr><td>AZT + 3TC</td></tr>
<tr><td colspan="3">▪ For intolerance to both NVP and EFV
Patient should have been tried on both NVP and EFV (except if there is a history of Stevens Johnson Syndrome) and documented as not tolerating, before requiring substitution for the NNRTI component.</td></tr>
<tr><td>NVP or EFV</td><td>LPV/r</td><td>Continue with the same NRTI backbone i.e. AZT/3TC or d4T/3TC if no problems</td></tr>
<tr><td colspan="3">Essentially this moves the patient to the PI-based regimen. Counsel for good adherence. If this regimen fails, there is no other optimal alternative/third line regimen.
These patients should be referred to the SACEP for review, then the pediatric Center of Excellence shall manage and provide LPV/r as substitution for intolerance to NNRTI.</td></tr>
</table>

See annex IV: Severity grading of clinical and laboratory toxicities of ARVs

C2.8 Monitor for ABC hypersensitivity in children initiated on first line alternative drug / second line ART especially within the first 6 weeks of treatment

Hypersensitivity reaction to Abacavir is known to occur with HLA-B 5701 status. Under the national programme, HLA-B*5701 testing is not feasible.

Children exhibiting two or more of the following symptoms should be discontinued therapy immediately and called for medical attention:

- Fever
- Skin rash
- Constitutional symptoms (malaise, fatigue, aches)
- Respiratory symptoms (eg, pharyngitis, dyspnea, cough), and
- Gastro-intestinal symptoms (such as abdominal pain, diarrhea, nausea, vomiting etc.)

Abacavir should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible and regardless of HLA-B*5701 status. Abacavir SHOULD NOT be restarted because more severe symptoms may occur within hours, including LIFE-THREATENING HYPOTENSION AND DEATH.

Fatal hypersensitivity reactions have occurred following the re introduction of Abacavir in patients whose therapy was interrupted (ie, interruption in drug supply, temporary discontinuation while treating other conditions). Reactions occurred within hours. In some cases, signs of hypersensitivity may have been previously present, but attributed to other medical conditions (eg, acute onset respiratory diseases, gastroenteritis, reactions to other medications). If Abacavir is restarted following an interruption in therapy, evaluate the patient for previously unsuspected symptoms of hypersensitivity. Do not restart if hypersensitivity is suspected or if hypersensitivity cannot be ruled out regardless of HLA-B*5701 status.

Figure 7: First line treatment for infants and children less than 24 months

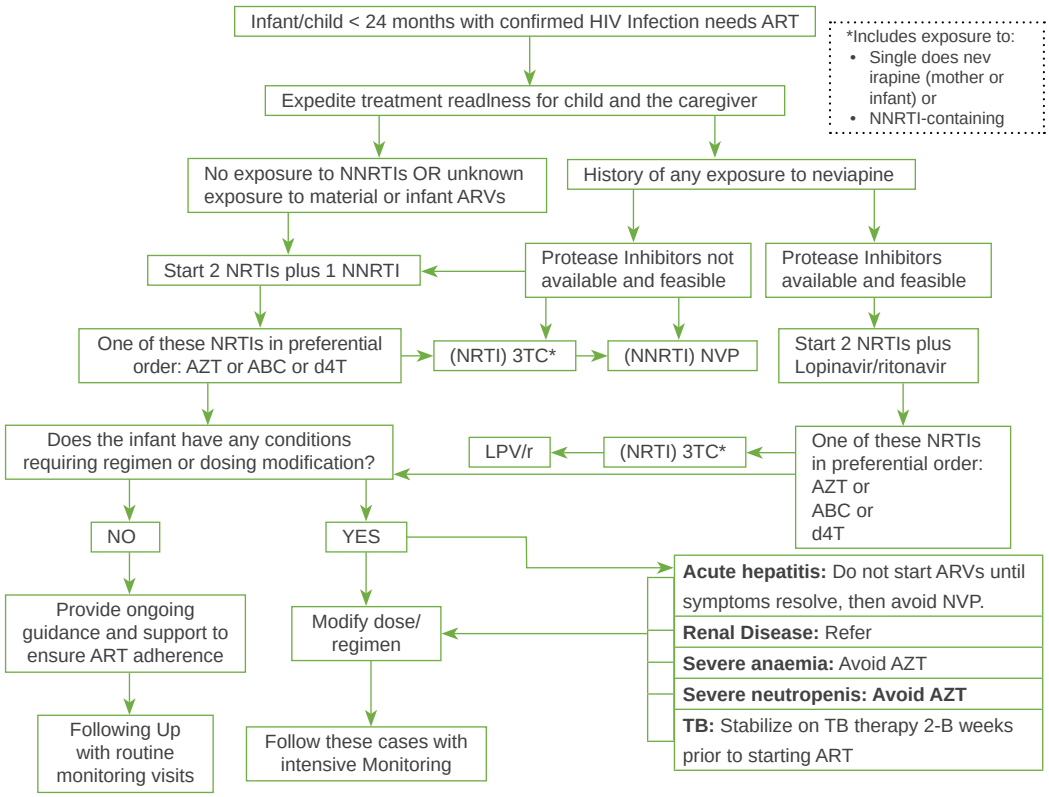
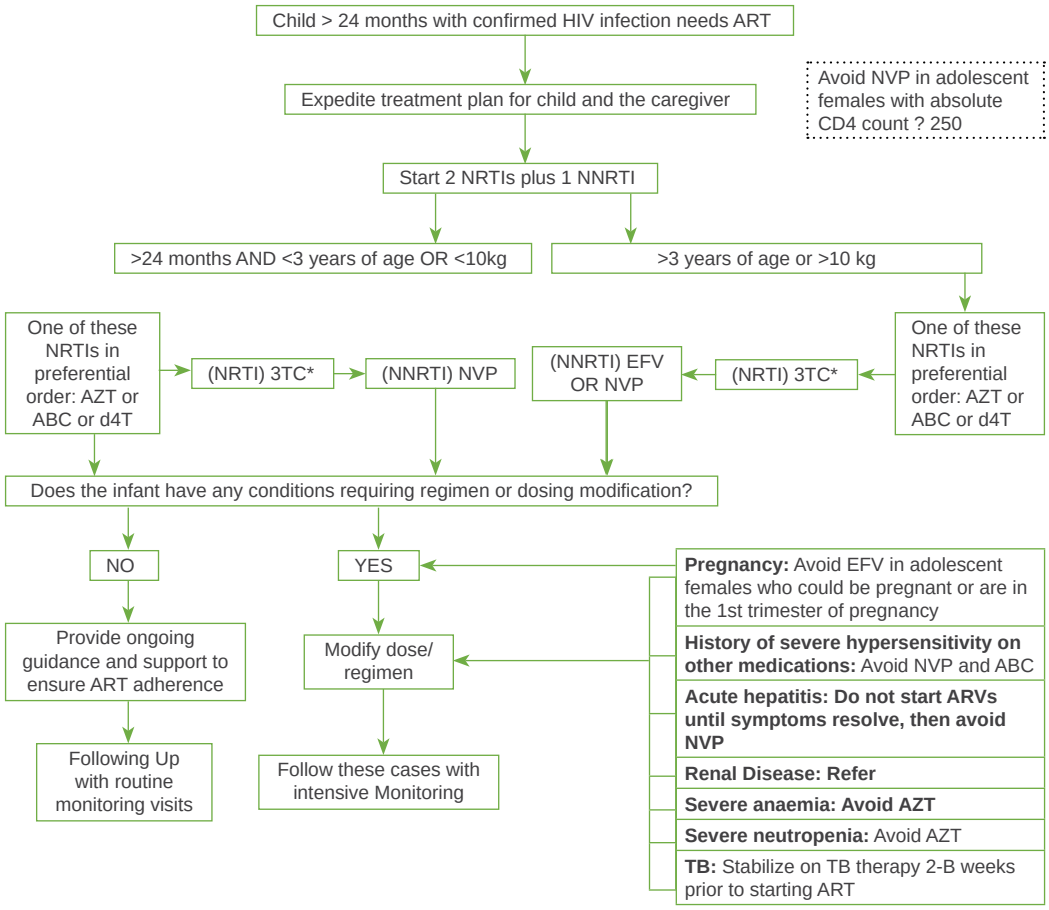


Figure 8: First Line ART for Children > 24 Months



C3: Clinical and Laboratory Monitoring while on 1st Line ART

Clinical and laboratory assessments are crucial as baseline assessment (entry into care), at the start of ART, followed by periodic checks at follow up visits, both for efficacy of the ART drugs as well as monitoring toxicity to these medications. This should be done as shown in the flowchart below:

Routine Follow up Visit

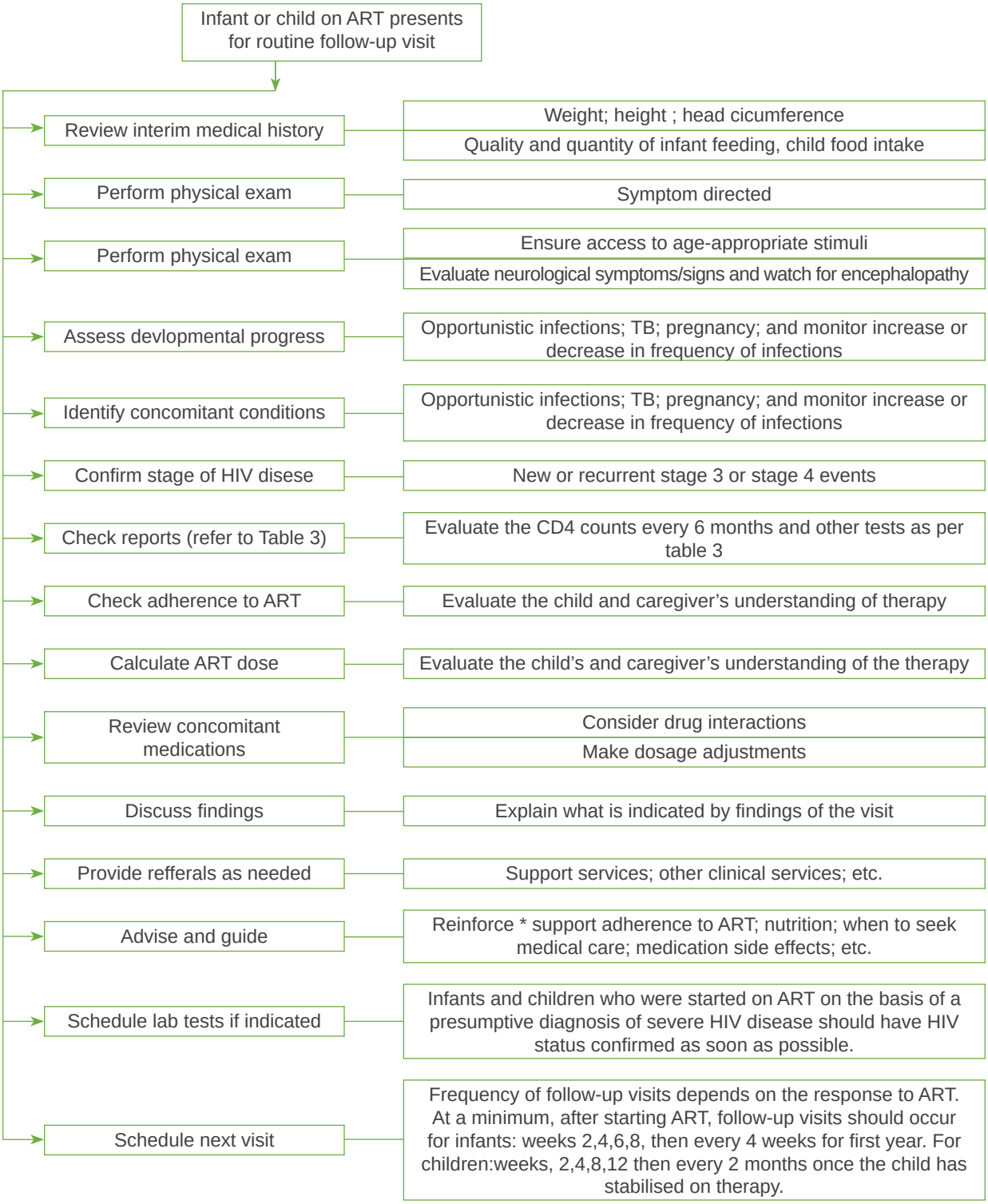


Table 3: Laboratory parameters for HIV-infected infants and children at baseline and monitoring during ART.

Tests	Day 0 (baseline)	At 15days	At 1 month	At 2 month	At 3 month	At 6 month[&]
Hb/CBC	√	√ (if on AZT)	√ (if on AZT)	√ (if on AZT)	√	√
Urea	√					
LFT[$]	√	√ (if on ATV)	√ (if on ATV)		√ (if on ATV)	√
ALT [@]	√	(if on NVP)	(if on NVP)			*
Urinalysis	√					√ (if on TDF)
Creatinine	√ (If planning for TDF)					√ (if on TDF)
Lipid profile	√ (if on EFV and PI)					√ (if on d4T, EFV or PI)
Random Blood sugar	√ (If on PI)					√ (if on PI)
CD4	√					√
Pregnancy testing	√ (if planning for EFV in adolescent girls)					
XrayChest & Mx	√					
CD 4 % or counts ^	√					√
Plasma Viral Load[#]	Not recommended under national programme					

Tests for special situations

- Hbs Ag for all patients if facility available but mandatorily for those with history of ,multiple blood & blood products transfusion, ALT> 2 times of ULN,on strong clinical suspicion. But ART not to be withheld if HBsAg testing is not available.
- Anti- HCV antibody only for those with history of , multiple blood & blood products transfusion, ALT> 2 times of ULN,on strong clinical suspicion.
- For patients to be switched to a PI based regimen, Blood sugar,LFT, and Lipid profile to be done at baseline.
- Other investigations during follow up as per requirement/availability.

& Additionally as per requirement on clinical consideration

** For HBV and/or HCV co-infected patients, 3-monthly screening of liver function is recommended. In this case , further tests may be required to assess for chronic active hepatitis.*

$ The predictive value of pre-emptive liver enzyme monitoring is considered very low by some experts. WHO recommends liver enzyme monitoring in a symptom-directed approach. However, regular monitoring during the first three months of treatment and symptom-directed measurement of liver enzymes thereafter has been considered by some experts for children on nevirapine-based regimens, or for adolescent girls with CD4 values over 250 cells/mm3 and for infants and children co infected with hepatitis B or hepatitis C virus or other hepatic disorders

 # At present, viral load measurement is not recommended for decision-making on the initiation or regular monitoring of ART in resource-limited settings. However, VL testing is done incase of Suspected Treatment Failure.

@ 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. ^ CD4% is used in children < 5 years of age. For children ≥ 5 years of age, CD4 count is mainly used.

Tests for Monitoring purpose

- Regular monitoring (every six months) of full chemistry, particularly lipid levels, liver enzymes and renal function, should be considered for infants and children on second-line drugs. Urine protein and serum creatinine in those on TDF.

C4: Adherence

Adherence to at least 95 % of doses is necessary to maximize the long-term benefits of ART. Counselling should be aimed at achieving adherence rates at least as high as 95 %. However, there are special challenges to long-term adherence in children, some of which are listed below.

C4.1 Factors influencing adherence:

1. Drug related Issues

- Pill burden (with concomitant medications)
- Poor palatability
- Adverse events to ARV drugs

2. Patient related issues:

- Age: difficulty in administration of medication to a young child
- Lack of age-appropriate disclosure to the child
- Poor expectation from therapy
- Psychosocial issues in adolescents

3. Caregiver related Issues

- Disruption in Family unit as a consequence of adverse health or economic conditions
- Ill health of parents/ care-takers
- Absence of committed responsible caregivers
- Uneducated/unmotivated care-giver

4. System related issues:

- Consistent availability of medications
- Ease of access to ART centre
- Quality of relationship between patient/care-giver and health care providers
- Availability of appropriate and on-going counseling & support services

C4.2 Measuring adherence

Continuously assessing adherence is vital to a comprehensive and sustainable approach to ART delivery. Adherence monitoring should be the duty of every health care provider participating in the care of HIV-infected children. It should be performed whenever there is a visit to a health centre, in order to identify children in need of the greatest support for adherence.

Methods to measure adherence include:

- Recall Method: Ask child or caregiver how many doses of medication have been missed during the past 3, 7 or 30 days
- Pill Count Method: Leftover pill counts if child is on tablets or capsules
- Comparing volumes of remaining syrup in the returned bottles with bottles with known quantities of syrup
- MCV measurements in patients on AZT – Should be usually elevated
- Review of pharmacy records
- Obtaining descriptions of impediments to adherence or problems encountered

C4.3 Maximizing and Supporting Adherence

Efforts to support and maximize adherence should begin before treatment is initiated. Developing an adherence plan is essential.

Elements of adherence plan should include the following:

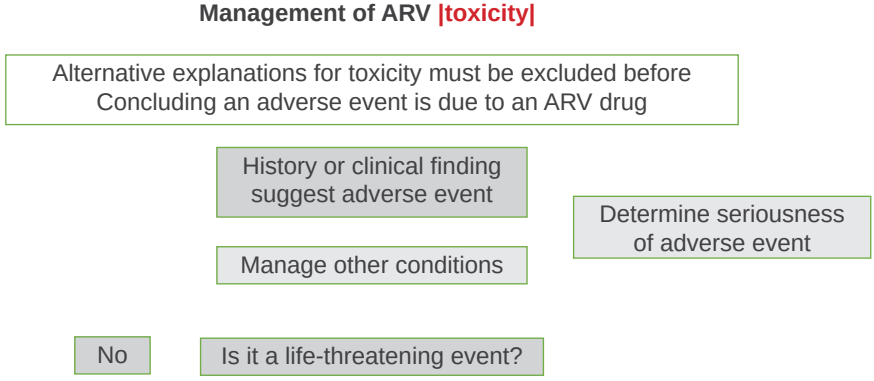
- Education regarding basics about HIV, its natural history, the importance of adherence and related outcomes, benefits and risks of ART
- Taking the medications properly—for example, if medications are mixed with food, consuming all food is important in order to ensure full administration
- Managing severe and non-severe adverse effects
- Training in pill swallowing
- Identifying a back-up informed caregiver to be involved in providing care
- Fitting ART into the child's (or caregiver's) lifestyle
- Match drug regimens for children to those for adult caregivers
- Use of calendars or other visual AIDS to illustrate dosing
- Pillboxes, blister packs
- Directly observed therapy
- Treatment supporters have been successful in some settings, especially in families where the caregiver is also HIV-infected and may be unwell
- Community and psychological support can be critical to caregivers as well as to children
- Peer support groups may be particularly beneficial for mothers with young children on ART
- Age appropriate and family disclosure also helps

Note that adherence may vary with time: families may have periods when adherence is excellent and periods when it fails, often because of changing life circumstances.

Adherence may also decrease once the child responds to therapy, and health improves, leading to a reduced motivation to take daily medication.

C4.3 Special Care with NNRTI based regimens

Adherence during the first days and weeks of treatment is critical to the long-term success of a regimen - especially for NNRTI drugs, which have been associated with rapid resistance development. NNRTI components have half-lives that are several days longer than the half-lives of NRTI components. Therefore, a sudden or periodic interruption of NRTIs results in virtually single drug (NNRTI) available, and may lead to developing NNRTI resistance.



C5: IRIS: Immune Reconstitution Inflammatory Syndrome

C5.1 IRIS is Immune Reconstitution Inflammatory Syndrome.

Immune Reconstitution Inflammatory Syndrome (IRIS) is defined as a atypical inflammatory disorder associated with immune recovery. When HIV infected patients are started on ART,they restore to their previously compromised immune functions. This qualitative and quantitative recovery of pathogen-specific cellular and antibody responses to multiple pathogens leads to some having an exaggerated inflammatory reaction to previously unrecognized or partially treated opportunistic infections. This paradoxical clinical deterioration as a result of immune reconstitution presents with a varied spectrum of clinical features and may present a diagnostic difficulty for the treating physician.

C5.2 Case definition:

The general case definition of an IRIS is when symptoms occur in a HIV infected patient recently started on ART with the following major factors:

- Immunological/Virological response to ART
  - ◊ Sudden rise in CD4 cell count from baseline
  - ◊ Rapid decline in HIV-1 RNA levels from baseline if done
- Clinical worsening
  - ◊ Signs and symptoms of infection or inflammation
  - ◊ Features as unexplained by
    - * Expected course of previously treated or newly diagnosed conditions.
    - * Drug side effects or toxicities.
    - * Treatment failure
    - * Non-adherence

C5.3 Risk Factors:

Risk factors for IRIS include a very low CD4 at initiation of ART, high viral loads, inadequate OI treatment and ART naïve children.

C5.4 Types of IRIS:

Two possible types of IRIS have been described as follows:

- **Paradoxical IRIS:** When clinical worsening occurs in a HIV infected patient with a previously diagnosed and/or treated infection after initiation of ART. As immune restitution ensues, antigens provoke inflammation that causes clinical deterioration despite ongoing or completed antimicrobial treatment. This deterioration most commonly manifests more than 3 months after initiation of ART, so-called late IRIS or paradoxical IRIS and is hypothesized to result from an inflammatory reaction to nonviable pathogens.
- **Unmasking IRIS:** An inflammatory reaction presenting with a spectrum of clinical features due to the immune recovery brought about by a response to ART. It is the result of unmasking of a latent or subclinical infection or reactivation of previously diagnosed and often treated conditions (infectious and non-infectious).

- The most common OI associated with IRIS is TB, although other infections such as cryptosporidiosis, PCP, HSV, Cryptococcal meningitis, CMV retinitis etc. can also develop IRIS (Table 19). It commonly occurs during the first week to 3 months of ART

C5.5 Time of occurrence of IRIS

IRIS may occur 1 week to 3 years after initiation of ART in HIV infected patients.

- Mycobacterium TB may occur 1-12 weeks after initiation of ART;
- Cryptococcus 1 week to 12 months;
- CMV and Herpes simplex 1 month to 3 years; and,
- autoimmune diseases 1 to 3 years . Studies in children have shown mean time to IRIS event is 2 weeks to 13 weeks after starting ART

C5.6 Features of TB-IRIS

The usual scenario in a HIV infected patient recently started on ART presents with unexplained clinical worsening having usually demonstrated initial improvement in spite of being adherent to ART and with no drug side effects or evidence of treatment failure .

The following are considered major features of TB-IRIS:

- New or enlarging or worsening lymphadenopathy,
- fistulas,
- cold abscesses or focal lesions;
- radiological lesions;
- meningitis or focal deficits;
- serositis or arthritis; or
- signs of hypersensitivity such as phlyctens or erythema nodosum . Constitutional features such as fever, night sweats, weight loss; worsening respiratory symptoms; and, abdominal features including new or worsening masses may occur

C5.7 IRIS presentations:

Table 19 : IRIS events.

IRIS presentations	Associated Pathogens	Comments
Hypoxia, lung infiltrates	TB, PCP	PCP may show organizing pneumonia after treatment
Pleuritis, pericarditis	TB	
Fever, constitutional features	TB, Cryptococcal	
Headache, meningeal signs, focal deficits	TB, Cryptococcal meningitis, Toxoplasmosis	Cryptococcal meninigitis may have high CSF cells, CSF pressure and a negative culture
Blurred vision, decreased visual acuity	CMV	CMV may show retinitis in preexisting retinal lesions, uveitis, vitreitis
Abdominal pain, hepatosplenomegaly	TB, Viral hepatitis	
Bone, Joint	TB, Autoimmune	

C5.8 Management of IRIS

- Assess and confirm adherence to ART and additional medications if indicated .
- Exclude possible drug side effects .
- Assess and confirm immunological response to ART ,sudden rise of CD4 counts from the base line.
- If mild clinical features are present supportive measures using NSAIDS and continuing ART and antimicrobial medications where relevant is recommended (IRIS are usually self-limiting up to 2 weeks).
- If severe clinical features are present, management includes in addition to the above a course of oral corticosteroids 1.5 mg/kg/day tapered off over weeks to tide over the crisis especially with life threatening space occupying lesions such as airway obstructive lymph nodes or intra-cranial tuberculomas. Aspiration drainage of pus for cold abscesses with IRIS or lumbar punctures for cryptococcal meningitis with IRIS may be the additional management measures required.
- In situations where treatment is not possible or life threatening condition like parvoviral infections or malignancy , is present consider discontinuing ART.

SECTION

D

Treatment Failure

D1: ARV treatment failure may be due to:

D2: Second-line Regimens

D1:ARV treatment failure may be due to:

- Poor adherence
- Inadequate drug levels
- Prior existing drug resistance
- Inadequate potency of the drugs

Fulfillment of certain criteria related to duration of therapy with ART, adherence, etc. are mandatory before determining treatment failure based on clinical, immunological and virologic criteria. These are as follows:

- The child should have received the regimen for at least 24 weeks
- Adherence to therapy should be assessed and considered optimal
- Any acute or opportunistic infections should be treated and resolved before interpreting CD4 counts
- Immune reconstitution inflammatory syndrome (IRIS) must be excluded
- Before considering a switch of treatment because of growth failure, ensure the child is receiving adequate nutrition

D1.1 Treatment failure is identified using

- Clinical criteria
- Immunologic (CD4 count or %) criteria, where available
- Virologic criteria, where possible

When treatment failure is confirmed, switching to a new second-line regimen becomes necessary.

D1.2 Defining treatment failure

D1.2.1 Definition of Clinical Treatment Failure The detection of a new or recurrent WHO clinical stage 3 or 4 event may reflect progression of disease

- Treatment failure should be considered if the child has been on therapy for at least 24 weeks and is adequately adherent to treatment.
- The clinical criteria as per staging while on treatment should be considered for a switch to a second line regimen after consulting SACEP / pSACEP, as shown in the table below:

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

New or recurrent event on ART[a,b]	Management options[c,d]
No new events or stage 1 events (T1)	▪ Do not switch to new regimen ▪ Maintain regular follow up
Stage 2 events (T2)	▪ 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
Stage 3 events (T3)	▪ Treat and manage staging event and monitor response ▪ Check if on treatment 24 weeks or more ▪ Assess and offer adherence support ▪ Assess nutritional status and offer support ▪ Check CD4 ▪ Institute more frequent follow-up ▪ Consider switching regimen

Stage 4 events (T4)	▪ Treat and manage staging event ▪ Check if on treatment 24 weeks or more ▪ Assess and offer adherence support ▪ Assess nutritional status and offer support ▪ Check CD4 ▪ Switch regimen irrespective of CD4 counts

[a] *A clinical event refers to a new or recurrent condition as classified in the WHO clinical staging 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 and that adherence to therapy has been assessed and considered adequate before considering switching to the second-line regimen.*

[c] *Differentiation of opportunistic infections from IRIS is important.*

[d] *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.*

[e] *Pulmonary or lymph node TB, which are clinical stage 3 conditions, may not be an indication of treatment failure, and thus may not require consideration of second-line therapy. The response to TB therapy should be used to evaluate the need for switching therapy.*

D1.2.2 Definition of Immunological Treatment Failure

Immunological criteria for recognizing treatment failure are supplemental to clinical criteria.

Comparing the present CD4 counts with previous CD4 values is required to recognize treatment failure on the basis of immunological values.

- Treatment failure is characterized by a drop in the CD4, after the initial immune recovery following ART initiation:
  - To values at or below the age-related CD4 threshold for treatment initiation OR
  - o 30% drop of CD4% or value from peak post therapy levels

In a fully adherent child, who has been on ART for at least 24 weeks, ART failure is considered in the following situations:

Immunological failure is recognized as developing or returning to the following age-related immunological thresholds after at least 24 weeks on ART, in a treatment-adherent child:

- A failure of the CD4 count to rise above these threshold values after 24 months of ART as per WHO guidelines

CD4 count of ≤200 cells/mm3 Or %CD4+ ≤10% for a child more than 2 years to less than 5 years of age

For children > 5 years of age

- CD4 counts below pre therapy baseline OR
- Drop in CD4 counts more than 50% from peak post therapy levels
- CD4 count of < 100 cells/mm3 persistently

Preferably at least two CD4 measurements should be available;

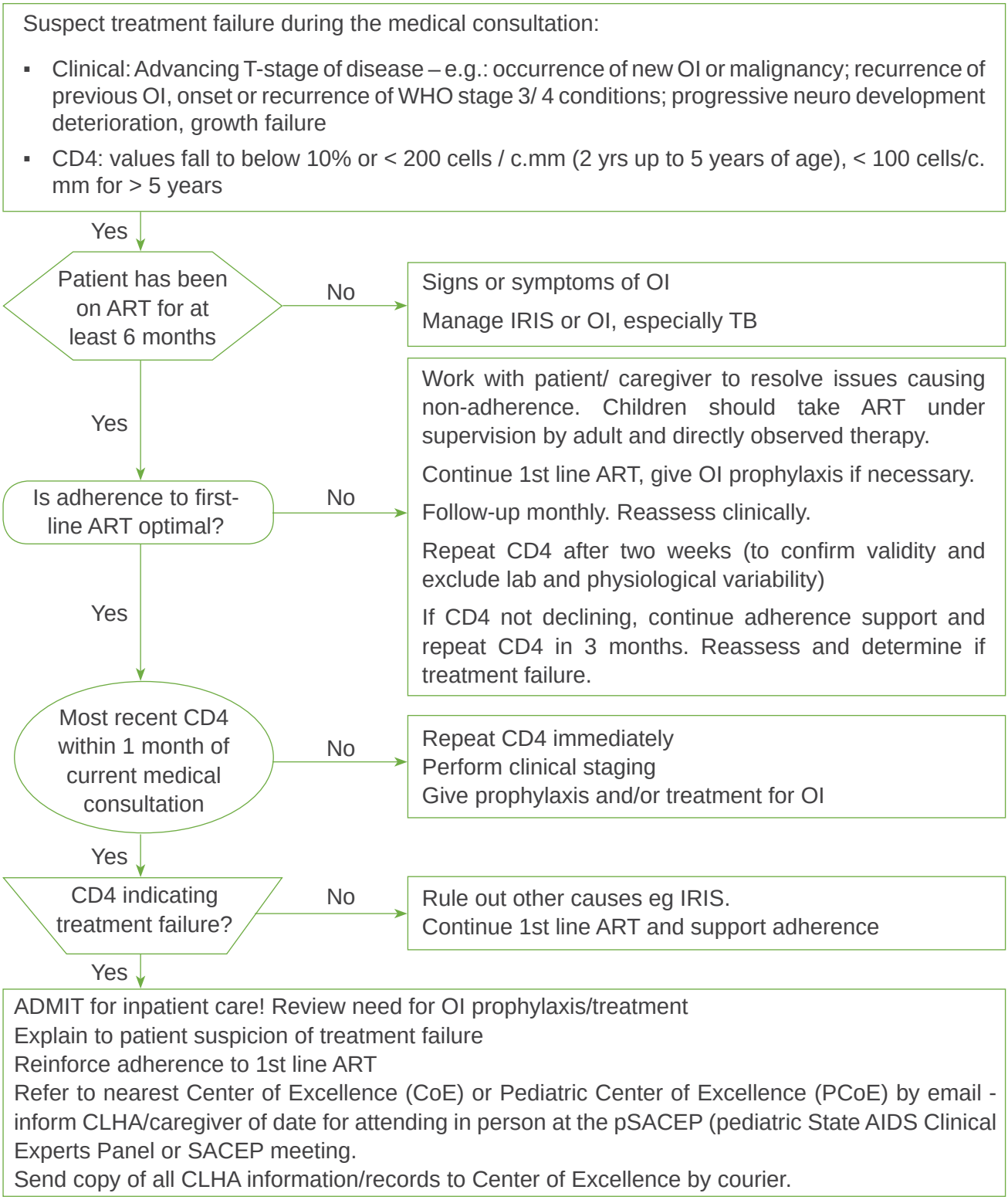
For < 2 years of age, in case of clinical suspicion of failure, child should be referred to SACEP or linked pCoE.

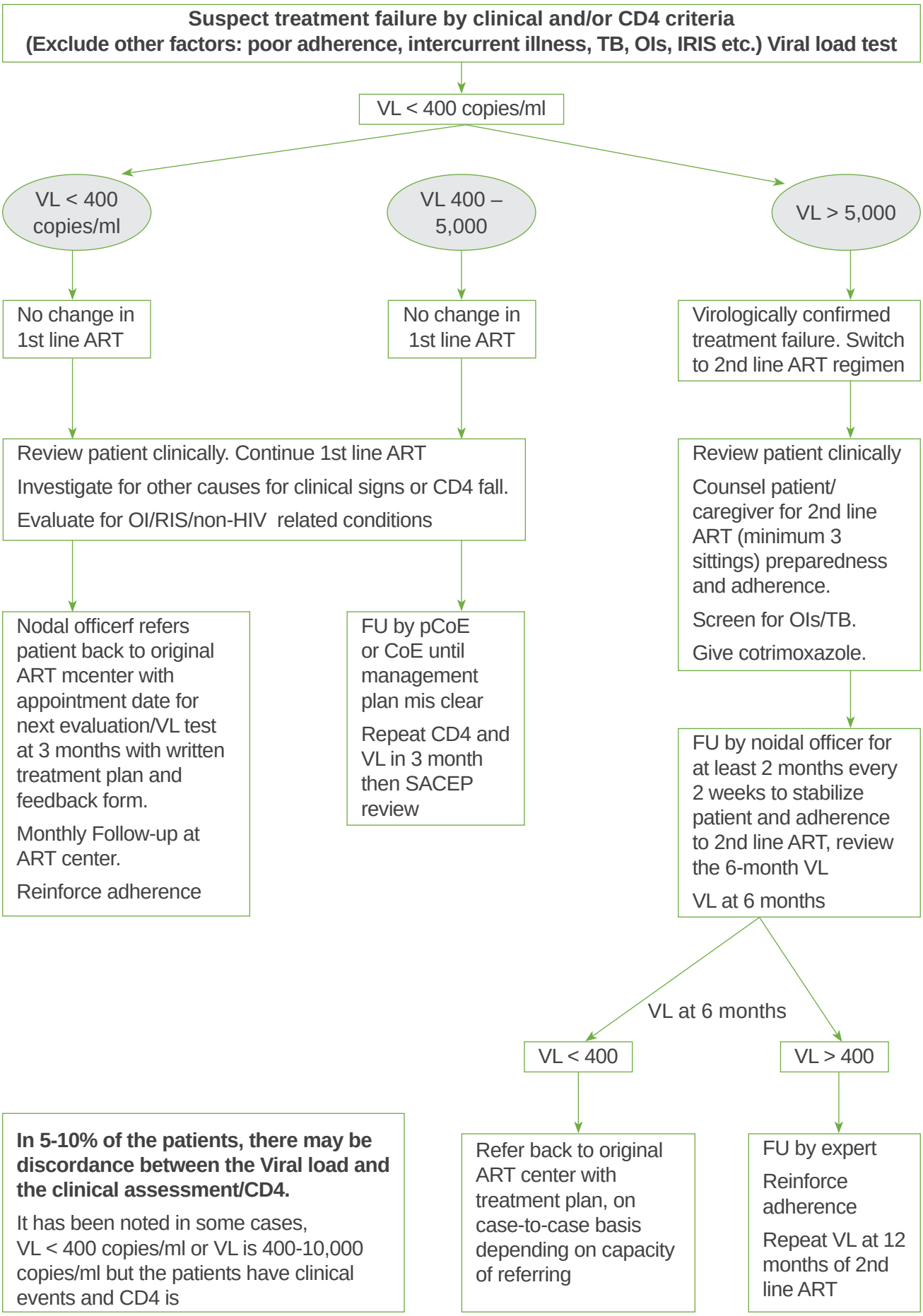
For infants and young children less than 2 years of age, the immunological thresholds given above cannot be used because they reflect very severe immune suppression. For any given CD4 threshold the likelihood of disease progression or death is greater the younger the child. When ART failure is suspected for such children, seek specialist advice.

D1.2.3 Virological failure is recognized as persistent viral load (VL) above 5000 copies/ml, after at least 24 weeks on ART, in a fully treatment adherent child.

(For details of interpreting viral loads for determining treatment failure, see Annexure or Figure 9 – WHO 2010 chart / Figure 11 below…..!)

Virological failure is recognised as persistent plasma viral load (VL) above 5000 copies/ml, after at least 24 weeks on ART, in a fully treatment adherent child.




Suspect treatment failure by clinical and/or CD4 criteria
(Exclude other factors: poor adherence, intercurrent illness, TB, OIs, IRIS etc.) Viral load test
VL < 400 copies/ml
VL < 400 copies/ml
VL 400 – 5,000
VL > 5,000
No change in 1st line ART
No change in 1st line ART
Virologically confirmed treatment failure. Switch to 2nd line ART regimen
Review patient clinically. Continue 1st line ART
Investigate for other causes for clinical signs or CD4 fall.
Evaluate for OI/RIS/non-HIV related conditions
Review patient clinically
Counsel patient/ caregiver for 2nd line ART (minimum 3 sittings) preparedness and adherence.
Screen for OIs/TB.
Give cotrimoxazole.
Nodal officerf refers patient back to original ART mcenter with appointment date for next evaluation/VL test at 3 months with written treatment plan and feedback form.
Monthly Follow-up at ART center.
Reinforce adherence
FU by pCoE or CoE until management plan mis clear
Repeat CD4 and VL in 3 month then SACEP review
FU by noidal officer for at least 2 months every 2 weeks to stabilize patient and adherence to 2nd line ART, review the 6-month VL
VL at 6 months
VL at 6 months
VL < 400
VL > 400
In 5-10% of the patients, there may be discordance between the Viral load and the clinical assessment/CD4.
It has been noted in some cases, VL < 400 copies/ml or VL is 400-10,000 copies/ml but the patients have clinical events and CD4 is
Refer back to original ART center with treatment plan, on case-to-case basis depending on capacity of referring
FU by expert
Reinforce adherence
Repeat VL at 12 months of 2nd line ART

D2: Second-line Regimens

D2.1 Choice of Second-line Regimens in the event of Treatment Failure

- In the event of treatment failure, the entire regimen should be changed from a first-line to a second-line combination as advised by pCoE/CoE at the pSACEP/SACEP meeting.
- The new second-line regimen should include at least two new drugs, one or more of them from a new class

Recommending potent and effective second-line regimens for infants and children is particularly difficult, due to: (a) the current lack of experience with use of second-line regimens in children in resource-limited settings, and (b) the limited formulary maintained.

This highlights the importance of choosing potent and effective first-line regimens and maximizing their durability and effectiveness by optimizing adherence.

Selecting a Second-line Regimen for Children with Treatment Failure on First-line Regimen

SITUATION	Preferred First line Regimen	Preferred Second line Regimen
INFANTS		
Infant not exposed to ARV	NVP + 2 NRTIs	LPV/r + 2 new NRTIs
Infant exposed to NVP	LPV/r + 2 NRTIs	NNRTI + 2 new NRTIs
Infant with unknown ARV exposure	NVP + 2 NRTIs	LPV/r + 2 new NRTIs

Recommended Second Line Regimens in Infants and Children in the event of First Line Treatment Failure			
	Preferred Second Line Regimens		
First Line Regimen at Failure	Second Line RTI Components (NRTI/NNRTI)	Plus	PI Component
2 NRTIs + NNRTI: AZT or d4T containing	ABC + 3TC Or ABC + ddI		LPV/r

In case of any other regimens being given as first line, refer to pSACEP or SACEP for further management.

The NACO standard pediatric second line regimen (ABC/3TC + LPV/r) aims to achieve viral suppression for as long as possible, so that survival can be prolonged.

GAPS

D2.2 Second-line ART and TB treatment

Tuberculosis is the most commonly detected serious co-infection among CLHAs in India. While tuberculosis has to be treated appropriately and on priority, in the context of second-line ART, drug-drug interactions must to be considered. Rifampicin alters the metabolism of Protease Inhibitors, including lopinavir and ritonavir, and reduces effectiveness of standard doses. However, the rifamycin-class of drugs are highly efficacious in treatment of tuberculosis.

In HIV-infected adults on protease inhibitor, rifabutin is used as a substitution for rifampicin. However in children, there is inadequate data on the pharmacokinetics, therapeutic levels and efficacy of rifabutin. Furthermore, there are no paediatric rifabutin formulations available at present. Adult tablets cannot be used as it is not recommended to split or cut adult rifabutin tablets.

In HIV-infected children on paediatric second line regimens, who require concurrent TB treatment, the current practice globally is ‘superboosting of LPV/r’ with additional doses of ritonavir (written as LPV/r

+ r) with the target ratio of LPV/r :: 1:1. This will ensure adequate protease-inhibitor levels during concurrent TB treatment with rifamipicin. However, the problems are increased pill burden and possible side-effects to ritonavir (usually GI intolerance). The side-effects need to be treated accordingly if mild to moderate. In case of severe side effects, alternative regimen have to be considered.

Table X : Dosing schedule : Super-boosting LPV/r + r

Drug	Formulation (mg)	10-13.9 kg	14-19.9 kg	20-24.9 kg	25-29.9 kg	30-34.9 kg
LPV/r bid	100 / 25	AM - 2 PM - 1	AM - 2 PM - 2	AM - 3 PM - 2	AM - 3 PM - 3	AM – 2* PM – 2* (*Use adult tablets – 200 / 50)
Additional ritonavir	100 mg	AM - 1 PM - 1	AM - 2 PM - 1	AM - 2 PM - 1	AM - 2 PM - 2	AM +2 PM +2
Total super-boosting pill burden LPV/r+r (per day)		5	7	8	10	8

For the initial operationalization of the paediatric second line ART regimen in the context of TB-HIV in children, contact pCoE / CoE / NACEP for case-to-case individual management of TB-HIV, where the child is receiving LPV/r for treatment failure

SECTION

E

Opportunity Infections in HIV Infected Children

E1: Opportunity Infections in HIV Infected Children

E1.1 General Consideration

Opportunistic infections (OIs) are infections caused by pathogens that usually do not cause disease in a healthy immune system. A compromised immune system, however, presents an opportunity for the pathogen to infect. The following are important considerations with respect to OIs in children:

- OIs in HIV infected infants are often primary infection with pathogen, which infects the child at the time when HIV infection has already established and the child's immune system is already in compromised state. This can lead to different clinical manifestations of specific OIs in infants. .
- Most OIs occur among children with substantially immune-compromised state i.e. when CD4 falls below 10%, but the serious bacterial infections, herpes Zoster and TB can occur across the spectrum of immune categories.
- Multiple difficulties can exist in making lab diagnosis of various infections in children.
- Treating OIs in children is also challenging as issues related to drug pharmacokinetics, formulation, ease of administering, dosing and toxicity require special consideration for children. Data is often lacking for children < 2 years and appropriate drug dosing recommendations are not available.

HAART has dramatically decreased rates of AIDS-related opportunistic complications and deaths in adults and children.

This section gives a brief description of the epidemiology, clinical features, investigations , treatment and prophylaxis of opportunistic infections in HIV infected children. TB and HIV co-infection and co-infection with hepatitis B and C are described separately.

E2: HIV-TB Co-infection in Children

The global impact of the dual epidemics of TB and HIV is one of the major public health challenges of our time. TB is the most common opportunistic infection in HIV infected patients as well as the leading cause of death. Treatment of HIV-TB co-infection is complex and requires coordination between TB and AIDS control programs in India.

E2.1 Pediatric TB

- Pediatric TB is a direct consequence of adult TB and is a marker of current transmission in the community. Increasing levels of co-infection with TB and HIV in children have been reported from countries with dual epidemics, Childhood TB with concurrent severe malnutrition and HIV infection, if untreated would contribute to mortality.
- Infection with HIV is a strong risk factor for progression from latent to active tuberculosis.

E2.2 Clinical Presentation

Pulmonary Tuberculosis: The common presenting symptoms are fever and cough > 2 weeks, weight loss and loss of appetite. A contact history especially with an adult with smear positive pulmonary tuberculosis is significant. However, one must remember that in an HIV infected child, the clinical presentation may be acute and run a rapid atypical course similar to bacterial or viral infections. So, a high degree of suspicion is needed.

Extrapulmonary tuberculosis: The common sites of extrapulmonary tuberculosis and the presenting clinical features are as follows:

- Lymph nodes (67%): Swellings in the neck/axilla.
- CNS (13%): Fever, convulsions, altered sensorium
- Serosal Involvement (6%): Pleural, peritoneal, pericardial effusions: Chest pain, breathlessness, abdominal distension
- Bone Tuberculosis(4%): Swelling and pain in joints, spine
- Disseminated /Miliary Tuberculosis (5%)

Clinical features suggestive of childhood Pulmonary TB include the following:

- Contact history
  * Significant especially with an adult with smear positive Pulmonary TB
- Persistent Fever
  * > 2 weeks
- Non-remittent, prolonged Cough
  * > 2 weeks
- Weight loss or poor gain in weight
  * Growth charts/Road to Health growth monitoring

However, one must remember that in an HIV setting especially in the young child, presentations may be acute and run a rapid atypical course similar to bacterial or viral infections and a high degree of suspicion is needed. Co-infections exist.

E2.3 Differential Diagnosis of Pulmonary TB in childhood

Investigations:

Pulmonary TB: The diagnosis of childhood Pulmonary TB is a common clinical challenge in TB-endemic regions. Bacteriological confirmation is difficult in young children, because of non-production of sputum and the paucibacillary disease process. Infants and young children are particularly susceptible to disease and TB needs to be differentiated from a number of other clinical conditions.

Diagnosis of Pulmonary TB usually depends on:

- Clinical features (non-remitting chronic cough, weight loss or failure to thrive, persistent fever, history of close contact with adult TB),
- A positive tuberculin skin test (TST) and
- Suggestive findings on the chest radiograph PA view (CXR).
- Early morning samples for smears from induced sputum collection in the older child, gastric aspirates from younger children
  - Tuberculin Skin Test/Mantoux Test : It can be done from 3 months of age onwards using 2 or 5 TU PPD solution injected intradermally. Induration more than 5 mm is considered positive in HIV infected children. However, a negative test may be seen in 50% children with tuberculosis. Thus, a negative test does not rule out tuberculosis.
  - Chest X-ray PA view: Typical radiological features consistent with TB are localized pulmonary infiltrates with hilar lymphadenopathy, middle lobe collapse and consolidation, pleural effusion, miliary pattern (< 2 mm interstitial infiltrates) and cavitatory parenchymal lesions. However, the coexistence of HIV infection especially severe immunodeficiency with low CD4

counts/percentages may lead to atypical radiological features including normal x-rays. In addition, other HIV associated conditions and OIs have overlapping radiological features. Bacteriological evidence remains a sole confirmation even though childhood TB is mostly pauci-bacillary and sampling is difficult. Attempts to obtain specimens for smears for acid fast staining must be attempted. Two early morning samples of sputum may be induced with 3% Saline nebulization for children greater than 3 years; and, of gastric aspirates through nasogastric tubes, buffering the aspirate with bicarbonate for children younger than 3 years.

Annexure (numbering) represents the diagnostic algorithm followed in RNTCP for the diagnosis of TB in children (25).

Extra-Pulmonary TB : The investigative approach to diagnosis in extra-pulmonary TB is outlined in Table 5

Table 5: Common forms of extrapulmonary TB and diagnostics in children

Site	Practical approach to diagnosis
Peripheral lymph nodes (especially cervical)	Lymph node biopsy or fine needle aspiration FNAC ZN smears for AFB.
Miliary TB (e.g. disseminated)	Fundus examination for choroid tubercles, Chest X-Ray (PA) and CSF studies following a lumbar puncture
TB meningitis	Neuroimaging and CSF studies following a lumbar puncture
Pleural effusion (older children and adolescents)	Chest X-ray (PA), Pleural tap fluid for biochemical analysis (protein and glucose concentrations), cell count and culture
Abdominal TB (e.g. peritoneal)	Abdominal ultrasound and ascitic tap fluid for analysis
Osteoarticular	X-ray, joint tap fluid for analysis or synovial biopsy
Pericardial TB	Ultrasound and pericardial tap fluid for analysis

Source: World Health Organization (WHO). Guidance for National Tuberculosis Programmes on the management of Tuberculosis in Children (WHO/HTM/TB/2006.362) Geneva, Switzerland: WHO 2006

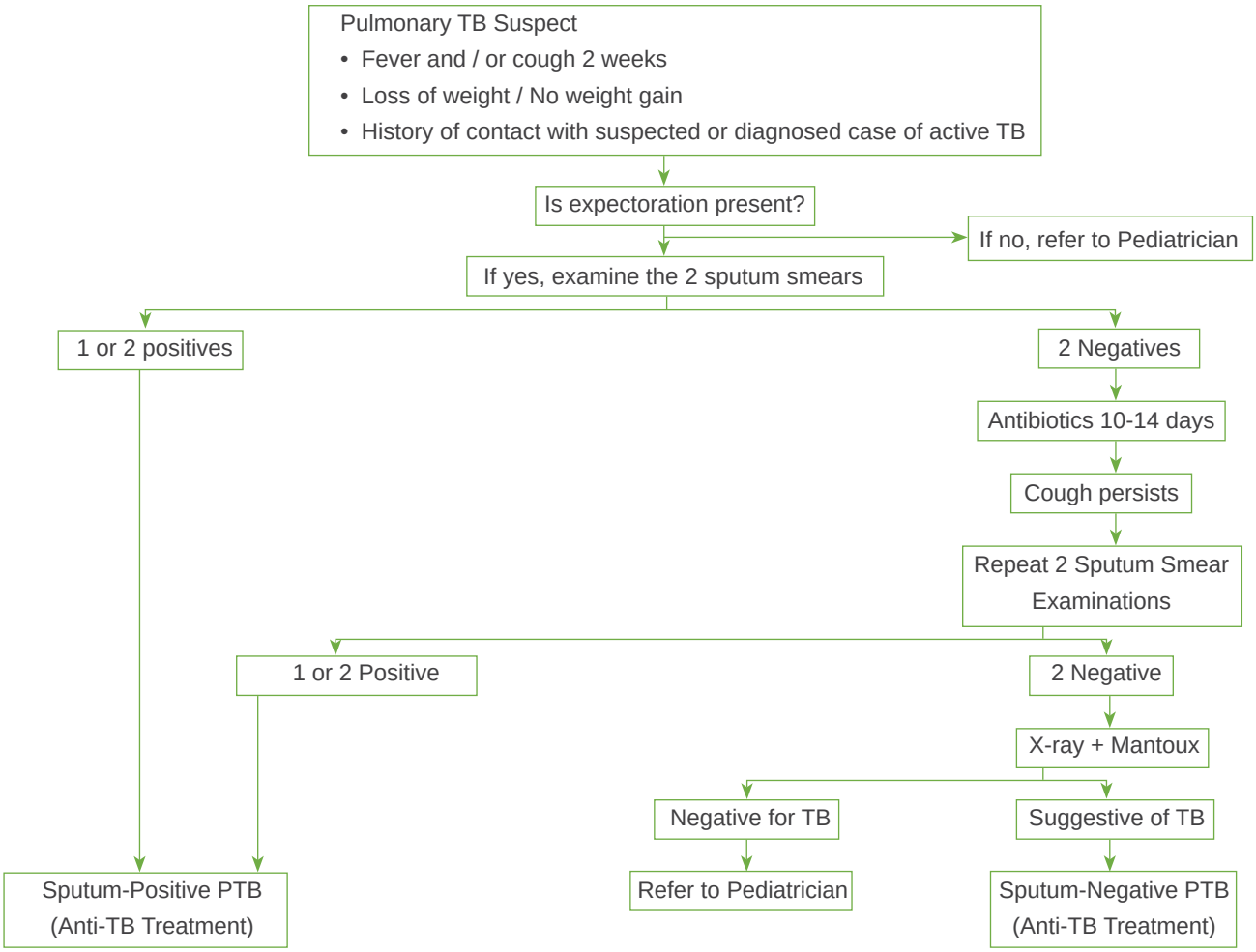
E2.4 Treatment of TB in HIV-infected children :

In the pre-HAART era, HIV-infected children showed poorer response to TB treatment and higher rates of mortality. Poor response may be due to severity of immune suppression; malnutrition; HIV-related co-infections and chronic lung disease; immune reconstitution inflammatory syndrome (IRIS); and greater problems of adherence to TB treatment. A decision to start anti-TB therapy must be carefully considered and once this decision is made, a full course of treatment should be completed. In case of a critically ill child with suspected TB such as with TBM or very severe pneumonia, there is greater urgency to start treatment as soon as possible.

Children co-infected with TB/HIV should routinely receive cotrimoxazole preventive therapy (CPT) and be considered for ART according to WHO guidelines. The commencement of ART is associated with a risk of developing IRIS in children with low CD4 counts and high viral loads, but the benefits are many and outweigh the risks.The salient points of treatment include:

- Anti-Tuberculosis Treatment (Short course, Daily, Directly Observed) is the priority
- Cotrimoxazole Prophylaxis is indicated
- Anti-retroviral therapy as early as possible once ATT is tolerated, within 2-8 weeks of initiation of ATT

Figure 3: Diagnosis of smear positive pulmonary TB. RNTCP New Guidelines, Effective from 1st April 2009



Source: Diagnosis of smear positive pulmonary TB. RNTCP New guidelines, effective from 1st April 2009

E2.5 Anti-TB drug regimens in HIV-infected children:

The regimen for HIV-infected children with newly diagnosed pulmonary tuberculosis(PTB) and extrapulmonary tuberculosis(EPTB) has four drugs in the intensive phase (2HRZE). The continuation phase is given for 4 months (4HR) for all patients except those with TB meningitis or osteoarticular tuberculosis. A 10-month continuation phase is now recommended for TB meningitis and osteo-articular TB. Streptomycin is no longer recommended in any first-line treatment regimens for children. TB treatment in HIV-infected children should be given daily (7 days per week) during the intensive and continuation phases of therapy. If there is poor response to at least 1-2 mo of therapy (no weight gain, persistent symptoms) children should be referred to the next level of care for an assessment. Specimens for culture and drug susceptibility testing (DST) should be collected in children who respond poorly to treatment.

Recommended treatment regimens for HIV-infected children (WHO, 2010)

TB Cases and Diagnostic category	Anti-TB Drug regimens	
	Intensive Phase	Continuation Phase
New Patient; Smear Positive PTB; Smear Negative PTB; All forms of EPTB except TBM and Osteo-articular TB	2 HRZE	4 HR
TB Meningitis and Osteo-articular TB	2 HRZE	10 HR

H: Isoniazid; R: Rifampicin; Z: Pyrazinamide; E: Ethambutol

All children with previously treated TB should ideally have specimens obtained for culture and drug sensitivity Testing (DST) before or at the start of treatment. DST should be performed for at least isoniazid and rifampicin.

Recommended dosages of first-line anti-TB drugs for children

Drug	Dose mg/kg/day
Isoniazid H	10-15 (max 300 mg /dose)
Rifampicin R	10-20 (max 600 mg/ dose)
Pyrazinamide Z	30-40 (max 2000 mg/ dose)
Ethambutol E	15-25 (max 1200 mg/ dose)
Streptomycin S	12-18 (max 1000 mg/ dose)

E2.6 Monitoring of therapy:

Each patient should be assessed clinically for symptoms, weight, adherence and any adverse effects. This is required initially at 2 weeks post initiation, 2 weekly henceforth in view of assessment to initiate ART, at the end of intensive phase and then every 2 months until treatment is completed. Follow-up CXRs are not routinely recommended as radiological clearance lag behind the clinical response but helpful for those children who are not responding to treatment in spite of good adherence.

Indications for Steroids

Prednisone should be given at a dose of 2 to 4mg/kg/d (max:60mg/day) in cases of TB Meningitis and TB Pericarditis. Duration of steroids may be from 4- 6 weeks in the latter two conditions. Of course, the absolute indication for life time steroids would be Addison's disease due to TB. Patient should be referred to the pediatrician if steroids are indicated.

Antiretroviral Therapy(ART) in Pediatric HIV with TB co-infection

There could be 2 situations related to HIV-TB co-infection:

- Child is already on ART before TB is diagnosed
- Child is diagnosed to have TB either before or along with HIV diagnosis

In the 1st situation, one needs to consider altering the ART regimen suitably when initiating ATT and in the 2nd situation, one would give atleast 2 weeks of ATT before commencing ART.

Indications:

- All TB-HIV co-infected children

When to start ART:

All children with TB-HIV co-infection should be initiated on ATT which generally contains Rifampicin. The appropriate ART regimen should be initiated as early as possible, within the next 2-8 weeks, while monitoring the child carefully for side-effects.

1. ART regimen choices in a child who is already on a Rifampicin based Anti-TB therapy:

Rifampicin induces the liver enzyme system that leads to reduction in blood concentrations of NNRTI and PI drugs. This risks patients to resistance due the presence of sub-therapeutic levels of ARVs (NNRTIs and PIs), hence the possibility of treatment failure. In addition, there are overlapping toxicities especially involving liver functions.

Whenever possible, Efavirenz EFV is the first choice NNRTI drug. Alternative first choices would be high dose Nevirapine if requiring an NNRTI and 1:1 equivalent Lopinavir/Ritinovir if requiring a PI regimen.

Preferred first line ART regimen:	
▪ Children > 3 years age or > 10 kg Regimen 2 NRTI plus EFV ▪ Children < 3 years age or < 10 kg Regimen 2 NRTI plus NVP (upper limit of normal dose[a])	AZT + 3TC + EFV d4T + 3TC + EFV AZT + 3TC + NVP d4T + 3TC + NVP
Alternative first line ART regimen:	
▪ Children< 3 years of age or < 10 kg not tolerating NVP, or,infants with prior exposure to NNRTI Regimen of 2NRTI plus LPV/RTV (LPV/r with additional RTV 1:1[b])	AZT + 3TC + LPV/r d4T + 3TC + LPV/r

[a]When Nevirapine is being co-administered with Rifampicin, the following points should be kept in mind:

- Nevirapine should be started at full dosage in children receiving Rifampicin to reduce the effect of liver enzyme induction. Nevirapine should be dosed at the maximum which is based on 200 mg/sq. m rather than mg/kg dose.
- Avoid the use of a once a day NVP lead in dose.
- Begin with the full twice a day dose of NVP. This will avoid a sub-therapeutic level of NVP while on Rifampicin and its liver enzyme induction.
- Side effects need to be monitored carefully.

[b]LPV/r needs additional boosting with ritonavir to reach a 1:1 mg equivalence by addition of 0.75 ml ritonavir per ml LPV/r. Side effects will need to be monitored but increased dose will protect against liver induction reducing therapeutic levels.

2. ART regimen changes in a child who is already on ART and now initiated on a Rifampicin based Anti-TB therapy:

Substitution depends upon age, weight and whether the child is on first or second line ART regimens. Rifampicin based Anti-TB treatment should be initiated and ART should be continued with modifications if required.

Remember, whenever possible, Efavirenz EFV is the first choice NNRTI drug. Alternative first choices would be high dose Nevirapine if requiring an NNRTI and 1:1 equivalent Lopinavir/Ritinovir if requiring a PI regimen

Recommended substitutions to ART regimens when adding on Rifampicin based ATT:

Child > 3 yr age or > 10 kg and on 2NRTI plus NVP (If on EFV based ART, no change)	▪ Change NVP to EFV
Child <3 yr age or < 10 kg and on 2NRTI plus NVP or LPV/r	▪ Change NVP to 1:1 equivalent LPV/RTV by boosting with added Ritonavir to reach 1:1 mg equivalence:by adding 0.75ml Ritonavir per ml LPV/r) OR ▪ Continue with NVP but adjusting dose to the maximum (i.e. 200 mg/sq.m)

3. If Infant or child is already on second-line ART:

Rifampicin based ATT should be initiated and like stated above the PI usually LPV/r will need to be boosted to 1:1 mg equivalence LPV/RTV by the addition of 0.75 ml RTV to each ml of LPV/r. If LPV/r is the used PI, then it should be maintained. If another PI is being used this should be changed to LPV/r with the necessary booster.

E2.7 Monitoring – Clinical and Laboratory:

All patients on Rifampicin based ATT and ART simultaneously will benefit from the following monitoring:

Clinical monitoring for features suggestive of hepatic dysfunction and Gastro-intestinal disturbances .

- Anorexia, Vomiting, Nausea and Jaundice are features seen due to Nevirapine or Isoniazid/ Rifampicin/ Pyrazinamide toxicity usually within the initial 8 weeks of initiation especially in the malnourished children.
- Gastrointestinal disturbances that includes many of the above features and diarrhea may occur due to side effects of PIs such as LPV/RTV.

Laboratory Monitoring

- Measure ALT/ serum bilirubin as a baseline and periodically (symptomatic driven or 2 weekly till atleast 6-8 weeks after initiation) looking for significant elevations. More than 3-5 times elevation from the baseline is considered as significant. A baseline pregnancy test prior to Efavirenz (EFV) use is essential.

Management of adverse drug reactions

Adverse reaction	Main ARV drug involved	Main antiaTB drug involved	Management
Peripheral neuropathy (early or late side effect)	Stavudine Didanosine	Isoniazid Cycloserine	Pyridoxine given as preventive therapy and treatment for isoniazid toxicity
Hepatitis (usually early side effect)	Nevirapine PI	Pyrazinamide Rifampicin Isoniazid Ethionamide	STOP all drugs: once resolved restart with TB therapy
Gastrointestinal dysfunction [diarrhoea, abdominal pain] (early or late side effect)	All	All	Symptomatic
Skin rash (usually early side effect)	Nevirapine Efavirenz Abacavir	Pyrampicin Isoniazid Pyrazinamide Cycloserine	Anti-histamine if mild: if severe STOP all drugs: once resolved restart with TB therapy
Central nervous system dysfunction (early or late side effect)	Efavirenz	Isoniazid Cycloserine	Pyridoxine given as preventive therapy and treatment for isoniazid toxicity
Anaemia (usually early side effect)	Zidovudine	Rifampicin	Change from zidovudine to stavudine

E2.8 Isoniazid Preventive Therapy (IPT)

- Latent TB is when children (or adults) are exposed and infected with mycobacterium tuberculosis but have no symptoms or signs of active disease. Young children especially under 6 years age are known to progress from latent to TB disease and hence IPT is recommended for this age group. Children with immunosuppressive diseases such as HIV and on immunosuppressive therapies such as Steroids also are known to progress from Latent to active disease thus warranting the need for IPT. Isoniazid Preventive Therapy is never recommended if there is evidence of active TB disease.

- Infants and children living with HIV should routinely be screened for TB as a part of standard clinical care, whether they are receiving TB prophylaxis or ART. The Guidelines Group recommends that children living with HIV without poor weight gain, fever and current cough are unlikely to have active TB and should be offered IPT. Children living with HIV who are more than 12 months of age and who are unlikely to have active TB on symptom-based screening, and have no contact with a TB case should receive six months of IPT (10 mg/kg/day) as part of a comprehensive package of HIV prevention and care services.
- In children living with HIV who are less than 12 months of age, only those who have contact with a TB case and who are evaluated for TB should receive six months of IPT if the evaluation shows no TB disease.
- All children living with HIV who have successfully completed treatment for TB disease should receive INH for an additional six months.
- Providing IPT to people living with HIV does not increase the risk of developing INH-resistant TB.
- Dose for INH should be 10 mg/kg/day for at least 6 months duration.

Treatment of Drug resistant TB

Multidrug-resistant (MDR) tuberculosis (TB) caused by Mycobacterium tuberculosis strains resistant to at least isoniazid and rifampin—has emerged as a global epidemic resulting largely from deficiencies in TB case management and program management. Approximately 425,000 MDR-TB cases occur annually worldwide, representing nearly 5% of the world's annual TB burden. The diagnosis of MDR-TB requires sophisticated laboratories with highly skilled microbiologists. Patients with MDR-TB require a much longer treatment period, usually 24 months, compared with the 6–8 months required for drug-susceptible TB.

Patients with suspected multi-drug resistant TB should be referred to pCOE (Pediatric Centres of Excellence) or the local hospital pediatrician for further treatment.

ART Regimens in Children Receiving or Requiring Rifampicin based Anti-TB (ATT) Treatment

Clinical Scenario	ART Regimen Decision and Time	ARV Dose Issues	Monitoring Issues
ART naïve Child's age > 3 yr and weight > 10 kg	▪ EFV based regimen is the first choice ▪ Initiate ART within 2-8 weeks of tolerating ATT	▪ Normal dose EFV	▪ Routine monitoring including support and adherence
ART naïve Child's age < 3 yrs and weight < 10 kg	▪ NVP based regimen is the first choice ▪ Alternative is Triple NRTI regimen (AZT or d4T/3TC/ ABC) OR 2 NRTIs with RTV boosted LPV/r ▪ Initiate ART within 2-8 weeks of tolerating Triple ART regimen	▪ Choose high dose, 200 mg/ sq. m per dose, 12 hourly ▪ No two weeks lead in period for NVP required ▪ LPV/r with a booster dose to obtain 1:1 ratio by adding 0.75 ml RTV / ml of LPV to regimen	▪ Routine monitoring including support and adherence ▪ Monitoring required especially for hepatitis, skin rash, hypersensitivity ▪ Monitor for Treatment failure
On NVP based ART, Child's age > 3 yrs and weight > 10 kg	▪ Substitute **NVP for EFV** in the regimen	▪ Normal dose EFV	▪ Routine monitoring including support and adherence ▪ Monitoring for Treatment failure

On NVP based ART, Child's age < 3 yrs and weight < 10 kg	▪ Continue NVP based regimen ▪ Alternative is Triple NRTI regimen (AZT or d4T/3TC/ABC)	▪ Adjust to high dose, 200 mg/ sq.m per dose, 12 hourly	▪ Routine monitoring including support and adherence ▪ Monitoring especially for hepatitis, skin rash, hypersensitivity ▪ Monitor for Treatment failure
On EFV based ART	▪ Continue EFV based regimen	▪ Normal dose EFV	▪ Routine monitoring including support and adherence ▪ Monitoring for Treatment failure
On or in need for a PI based ART(2nd Line)	▪ Continue PI (LPV/r) based regimen ▪ If initiating, then do so within 2-8 weeks of tolerating ATT	▪ LPV/r with a booster dose to obtain 1:1 ratio by adding 0.75 ml RTV / ml of LPV to regimen	▪ Routine monitoring including support and adherence ▪ Monitoring especially for hepatitis, GI upsets ▪ Monitor for Treatment failure

E3: Other Common Opportunistic Infections

E3.1 Bacterial Infections: Serious and recurrent

Epidemiology

Serious and recurrent bacterial infections are a major cause of morbidity and mortality in HIV-infected children worldwide. Immunologic defects in both cell-mediated (T cell) and humoral (B cell) immunity, functional asplenia, decrease in neutrophil number and function, and defects in complement components all contribute to the increased susceptibility to bacterial agents in these children.

Chronic lung disease such as lymphoid interstitial pneumonitis, often seen in children with HIV infection, may predispose to development of acute pneumonia.

Acute pneumonia has been associated with increased risk of long-term mortality in HIV-infected children, although multiple episodes of acute pneumonia likely represent a marker of progressive disease and immunologic dysfunction rather than being causally associated with increased long-term mortality. Common bacterial infections other than pneumonia include sepsis, otitis, abscess and other soft tissue infections, osteomyelitis, arthritis and bacterial meningitis.

Streptococcus pneumoniae is the most prominent invasive bacterial pathogen in children with HIV infection worldwide, accounting for more than 50% of bacterial blood-stream infections. The rate of antibiotic resistance to S. pneumoniae varies throughout the world.

Haemophilus influenzae type b (Hib) was reported to be the most common cause of bacterial meningitis in infants and children age five years or younger. HIV-infected children are at greater risk of overall invasive Hib disease and of developing bacteremic pneumonia than are uninfected children.

While the frequency of gram-negative bacteremia is lower than gram-positive bacteremia in HIV-infected children, gram-negative bacteremia is more common in children with advanced HIV disease or immunosuppression or those with central venous catheters. Gram-negative bacteria such as E. coli and Klebsiella pneumoniae commonly cause urinary tract infections. However, in children age five years or younger, gram-negative bacteremia is also seen in children with milder levels of immune suppression.

The presence of a central venous catheter increases the risk of bacterial infections in HIV-infected children, but the incidence is similar to that seen in children with cancer. S. aureus is the most commonly isolated pathogen in catheter-associated bacteremia in HIV-infected children; P. aeruginosa is also common. Other organisms associated with catheter-associated bacteremia include S. epidermidis, Enterococcus, and Bacillus cereus.

Clinical Manifestations

HIV-infected children with invasive bacterial infections generally have a clinical presentation similar to children without HIV infection. The classical signs, symptoms, and laboratory test abnormalities that usually indicate invasive bacterial infection (fever, elevated white blood cell [WBC] count) are usually present but may be lacking in immunocompromised HIV-infected children. Due to difficulties in obtaining appropriate specimens, such as sputum, from young children, bacterial pneumonia is most often a presumptive diagnosis in a child with fever, respiratory symptoms, and an abnormal chest radiograph unless there is an accompanying bacteremia. One-third of HIV-infected children who develop acute pneumonia have recurrent episodes.

Diagnosis Attempted isolation of a pathogenic organism from normally sterile sites (blood, CSF, pleural fluid) is strongly recommended. This is particularly important in the face of an increasing

incidence of antimicrobial resistance, including penicillin resistant S. pneumoniae and community-acquired methicillin resistant S. aureus. The diagnosis of pneumonia is typically made on the basis of clinical (e.g. fever, dyspnoea, tachypnea, cough, rales) and radiographic findings, although it is difficult to differentiate viral from bacterial pneumonia clinically. Culture of blood and pleural fluid, if present, should be done.

In bacteremic children, a source for the bacteremia should be sought. In addition to routine chest x-rays, other diagnostic radiological evaluations may become necessary (CT chest, abdomen, ultrasound studies) in HIV-infected children with compromised immune systems in order to identify less apparent foci of infection such as bronchiectasis or internal organ abscesses. In children with central venous catheters, both a peripheral and catheter blood culture should be obtained; if the catheter is removed, the catheter tip should be sent for culture.

Treatment

The local prevalence of resistance to common infectious agents when known (penicillin resistant S. pneumoniae, methicillin resistant S. aureus), and the recent use of prophylactic or therapeutic antibiotics need to be taken into consideration when initiating empiric therapy. Once the organism is identified, antibiotic susceptibility testing should be performed and therapy commenced based on the results of susceptibility testing.

HIV-infected children whose immune systems are not seriously compromised (CDC Immune Class I) and who are not neutropenic can be expected to respond like HIV-uninfected children and should be treated with the usual antimicrobial agents recommended for the most likely bacterial organisms. Severely immune compromised HIV-infected children presenting with invasive or recurrent bacterial infections may require expanded empiric antimicrobial treatment covering a broad range of resistant organisms (similar to that chosen for suspected catheter sepsis) pending results of diagnostic evaluations and cultures.

E3.2 Mycobacterium Avium Complex (MAC)

Epidemiology

Mycobacterium avium complex (MAC) is caused primarily by the environmental nontuberculous mycobacteria M. avium, M. intracellulare, and M. paratuberculosis. Respiratory and gastrointestinal colonisation by inhalation or ingestion can subsequently lead to disseminated infection.

MAC can present as isolated lymphadenitis in HIV-infected children. Presentation with isolated MAC pulmonary disease is a marker of high risk for dissemination. Disseminated infection with MAC in paediatric HIV infection rarely occurs during the first year of life; its frequency increases with age and declining CD4+ T cell count, and it is a frequent complication of advanced immunologic deterioration in HIV-infected children. In children age two years or younger, disseminated MAC may occur at higher CD4+ T cell counts than it does in older children or adults.

Clinical Manifestations

Recurrent fever, weight loss or failure to thrive, neutropenia, night sweats, fatigue, chronic diarrhoea, malabsorption, and persistent or recurrent abdominal pain are the symptoms most commonly associated with disseminated MAC infection in children. Lymphadenopathy, hepatomegaly, and splenomegaly may also be found.

Isolated pulmonary disease is rare.

Laboratory abnormalities may include anemia, leukopenia, and thrombocytopenia.

Diagnosis

Procedures used to diagnose MAC in children are the same as those used in HIV-infected adults. Definitive diagnosis is based on isolation of the organism from blood or biopsy specimens from normally sterile sites, such as bone marrow, lymph node, or other tissues. Several mycobacterial blood cultures over time may be required to yield a positive result. Culture is essential to differentiate nontuberculous mycobacteria from M. tuberculosis as well as to determine which nontuberculous mycobacteria is the cause of infection and the organism's drug susceptibilities. Identification of MAC in stool or respiratory tract secretions indicates colonisation but not necessarily invasive disease.

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 two drugs is recommended for treatment of MAC infections (Table 24). Monotherapy with a macrolide results in emergence of high-level drug resistance within weeks.

Initial empiric therapy consists of clarithromycin plus ethambutol (EMB). Azithromycin may be substituted in patients with significant intolerance to clarithromycin or when drug interactions with clarithromycin are a concern. Rifabutin may be added as a third drug to the clarithromycin/EMB regimen, particularly in patients with more severe symptoms or disseminated disease.

Additional drugs can be considered depending on the severity of illness. For disseminated disease, 3 or 4 drugs are essential. In a patient with severe disease, if rifabutin cannot be given, ciprofloxacin, levofloxacin, and/or amikacin or streptomycin can be used. Most patients show improvement within 4-6 weeks. Treatment should then be continued with 2 drugs.

The most effective way to prevent disseminated MAC in HIV-infected children is to preserve immune function through use of effective ART. Additionally, improved immunologic status is important for control of MAC disease in children with disseminated disease; ART should therefore be initiated in children with MAC disease who are ARV-naïve.

Table 24 : 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 of MAC infection, secondary prophylaxis is recommended for life time.
- Any child in WHO Stage IV.

As per CD4 counts, as below

Table 25 : Indications for MAC prophylaxis

Age	CD4 count (cells/mm3)	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 26 : 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.

E3.3 Syphilis

Epidemiology

Treponema pallidum can be transmitted from mother to child at any stage of pregnancy or during delivery. Among women with untreated primary, secondary, early latent, or late latent syphilis at delivery, approximately 30%, 60%, 40%, and 7% of infants, respectively, will be infected. Treatment of the mother for syphilis ≥30 days before delivery is required for effective in utero treatment.

Congenital syphilis has been reported despite adequate maternal treatment. Factors that

contribute to treatment failure include maternal stage of syphilis (early stage, meaning,

primary, secondary, or early latent syphilis), advancing gestational age at treatment, higher Venereal Disease Research Laboratory (VDRL) titers at treatment and delivery, and short interval from treatment to delivery (<30 days).

Mother-to-child HIV transmission might be higher when syphilis co-infection is present during pregnancy, transmission does not appear to be higher if the mother's syphilis is effectively treated before pregnancy

Clinical Manifestations

Among children with congenital syphilis, two characteristic syndromes of clinical disease exist: Early congenital syphilis refers to clinical manifestations appearing within the first 2 years of life. Late congenital syphilis refers to clinical manifestations appearing in children >2 years old. At birth, infected infants may manifest such signs as hepatosplenomegaly, jaundice, mucocutaneous lesions (e.g., skin rash, nasal discharge, mucous patches, condyloma lata), lymphadenopathy, pseudoparalysis of an extremity, anemia, thrombocytopenia, pneumonia, and skeletal lesions (e.g., osteochondritis, periostitis, or osteitis).

The manifestations of acquired syphilis in older children and adolescents are similar to those of adults. HIV-infected persons with acquired early syphilis might be at increased risk for neurologic complications and uveitis and have higher rates of treatment failure.

Diagnosis

The standard serologic tests for syphilis in adults are based on the measurement of IgG antibody. Because IgG antibody in the infant reflects transplacental passively transferred antibody from the mother, interpretation of reactive serologic tests for syphilis among infants is difficult. Therefore, the diagnosis of neonatal congenital syphilis depends on a combination of results from physical, laboratory, radiographic, and direct microscopic examinations.

All infants born to women with reactive nontreponemal and treponemal test results should be evaluated with a quantitative nontreponemal test (e.g., VDRL slide test, rapid plasma regain [RPR], or the automated reagin test). Neonatal serum should be tested because of the potential for maternal blood contamination of the umbilical cord blood specimens. Specific treponemal tests, such as the fluorescent treponemal antibody absorption (FTA-ABS) test and T. pallidum particle agglutination (TP-PA) test, are not necessary to evaluate congenital syphilis in the neonate. Congenital syphilis can be definitively diagnosed if T. pallidum is detected by using darkfield microscopic examination or direct fluorescent antibody staining of lesions or body fluids such as umbilical cord, placenta, nasal discharge, or skin lesion material from the infant.

A presumptive case of syphilis is defined as maternal untreated or inadequately treated syphilis at delivery, regardless of findings in the infant, or a reactive treponemal test result and signs in an infant of congenital syphilis on physical examination, laboratory evaluation, long bone radiographs, positive CSF VDRL test, or an abnormal CSF finding without other cause.

Treatment of Disease

Penicillin remains the treatment of choice for syphilis, congenital or acquired, regardless of HIV status. Treated syphilis (including treatment with erythromycin or any other nonpenicillin regimen), no documentation of having received treatment, receipt of treatment ≤4 weeks before delivery, treatment with penicillin but no fourfold decrease in nontreponemal antibody titer, or fourfold or greater increase in nontreponemal antibody titer suggesting relapse or reinfection. Infants should be treated regardless of maternal treatment history if they have an abnormal examination consistent with congenital syphilis, positive darkfield or fluorescent antibody test of body fluid(s), or serum quantitative nontreponemal serologic titer that is at least fourfold greater than maternal titer.

Treatment for proven or highly probable congenital syphilis (i.e., infants with findings or symptoms or with titers fourfold greater than mother's titer) is aqueous crystalline penicillin G at 100,000--150,000 units/kg/day, administered as 50,000 units/kg/dose intravenously every12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days. If congenital syphilis is diagnosed after 1 month of life, the dosage of aqueous penicillin G should be increased to 50,000 units/kg/dose intravenously every 4--6 hours for 10 days. An alternative to aqueous penicillin G is procaine penicillin G at 50,000 units/kg/dose intramuscularly (IM) daily in a single dose for 10 days. However, aqueous penicillin G is preferred because of its higher penetration into the CSF.

Asymptomatic infants born to mothers who have had adequate treatment and response to therapy, and with a normal physical examination and CSF findings, and who have a serum quantitative nontreponemal serologic titer that is less than fourfold higher than maternal titer might be treated with a single dose of benzathine penicillin G 50,000 units/kg/dose IM with careful clinical and serologic follow-up.

Acquired Syphilis : Acquired syphilis in children is treated with a single dose of benzathine penicillin G 50,000 units/kg IM (up to the adult dose of 2.4 million units) for early-stage disease(e.g., primary, secondary, and early latent disease). For late latent disease, three doses of benzathine penicillin G 50,000 units/kg (up to the adult dose of 2.4 million units) should be administered IM once weekly for three doses (total 150,000 units/kg, up to the adult total dose of 7.2 million units. Neurosyphilis should be treated with aqueous penicillin G 200,000-300,000 units/kg intravenously every 4-6 hours (maximum dosage: 18-24 million units/day) for 10-14 days.

Prevention

Congenital Syphilis: Effective prevention and detection of congenital syphilis depend on the identification of syphilis in pregnant women and, therefore, on the routine serologic screening of pregnant women during the first prenatal visit. In communities and populations in which the risk for congenital syphilis is high, serologic testing and a sexual history also should be obtained at 28 weeks' gestation and at delivery. Moreover, as part of the management of pregnant women who have syphilis, information about treatment of sex partners should be obtained to assess the risk for re-infection. No HIV-exposed infant should leave the hospital unless the maternal serologic status has been documented at least once during pregnancy and at delivery in communities and populations in which the risk for congenital syphilis is high.

E4: Opportunistic Infections: Fungal

E4.1 Pneumocystis jiroveci pneumonia (PCP)

Epidemiology

Pneumocystis spp. are found worldwide in the lungs of humans and lower animals. The organisms are host specific, and cross-infection between humans and other animals does not occur. Airborne human-to-human transmission is likely. Pneumocystis has been designated a fungus on the basis of DNA analysis, but it has several biologic features of protozoa. Pneumocystis pneumonia (PCP) occurs almost exclusively in the immunocompromised host.

PCP remains a common AIDS-indicator disease among HIV-infected children. The highest incidence of PCP in HIV-infected children is in the first year of life, with cases peaking at age 3-6 months. Severe immunosuppression, reflected by a marked decrease in CD4 count and percentage, is the hallmark of high risk for PCP. Unlike in older children and adults, CD4+ T cell counts are not a good indicator of risk for PCP in infants age one year or younger; many young infants with PCP have CD4+ T cell counts of >1,500 cells/mm3, and counts can drop very rapidly shortly before PCP develops in infants.

Pathogenesis

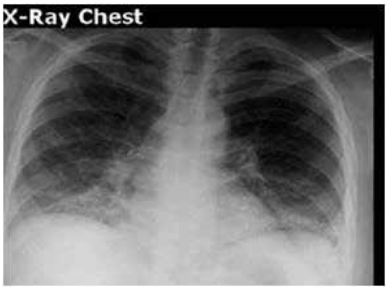
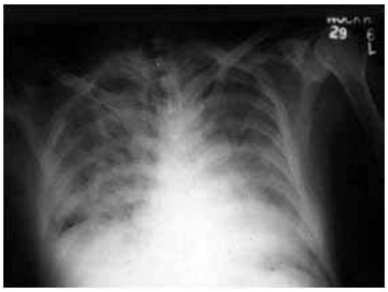
PCP is usually acquired in childhood. Serum antibodies are found in over 80% of children by 4 years of age. In immuno-competent infants, it may lead to mild respiratory symptoms or children are usually asymptomatic. In immunodeficient individuals it infects the alveoli, leads to interstitial edema and 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 Manifestations

Clinical features of PCP in HIV-infected children are similar to those in adults. Fever, tachypnea, dyspnoea, and cough are seen most commonly, especially in the younger child. Onset can be abrupt or may be insidious in the older child. Most young children have acute onset with tetrad of symptoms- fever, cough, tachypnea and dyspnea. Older children with insidious onset have non-specific symptoms such as mild cough, dyspnoea, poor feeding, and weight loss. Almost all children will have tachypnea by the time pneumonitis is seen on chest radiograph. Bibasilar rales with evidence of respiratory distress may be heard on physical examination. Most children with PCP have significant hypoxia with low arterial oxygen pressure [pO2] and an alveolar-arterial oxygen gradient [(A-a)DO2] of >30mmHg.

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.

 	Chest radiographs most commonly show bilateral diffuse parenchymal infiltrates with "ground-glass" or reticulogranular appearance, but they also may be normal or show only mild parenchymal infiltrates. The earliest infiltrates are perihilar, progressing peripherally but sparing the apical portions of the lung until last. Lobar, cavitary, nodular, or miliary lesions; pneumothorax; or pneumomediastinum are seen rarely.
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	Definitive diagnosis of PCP requires demonstration of the organism in pulmonary tissues or fluids. Diagnostic procedures are the same as those used for adults with suspected PCP, but some procedures may be more difficult to perform in children. Induced sputum analysis, bronchoscopy with bronchoalveolar lavage (BAL), fiberoptic bronchoscopy with transbronchial biopsy, and open-lung biopsy are not uniformly available. If possible, a specific diagnosis should be sought rather than relying on presumptive diagnosis.
Stains:	When an appropriate sample is available, three types of stains may be used to diagnose P. jiroveci organisms in specimens. Gomori's methenamine-silver stain stains the cyst wall brown or black. Toluidine Blue stains the cyst wall blue or lavender and also stains fungal elements. Giemsa or Wright's stains stain the trophozoites and intracystic sporozoites pale blue with a punctate red nucleus. Unlike the other stains, this does not stain the cyst wall.

Treatment Recommendations

Table 27: Treatment of PCP

Drugs	Dosing	Side Effects	Remarks
TMP/SMX	15-20 mg/kg of TMP IV/PO in 4 divided doses for 21days 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:

Cotrimoxazole (TMP/SMX) is the drug of choice for PCP prophylaxis. 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.)

E4.2 Candidiasis:

Epidemiology

The most common fungal infections among HIV-infected children are caused by Candida spp. Oral thrush and diaper dermatitis occur among 50%--85% of HIVinfected Children. Localized disease caused by Candida is characterized by limited tissue invasion to the skin or mucosa. Examples of localized candidiasis include oropharyngeal and esophageal disease, vulvovaginitis, and diaper dermatitis.

Disseminated candidiasis is infrequent among HIV-infected children, but Candida can disseminate from the esophagus particularly when co-infection with herpes simplex virus (HSV) or CMV is present. Candidemia occurs in up to 12% of HIV-infected children with chronically indwelling central venous catheters for total parental nutrition or IV antibiotics.

Approximately 50% of reported cases of Candida bloodstream infections in HIV infected children are caused by non-albicans Candida spp.

Clinical Manifestations

Oral candidiasis Recurrent oral candidiasis is one of the clinical indicators of HIV infection in infants beyond 8 weeks of age .Oropharyngeal candidiasis (OPC) may present as pseudomembranous (thrush) and erythematous (atrophic), hyperplastic (hypertrophic), and angular cheilitis. Thrush appears as creamy white curdlike patches with inflamed underlying mucosa that is exposed after removal of the exudate. It can be found on the oropharyngeal mucosa, palate, and tonsils. Erythematous OPC is characterized by flat erythematous lesions on the mucosal surface. Hyperplastic candidiasis comprises raised white plaques on the lower surface of the tongue, palate, and buccal mucosa and cannot be removed. Angular cheilitis occurs as red fissured lesions in the corners of the mouth.

Esophageal candidiasis is seen in patients with low CD 4 cell count (<100/cumm), high viral load and neutropenia (<500/cumm). It often presents with odynophagia, dysphagia, and nausea ,vomiting or retrosternal pain. Children may sometime be seen accompanied with dehydration and weight loss.

Disseminated form in blood can take from chronic catheter infection in sever immune suppression, and it can spread to eyes as endopthalmitis. Renal candidiasis presents with candiduria and ultrasonographically demonstrated renal parenchymal lesion. It may also present as hepatic, splenic, and bone involvement.

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 a classic cobblestoning appearance on barium swallow. In refractory symptomatic cases, endoscopy should be performed to rule out other causes of refractory esophagitis (e.g., HSV, CMV, MAC, and azole-resistant Candida spp.). Endoscopy might show few small white raised plaques to elevated confluent plaques with hyperemia and extensive ulceration.

Candidemia is best diagnosed with blood cultures using lysis-centrifugation techniques. When candidemia is present, depending on clinical suspicions, retinal examination for endophthalmitis, abdominal CT or ultrasound for hepatic or renal involvement, and bone scans for osteomyelitis can be considered.

Disseminated form in blood can take from chronic catheter infection in sever immune suppression, and it can spread to eyes as endopthalmitis. Renal candidiasis presents with candiduria and ultrasonographically demonstrated renal parenchymal lesion. It may also present as hepatic, splenic, and bone involvement.

Treatment (Table 28)

Oropharyngeal candidiasis (OPC) as uncomplicated infection can be effectively treated with topical therapy using clotrimazole troches or oral polyenes (such as nystatin or amphotericin B suspension). Troches should not be used in infants . Resistance to clotrimazole can develop as a consequence of previous exposure to clotrimazole itself or to other azole drugs; resistance correlates with refractory mucosal candidiasis.

Systemic therapy with one of the oral azoles (e.g., fluconazole, ketoconazole, or itraconazole) also is effective for initial treatment of OPC . Oral fluconazole is more effective than nystatin suspension for initial treatment of OPC in infants; is easier to administer to children than the topical therapies; and is the recommended treatment if systemic therapy is used. Itraconazole solution has comparable efficacy to fluconazole and can be used to treat OPC, although it is less well tolerated than fluconazole

In esophageal disease, systemic therapy is essential and should be initiated empirically, among HIV-infected children who have OPC and esophageal symptoms.. Conventional amphotericin B (sodium deoxycholate complex) is the drug of choice for most invasive Candida infections in children. Therapy should be continued until 2--3 weeks after the last positive blood culture and until signs and symptoms of infection have resolved.

Voriconazole has been used in a limited number of children without HIV infection to treat invasive fungal infections, including esophageal candidiasis or candidemia. Usually children have been initiated on voriconazole intravenously and then switched to oral administration to complete therapy after stabilization.

Table 28 : 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
Fluconazole	3-6 mg/kg/ OD PO for 7-14 days (max: 400 mg/dose) for oral thrush.	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.

3-6 mg/kg/day IV/PO for 14-21 days (max: 400mg/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.	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.
Oral fluconazole is used for oral candidiasis if topical therapy fails.	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
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, thrombocytopenia, leukopenia, pruritis .	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.	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.
Itraconazole is a second line drug for esophageal candidiasis.	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
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, nemia, 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.
Voriconazole	6--8 mg/kg intravenously, or 8 mg/kg orally every 12 hours.	Dissturbance of vision skin rashes, elevations in hepatic enzymes level	limited experience of this drugs in children

Table 29 : 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)

E4.3 Cryptococcosis

Epidemiology

Cryptococcus neoformans var neoformans is the most common fungal meningitis in AIDS and occurs primarily in tropical and sub tropical regions. It affects about 1% of HIV infected children in contrast to10 % in adults .The majority of cases are seen when the CD4+ counts are <50 cells/ mm3 or indicating severe immune suppression ..

Clinical Manifestation

It often presents as subtle and non specific findings such as fever, headache, photophobia and altered consciousness. Neck rigidity and focal neurological signs are rare.

Disseminated cryptococcosis can be associated with cutaneous lesions, including small translucent umblicated papules which may resemble molluscum, may become infiltrated papules resembling cellulitis. Ocassionally pulmonary cryptococcosis can be seen in children indicating severe immune suppression

Diagnosis

CSF examination shows raised intracranial pressure, elevated proteins and mononuclear pleocytosis. However, CSF cell count, glucose and protein may be virtually normal. India ink staining of CSF shows budding yeast.

Cryptococcal antigen can be detected in CSF or serum by latex agglutination test.

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 blood and sputum can identify the organism.

Wright stain of skin scraping should show budding yeast.

Treatment

CNS Disease (Table 30) –A combination therapy with amphotericin B and flucytosine for 2 weeks is given as induction phase.

After a minimum of 2 weeks of induction therapy with evidence of clinical improvement and negative CSF culture after repeat lumbar puncture, consolidation phase can be initiated with flucanozole.

Fluconazole is given for a minimum of 8-10 weeks. Itraconazole is an alternative to fluconazole for consolidation phase of CNS therapy.

For raised intracranial pressure repeated lumbar punctures are performed .Corticosteroid and acetazolamide should not be used to reduce intracranial pressure

Pulmonary and extra pulmonary Disease- After CNS disease is excluded children should be treated with amphotericin B without any additional drug. Mild to moderate localized disease can be managed by flucanazole monotherapy.

Table30 : 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 children 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 31 : 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.

E.4.4 Penicilliosis

Epidemiology:

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.

Clinical Features:

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:

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

E5: Opportunity Infections: Parasitic

E5.1 Toxoplasmosis

Epidemiology

Toxoplasmosis, a protozoan disease, causes severe disease in foetus during pregnancy and deadly encephalitis in HIV patients. The infection is mainly acquired by ingestion of undercooked or raw meat containing viable tissue cysts, or by ingestion of food and water that is contaminated with oocysts shed by felines. Additionally, the reactivation of latent infection occurs in immune compromised patients, causing life-threatening disease, especially encephalitis . Encephalitis due to reactivated toxoplasmosis is one of the most common opportunistic neurological infections in AIDS patients, typically observed in the later stages of human immunodeficiency virus (HIV) infection.The incidence of central nervous system (CNS) toxoplasmosis among HIV-infected patients in India and the world has been reported to be about 1.33-3.33 percent in various studies.

The major mode of transmission of Toxoplasma gondii infection among infants and young children is congenital, occurring almost exclusively among neonates born to women who sustain primary Toxoplasma infection during pregnancy. The overall risk for maternal-fetal transmission in HIV-uninfected women who acquire primary Toxoplasma infection during pregnancy is 29 percent. The risk for congenital infection is low among infants born to women who become infected during the first trimester (range: 2 percent--6 percent) but increases sharply thereafter, with a risk as high as 81 percent for women acquiring infection during the last few weeks of pregnancy. Infection of the fetus in early gestation usually results in more severe disease than does infection late in gestation.

CNS infection with T. gondii was reported as an AIDS-indicator condition in <1 percent of pediatric AIDS cases before the advent of HAART . During the HAART era, this condition is rarely encountered in developed countries. Development of CNS toxoplasmosis in HIV-infected children during the HAART era is 0.2 percent.

Clinical Manifestations

In studies of non immunocompromised infants with congenital toxoplasmosis, most infants (70%--90%) are asymptomatic at birth. However, most asymptomatic children develop late sequelae (e.g., retinitis, visual impairment, and intellectual or neurologic impairment), with onset of symptoms ranging from several months to years after birth. Symptoms in newborns take either of two presentations:

- generalized lymphadenopathy;
- hepatosplenomegaly;
- jaundice;
- hematologic abnormalities, including anemia, thrombocytopenia, and neutropenia; and
- substantial CNS disease, including hydrocephalus, intracerebral calcification, microcephaly, chorioretinitis, and seizures.

Diagnosis

HIV-infected women might be at increased risk for transmitting T. gondii to their foetus, and serologic testing for Toxoplasma should be performed for all HIV-infected pregnant women. All infants whose mothers are both HIV-infected and seropositive for Toxoplasma should be evaluated for congenital toxoplasmosis . Congenital toxoplasmosis can be diagnosed by EIA or an immunosorbent assay to detect Toxoplasma-specific IgM, IgA, or IgE in neonatal serum within the first 6 months of life or persistence of specific IgG antibody beyond age 12 months. IgA might be more sensitive for detecting congenital infection than IgM or IgE . However, approximately 20%--30% of infants with congenital toxoplasmosis will not be identified during the neonatal period with IgA or IgM assays.Serologic testing is the major method of diagnosis, but interpretation of assays often is confusing and difficult.

Similarly, toxoplasmosis acquired after birth is most often initially asymptomatic. When symptoms occur, they are frequently nonspecific and can include malaise, fever, sore throat, myalgia, lymphadenopathy (cervical), and a mononucleosis-like syndrome featuring a maculopapular rash and hepatosplenomegaly. TE (toxoplasmosis encephalitis) should be considered among all HIV-infected children with new neurologic findings. Although focal findings are more typical, the initial presentation can vary and reflect diffuse CNS disease. Other symptoms include fever, reduced alertness, and seizures. Isolated ocular toxoplasmosis is rare and usually occurs in association with CNS infection. As a result, a neurologic examination is indicated for children in whom Toxoplasma chorioretinitis is diagnosed. Ocular toxoplasmosis appears as white retinal lesions with little associated hemorrhage; visual loss might occur initially. Less frequent presentations among HIV-infected children with reactivated chronic toxoplasmosis include systemic toxoplasmosis, pneumonitis, hepatitis, and cardiomyopathy/myocarditis .	CNS toxoplasmosis is presumptively diagnosed on the basis of clinical symptoms, serologic evidence of infection, and presence of a space-occupying lesion on imaging studies of the brain. TE rarely has been reported in persons without Toxoplasma-specific IgG antibodies; therefore, negative serology does not definitively exclude that diagnosis. CT of the brain might indicate multiple, bilateral, ring-enhancing lesions in CNS toxoplasmosis, especially in the basal ganglia and cerebral corticomedullary junction. MRI is more sensitive and will confirm basal ganglia lesions in most patients.

Table 32: 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/do 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
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.

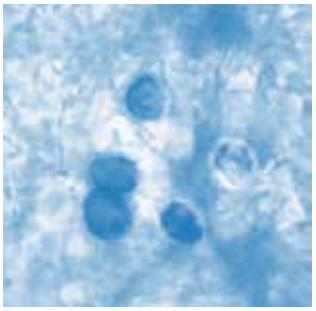
E5.2 Cryptosporidium parvum, Isospora belli, Microsporidia, Cyclospora*

(* More discussion about these parasitic infection is dealt with in section of approach to an HIV infected child with diarrhea)

Cryptosporidium:	**Microsporidia:**	**Isospora belli and Cyclospora:**
Patients with CD4 counts <100 cells/mm3are more prone to such infections with cryptosporidial species.	Microspora are obligate spore forming protozoa that cause moderate to severe diarrhea with weight loss. They are	These organisms are rarer causes of chronic diarrhoea in HIV infected
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 (common in India), and C. meleagridis. The prevalence among children ranges from 3.0 to 3.6 % and may occur more frequently among children in developing countries .In Indian children it ranges from 1.1% to 18.9%. 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.	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.	children. Diagnosis is established by characteristic oocytes on microscopic examination of the stool with a 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.



Cryptosporidiosis

Treatment	**Treatment**	**Treatment for Isospora**
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:	Immune restoration after HAART frequently results in clearance of microsporidia. No consistently effective therapy exists for microsporidia. Agents used:	TMP/SMX – 20 mg/kg/ day of TMP in 4 divided doses for 10 days and then twice a day for 3 days.
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	**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	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.

Prophylaxis

Cotrimoxazole prophylaxis(CPT) also protects against Isospora and cyclospora.

Secondary prophylaxis with cotrimoxazole [5mg/kg/day of TMP] is recommended to prevent relapse.

E6: Opportunistic Infections: Viral

E6.1 Cytomegalovirus

Epidemiology:

CMV constitutes 8-10 percent of pediatric AIDS defining illness. The infant can have CMV infection through vertical transmission from an infected mother during pregnancy, or through contact with virus-containing body fluid during delivery. During childhood, infection can be acquired through ingestion of infected breast milk, exposure to infected saliva or urine, infected blood or transplantation of infected organs. In adolescents sexual transmission may occur.

HIV-infected women with CMV infection have a higher rate of CMV shedding from the cervix than women without HIV infection. The risk for mother-to-infant transmission of CMV may be higher among infants born to women dually infected with CMV and HIV. HIV-infected children co-infected with CMV may have faster progression of HIV disease.

Clinical Features:

Most infants with perinatal CMV are asymptomatic at birth. About half of neonates with symptomatic congenital CMV disease are small for gestational age, and may have petechiae, jaundice, hepatosplenomegaly, chorioretinitis, microcephaly, intracranial calcifications, and hearing impairment. 10 percent--15 percent infants with CMV are at risk for late complications, including substantial hearing loss, mental retardation, chorioretinitis, optic atrophy, seizures, or learning disabilities. HIV infected children with CMV co-infection have a rapid HIV disease progression and are likely to have CNS disease .

CMV retinitis is the most frequent and severe manifestation of CMV disease in HIV-infected children. It is frequently asymptomatic and discovered on routine examination. Older children with CMV retinitis present with floaters, loss of peripheral vision, or reduction in central vision. Fundus evaluation reveals white peri-vascular retinal infiltrates and retinal haemorrhages.

Children with systemic CMV disease present with fever, poor weight gain, and loss of developmental milestones. The Gastro-intestinal manifestations include CMV colitis, oral and esophageal ulcers, hepatic involvement, ascending cholangiopathy, or gastritis.

CNS manifestations of CMV include sub-acute encephalopathy, myelitis, and poly-radiculopathy. It is difficult to differentiate clinically between sub-acute or chronic encephalopathy of CMV from HIV dementia or encephalopathy. Disseminated disease can present with hepato-splenomegaly, generalized lymphadenopathy, fever and respiratory symptoms. CMV pneumonia is an interstitial pneumonia with dry cough, hypoxemia, with X-ray showing diffuse interstitial infiltrates. CMV may also manifest as part of IRIS.

Diagnosis

CMV infection can be difficult to diagnose in HIV-infected children because of trans-placental transfer of antibody in infants Below 12 months. In an infant aged >12 months, a positive CMV antibody assay indicates presence of CMV infection but not necessarily active disease. During infancy active infection with CMV can be diagnosed by PCR or viral culture of CMV from urine, saliva, throat swab specimens or other body tissues

Histological diagnosis is established by demonstrating characteristic “owl’s eye”, intra-nuclear and smaller intracytoplasmic inclusion bodies in biopsy specimens. Staining with CMV monoclonal antibodies can also be done. CMV DNA detection in CSF by DNA PCR is highly sensitive for CMV CNS disease.

Children with HIV infection should have a fundus examination annually or, as clinically indicated to identify CMV retinitis.

Prevention

For preventing severe CMV disease, recognition of the early manifestations of the disease is the key. Therefore all children should have a detailed fundus examination at baseline, and then yearly for diagnosing CMV retinitis. Risk for CMV infection can be diminished by optimal hygienic practices.

Treatment:

Table 33: Treatment of cytomegalovirus

Drugs	Dosage	Adverse Effects	Remarks
Ganciclovir	Initially: 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] Maintenance therapy: lifelong For CMV retinitis: 30 mg/kg, PO, every 8 hours	Neutropenia, myelo-suppression, renal toxicity, CNS effects, GI dysfunction, thrombophlebitis and elevated liver enzymes	Valganciclovir may also be used but appropriate dose of this drug in children is not known.
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 CNSsymptoms	Alternative drug in case of ganciclovir resistant CMV

All children with CMV infection should be treated as in-patients. Combination therapy with ganciclovir and foscarnet may be used in patients whom monotherapy fails and as initial therapy among children with sight-threatening disease. Intra-vitreous injections of ganciclovir & foscarnet given bi-weekly, have been used to control retinitis.

E6.2 Herpes Simplex

Epidemiology:

HSV is transmitted as vertical transmission, and horizontal transmission through direct contact, infected oral secretions or lesions. Vertical transmission is predominantly intra-partum when the fetus passes through the birth canal and is exposed to genital ulcers. The risk factors associated with increased rate of vertical transmission include primary infection in mother, genital shedding of HSV at the time of delivery, prolonged rupture of membranes > 6 hours resulting in ascending infection from the cervix Neonatal infections are usually caused by HSV -2. Recurrent or persistent HSV infection is an AIDS-indicator condition.

Clinical features:

HIV-infected children have more frequent and severe episodes of HSV reactivation. They can also shed virus for a longer period in both primary and re-activation HSV infection as compared to HIV-uninfected children.

Neonatal HSV may manifest as disseminated multi-organ disease involving CNS, skin, eyes and mouth. Infants with disseminated disease usually present in the neonatal period; encephalitis occurs in 60 percent--75 percent of these infants. A localized form of the disease with involvement of skin, eyes and mouth may also be seen. Although morbidity and mortality is reduced by anti-viral treatment, infants remain at risk for neurological Sequel.

Outside the neo-natal period, the most common manifestation is orolabial ulcers which are often extensive. The are 4-5 mm in diameter, painful and may be seen on tongue, lips and mucosal surfaces (Gingivo-stomatitis). Fever; irritability; tender submandibular lymphadenopathy may be associated. Involvement of other sites such as esophagus, CNS, genitals and systemic disease involving the liver, adrenals, lung, kidney, spleen, and brain occur less frequently; depending on severity of immune suppression.

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. HSV DNAPCR can be used to detect infection in children, even in neonates after 48 hours of life. The test can be performed on blood, skin vesicles, mouth, or nasopharynx, CSF etc. It is the test of choice in patients with suspected HSV encephalitis. Rising antibody titres of HSV 1 and 2 are also useful.

Treatment:

Table 34 : Treatment of Herpes simplex

Drugs	Dosages	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 Gingivo-stomatitis 5-10 mg/kg/dose IV tds x 14 days Mild Gingivo-stomatitis and genital herpes 20 mg/kg/dose POtds x 7-14 days (max: 400 mg/dose) Disseminated HSV and HSV Encephalitis 20 mg/kg/dose IV tds x 21 days	Phlebitis, renal toxicity, nausea, vomiting, rash, neutropenia	Drug of choice for Herpes simplex 1 and 2 valacyclovir, famciclovir are not used in children due to lack of data & availability of pediatric formulations.
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.

E6.3 Varicella

Epidemiology:

Varicella or chickenpox is caused by Varicella Zoster virus (VZV). Varicella is a highly contagious disease. It is transmitted mainly through skin lesions but can also spread through air. Second attacks of varicella are uncommon. However, VZV may persist in the host in a latent form for life.

Clinical Features:

Varicella is a mild disease in immune-competent children. However, in HIV infected children, it has a prolonged and more severe course. The vesicles can persist for weeks and coalesce to form large lesions resembling a burn. HIV infected children are also more prone to complications like bacterial super-infection of skin, encephalitis, cerebellar ataxia, retinitis, transverse myelitis; and rarely vasculitic stroke, hepatitis, and pneumonia. The complications are less in children on antiretroviral therapy or those having higher CD4 counts. Varicella infection should be considered for differential diagnosis of retinitis in HIV infected child.

Diagnosis:

Chickenpox is a clinical diagnosis. Giemsa-staining (Tzanck smear) of cell scrapings from lesions may show multinucleated giant cells but is non-specific. Laboratory tests such as demonstration of VZV antigen or isolation of virus in culture from the fluid in skin lesions, can help in confirmation of diagnosis. A significant rise in VZV IgG antibody during convalescence, or demonstration of VZV IgM antibody can also help to confirm diagnosis. PCR is extremely sensitive and specific in detecting VZV and can also differentiate between wild-type and vaccine VZV.

Prevention: Refer to Section on Immunization (Refer to Table 7)

Treatment:

Table : 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. Consider treatment failure if lesions continue to develop or fail to heal after 10 days of treatment
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

E6.4 Herpes Zoster

Epidemiology:

Herpes zoster is caused by reactivation of latent VZV among persons previously infected with VZV. Reactivation, causing clinical zoster, is less contagious than varicella.

It is rare in immuno-competent children and if it occurs in a child, HIV infection should be suspected.

Clinical Features:

In immune-competent adult, herpes zoster typically causes vesicular lesions, usually unilateral in a dermatomal distribution accompanied by pain and fever. In contrast, in HIV infected children, vesicles or less typical rashes occur in multiple dermatomes, may extend beyond dermatomal boundaries or have bilateral or generalized distribution.There can be recurrent episodes. The frequency of recurrence correlates with the CD4 count.

Patients may have associated retinitis, pneumonitis, hepatitis and even encephalitis.

Diagnosis:

Diagnosis is mainly clinical. Diagnostic laboratory studies are useful in unusual clinical manifestations. These include viral isolation or detection of viral antigens in the skin lesions.

Treatment:

Table : 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
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

Prevention: There is no available prevention for zoster in HIV-infected adolescents & children. The vaccine for prevention of herpes zoster in immunocompetent adults > 60 yrs of age is not recommended for use in HIV-infected individuals at present.

E7: Approach to Common Symptoms

E7.1 Approach to a child with cough or difficult breathing:

Respiratory morbidity is very common in children with HIV infection. While evaluating CLHA with cough and/ or difficult breathing, one must remember that OIs are not responsible for respiratory symptoms in all cases. Respiratory symptoms may be on account of lung conditions other than infections or OIs or some extra/ non-pulmonary conditions. Following are important causes of cough and difficult breathing in HIV infected children in developing countries:

A. Pulmonary Causes:

- Acute bacterial pneumonia and its complications including empyema and / or pneumothorax.
- Acute pneumonia due to opportunistic organisms (PCP, CMV etc).
- Bronchial asthma and related disorders such as wheeze associated lower respiratory infection (WALRI).
- Pulmonary TB and its complications.
- Bronchiectasis.
- Lymphoid Interstitial Pneumonitis (LIP).

B. Non-pulmonary causes:

- Severe anemia.
- Congestive failure.
- Malaria.
- Raised intracranial pressure as in bacterial meningitis / encephalitis.
- Sepsis.

Children with symptoms due to pulmonary causes have cough as a prominent symptom while cough is not that significant in those who have non-pulmonary diseases or conditions leading to respiratory distress.

Acute pneumonia and PCP have been discussed elsewhere. Complications of pneumonia such as empyema and pneumothorax can easily be identified by clinical and radiological examination. Both these conditions require urgent medical attention.

TB is suspected in cases with failure to thrive or weight loss in addition to persistent fever and persistent pneumonia which responds poorly to antibiotics. History of contact with a TB patient can be elicited. TB can be diagnosed by chest radiography, sputum/ GA or bronchoalveolar lavage for AFB and FNAC of enlarged nodes if present.

Bronchiectasis is a disease characterized by irreversible abnormal dilatation of the bronchial tree, and represents a common end stage of a number of nonspecific and unrelated antecedent events. Bronchiectasis is classified as WHO Stage 3 disease.

Persistent cough and fever with productive purulent sputum or hemoptysis should arouse suspicion of bronchiectasis. Clubbing is usually present. Chest examination reveals localized signs which do not easily resolve with usual antibiotic treatment. Chest x ray may show cystic spaces, occasionally with air-fluid levels and honeycombing. However, these findings are seen in more severe forms. Milder cases will show loss of broncho-vascular markings, crowding of bronchi, and loss of lung volume. Bronchiectasis needs careful management. Acute exacerbations need to be treated with adequate antibiotic therapy (2-4 weeks) and postural drainage of sputum. Antibiotics should be carefully chosen to cover broad spectrum of micro-organism, including Gram –ve bacteria. Attempt should

be made to isolate the organism by culture of sputum or induced sputum, or secretions obtained through bronchoscopy. Bronchodilators are usually required. Tuberculosis and LIP may be frequently underlying and need to be looked for. Surgical treatment may be necessary if the symptoms are severe or refractory to medical management and the disease is limited to one segment or a lobe.

LIP, a clinical stage 3 criterion is a lymphoproliferative, non-infectious pulmonary disorder that is characterized by diffuse infiltration of CD4 lymphocytes, plasma cells, and histiocytes in alveolar septa and along the lymphatics. It is most common in children infected with HIV, especially those aged >2-3 years. Disease usually has an insidious onset of mild but persistent cough, with or without exertional dyspnoea, and breathing difficulty. The patients also have associated clubbing. LIP should be suspected if a child does not respond, or if CXR findings persist or worsen despite appropriate antibacterial and anti-tuberculosis treatment. Treatment of LIP includes bronchodilators and corticosteroids (short course for mild intermittent symptoms and long course with slow taper in cases with chronic course).

While evaluating a HIV infected child with respiratory symptoms, it should be remembered that patient may be having more than one clinical entity responsible for their symptoms. It is not infrequent for a patient to have TB and bronchiectasis or TB and LIP or LIP and bronchiectasis.

The tables below give important differential diagnosis of lung disease in children > 1 year of age and in those beyond 1 year.

Table 37: Causes of lung disease in HIV-infected infants (<1 year of age)

Cause	Importance	Clinical features	Management (a,b)
Bacterial pneumonia, common etiological agents: Pneumococcus, Staphylococcus, Gram negative organisms	Very high incidence	Acute onset of cough, fever and fast breathing Can be very severe with hypoxia	Broad-spectrum antibiotics including coverage of Gram-negative organisms
PCP	Common cause of severe, fatal pneumonia especially in 2 to 6 months age group	Severe respiratory distress with hypoxia not improving with broad-spectrum antibiotics; Often afebrile; CXR: diffuse interstitial infiltration or hyperinflation	Add high-dose cotrimoxazole Consider steroids
CMV pneumonitis	Common co-infection with PCP, but few data from resource-poor settings	Severe respiratory distress with hypoxia not improving with broad-spectrum antibiotics and high-dose cotrimoxazole	Add ganciclovir
Tuberculosis	Depends on prevalence of TB/HIV in adult population	TB contact usually identifiable, often mother; Presentation often acute and severe or disseminated	Anti-TB treatment
Viral pneumonia e.g. RSV	Common and associated with bacterial co-infection	Acute onset of cough, fever, fast breathing; Wheezing less common than in HIV uninfected	Broad-spectrum antibiotics if suspect bacterial co-infection
Mixed infection	Common problem: PCP, bacterial pneumonia, viral, TB	Consider when poor response to first-line empiric management	Anti-TB treatment plus treatment for additional and presumed respiratory infections

Measles	In communities with poor measles immunization coverage	Conjunctivitis, typical rash, fever and cough, respiratory distress	Broad-spectrum antibiotics Vitamin A
LIP	Uncommon in infants and associated with bacterial co-infection	Generalised lymphadenopathy, clubbing, parotid enlargement. CXR: diffuse reticulonodular pattern	If symptomatic and close follow-up, steroids and broad-spectrum antibiotics

PCP = Pneumocystis pneumonia; CMV = cytomegalovirus; RSV = respiratory syncitial virus; LIP = lymphoid interstitial pneumonitis

(a) Oxygen may be indicated irrespective of cause; (b) CPT and ART when indicated for all casesCauses of lung disease in HIV-infected children (1-14 years)

Cause	Importance	Clinical features	Management (a)
Bacterial pneumonia, common etiological agents: Pneumococcus, Staphylococcus, Gram negative organisms	Very high incidence Often recurrent	Acute onset of cough, fever and fast breathing Can be very severe with hypoxia	Broad-spectrum antibiotics including coverage of Gram-negative organisms
Tuberculosis	Common in TB-endemic regions	Persistent respiratory symptoms; fever, weight loss, positive TB contact especially in younger children; CXR: focal abnormalities and perihilaradenopathy	Anti-TB treatment
LIP			
	Common especially around 2-6 Years; may present with acute bacterial pneumonia	Persistent or recurrentrespiratory symptoms, Generalisedlymphadenopathy, clubbing, parotid enlargement. CXR: diffuse, coarse reticulonodularpattern and bilateral perihilaradenopathy	If symptomatic, steroids and broad-spectrum antibiotics Anti-retroviral treatment
Bronchiectasis	Common Complicates recurrent bacterial pneumonia, LIP or TB	Cough productive of purulent sputum; clubbing; CXR: honeycombing usually of lower lobes	Broad-spectrum antibiotics Physiotherapy
Viral pneumonia	Common and associated with bacterial co-infection	Acute onset of cough, fever, fast breathing; Wheezing less common than in HIV and uninfected	Broad-spectrum antibiotics if suspect bacterial coinfection
Mixed infection	Common problem: PCP, bacterial pneumonia, viral, TB	Consider when poor response to first-line empiric management	Anti-TB treatment plus treatment for additional and presumed respiratory infections plus co-trimoxazole
Measles	In communities with poormeasles immunizationcoverage	Conjunctivitis, typical rash, fever and cough, respiratory distress	Broad-spectrum antibiotics Vitamin A

Kaposi sarcoma	Especially in tropical Africa	Characteristic lesions on skin or palate	Chemotherapy
Pneumocystis jirovecci pneumonia	Rarely described in this age group	Severe respiratory distress not improving with broadspectrum antibiotics; CXR: diffuse interstitial infiltration	High-dose cotrimoxazole Consider steroids
Other fungal pneumonia e.g. cryptococcosis, candidiasis	Little clinical data but autopsy studies suggests rarity		
Penicilliosis Melioidosis	Older children in South-East Asia		

PCP = Pneumocystis pneumonia; LIP = lymphoid interstitial pneumonitis; TB = tuberculosis

E7.2 Approach to a child with Diarrhoea

Diarrhea is one of the most common complaints in HIV infected children. It is usually associated with moderate to severe malnutrition; because of this AIDS was earlier known as “Slims Disease”. A child with HIV infection can have acute diarrhea (Liquid stools >3 episodes /day of, duration <14 days), dysentery (diarrhea along with blood in stools)or persistent diarrhea (diarrhea lasting for > 14 days). Severity of diarrhea is influenced by many factors including etiological agent (see Table-39) and host characteristics such as immunodeficiency, nutritional status and age. Other systemic bacterial infections can be present concomitant with diarrhea. Therefore a child with Diarrhoea should have a complete clinical evaluation.

Table 39 : Common etiological agents of persistent and bloody diarrhea

Persistent or Chronic Diarrhea	Bloody Diarrhea
▪ Persistent or Chronic Diarrhea ▪ Enteropathogenic,& aggregative E.coli ▪ Non typhoidal SalmonellaCryptosporidium ▪ Microsporidia ▪ Giardia lamblia ▪ Ascaris lumbricoids ▪ Cytomegalovirus ▪ Cyclospora ▪ Isospora belli	Bloody Diarrhea Shigella ,E.coli Non typhoidal Salmonella Entamoeba histolytica

Persistent diarrhoea

Persistent diarrhoea is described as diarrhoea of 14 days or more in duration. The differential diagnosis of persistent diarrhoea in HIV-infected children includes opportunistic infections (viral, bacterial, protozoal, parasites), secondary conditions (allergies, lactose intolerance), HIV-related medication side effects, and nutritional deficiencies. In resource-constrained settings, the available investigations do not often identify specific pathogens and aetiology. Therefore, an empirical treatment approach is needed. The presence of unexplained persistent diarrhoea places an HIV-infected child into WHO Stage 3 disease, thereby making the child eligible for ART.

Investigations in persistent diarrhea

Stool microscopy for WBCs and parasites is an important investigation. Stool WBC > 10 /hpf suggests possible infection with Shigella, Entamoebahistiolytica, CMV or invasive E.coli. Patients having infections with Giardia, Cryptosporidia, Cyclospora, MAC usually do not demonstrate WBCs in stool.

Specific organisms such as Giardia lamblia and Entameoba may be identified on routine stool microscopy by demonstrating trophozoites or cysts. Modified ZN stain may identify Cryptosporidia, Cyclospora. Stool pH < 5.5 and positive reducing substances suggests lactose intolerance.

Treatment of Diarrhoea

A child with diarrhoea should be assessed for dehydration. Children with no or some dehydration will need correction with oral fluids and ORS. If signs of severe dehydration are present intravenous fluids are required. Zinc supplementation is recommended for 14 days (10 mg/day for infants under 6 months and 20 mg /day for infants and children over 6 months). Feeding should continue along with fluid replacement to prevent malnutrition. If there is blood in the stool, ciprofloxacin at an oral dose of 15 mg/kg /day for 3 days is recommended. Sick children with dysentery requiring hospitalization should be given ceftriaxone. Antibiotic may need to be changed if indicated on stool culture & sensitivity report. Specific treatment is needed as described earlier in case of demonstration of cryptosporidium, microsporaetc on stool examination.

The non-hospitalised child with diarrhoea is re-evaluated after 2 days, for the signs of improvement i.e., absence of dehydration, weight gain, improved appetite, no fever and no blood in stool or passage of fewer stools. If there is no improvement or clinical worsening, the child may require to be admitted.

Management of persistent diarrhoea includes correction of dehydration if present. Systemic infection such as UTI, pneumonia or otitis media should be looked for and adequately treated. Administration of zinc and vitamin A (as per IMNCI protocol), other vitamins and micronutrients for 2 weeks to all HIV exposed and infected children with persistent diarrhoea is recommended. Dietary modification (giving low lactose diet) is required particularly if lactose intolerance is present. Methods to control and prevent infections such as good hygiene, clean drinking water and clean and home cooked food are also to be emphasized.

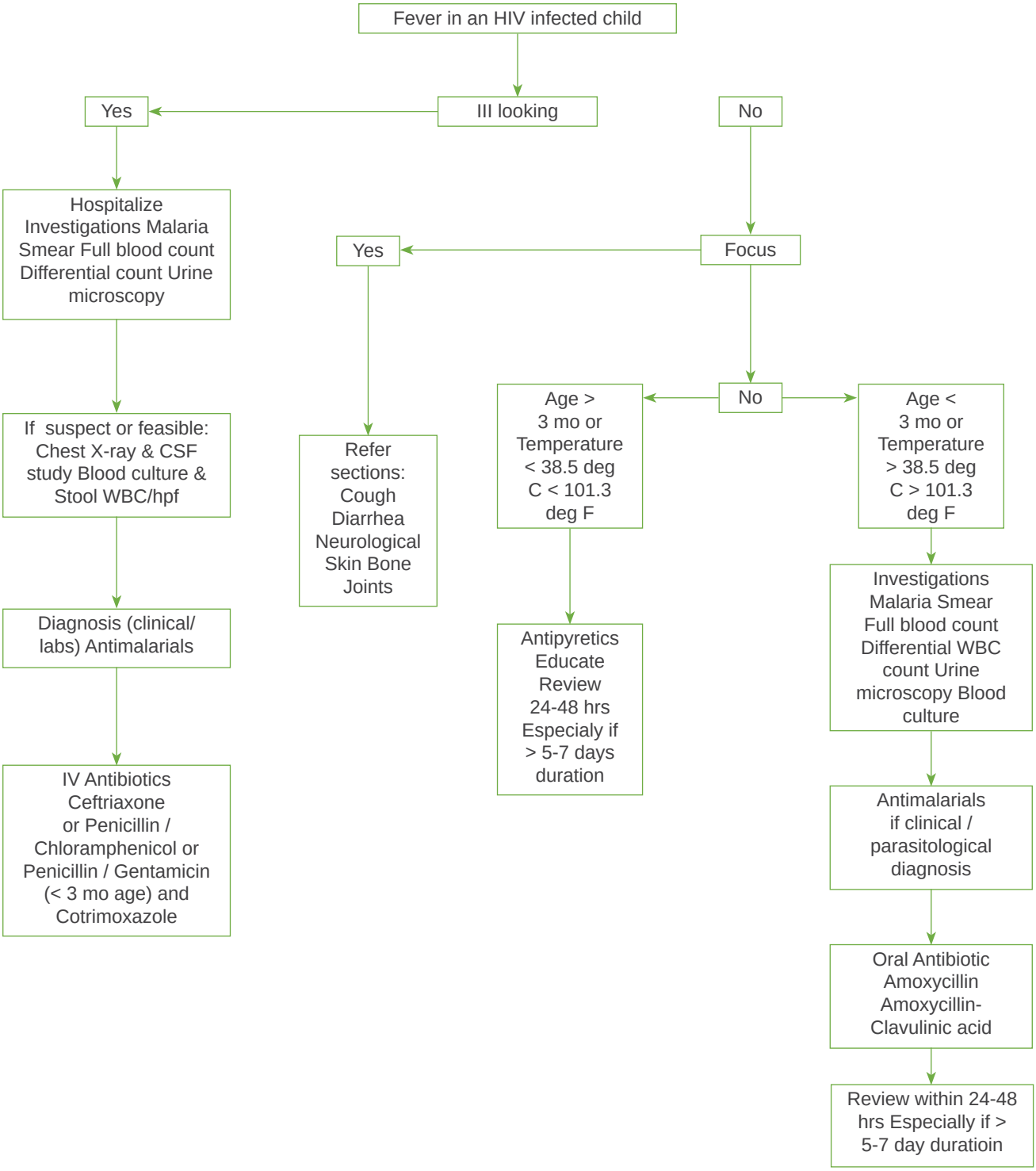
E7.3 Approach to a child with Persistent or recurrent fever

Causes of fever in HIV-infected children are often similar to causes of fever in children not infected with HIV. However, clinical presentation in HIV-infected children may be atypical, and the course prolonged, which requires prompt diagnosis and intervention.

Careful history for related symptoms should be taken. It should be noted that if the child is a resident of regions where malaria and dengue is prevalent.

Children in high-risk malaria areas need appropriate anti-malarial drugs based on clinical, and if possible, parasitological diagnosis. Fever lasting longer than 7 days is more likely to be due to bacterial or parasitic infections than common viral presentations. If the duration is further prolonged, mycobacterium tuberculosis, connective tissue disorders, and malignancies become priorities. Fever associated with a cold, cough, or conjunctivitis that precedes an erythematous, maculopapular rash is typical of measles that may be complicated with secondary bacterial infections and tuberculosis. The figure below describes the algorithmic approach to a HIV infected child with fever.

Figure 2. Flow diagram to diagnos the child presenting with fever



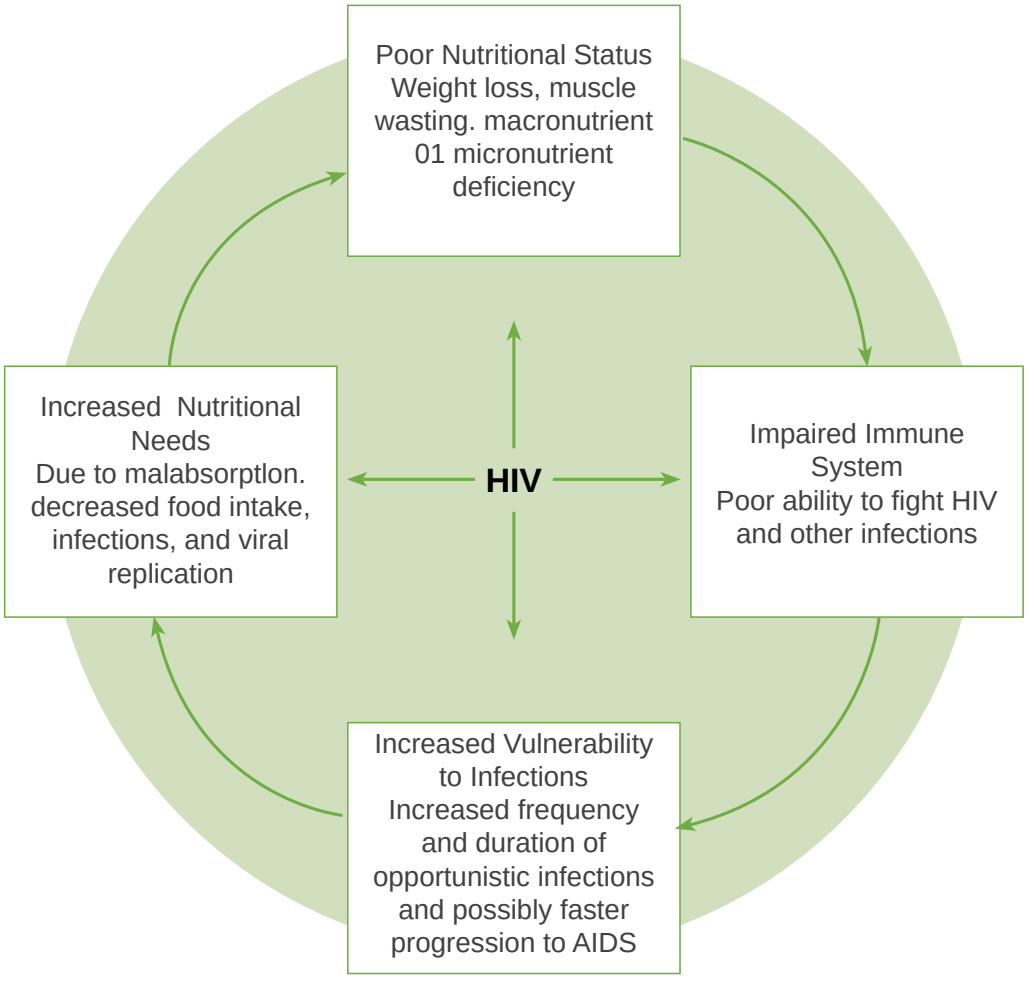
SECTION

Nutrition in HIV Infected Infants and Children

F1: Introduction

Nutritional care is a crucial part of continuum of care for HIV infected children. HIV and associated infections increase the need for energy, proteins, and micronutrients like iron, zinc, vitamin C etc. Failure to meet these increased needs may lead to malnutrition and further weakening of immune system. This makes the child more vulnerable to opportunistic infections like TB, pneumonia, diarrhoea etc that further increase the nutritional demands on the body, accelerating the decline in nutritional status. Thus, a vicious cycle exist between HIV infection and malnutrition (figure 1). .

Figure 1. Malnutrition and HIV : A vicious cycle



Source: Adapted from RCQHC and FANTA 2003a.

Appropriate nutritional support from early stages of HIV infection can prevent onset of malnutrition and other nutritional deficiencies. It will also help maintain the performance of immune system. The nutritional care of HIV exposed infants has already been covered in the section on 'Care of HIV exposed infants". These guidelines are based upon the WHO document "Guidelines for an integrated approach to the nutritional care of HIV infected children (6 months-14 years), 2009", and current National recommendations for nutrition of HIV infected children dealt with in detail in the document "Nutrition guidelines for HIV exposed and infected children 0-14 years of age" by NACO and WHO, India.

F2: Assessment of nutritional status

Assessing a child's growth provides valuable information about adequacy of his nutritional status and health. Growth is assessed by measuring weight and height (length for children less than 2 years of age) and interpreting these parameters in relation to age, sex of established reference standards. It is recommended that WHO growth reference standards be used for assessing a child's growth parameters. These are available as growth charts as well as reference tables for boys and girls separately.

(See Annexure 7 and 8) The parameter "weight for age" reflects body weight in relation to age. While a single reading gives limited information, serial recording of weight on a 'weight for age' chart gives a good idea about the child's growth over a period of time. 'Weight for age' chart is the most commonly used growth chart. 'Height for age' is a measure of linear growth. Plotting length/height on the "length/height for age" chart helps in detecting stunting, a common finding in HIV infected children. The parameter 'weight for length' reflects body weight in relation to linear growth. Evaluating 'weight for length' for children up-to 5 years of age helps in early detection of weight faltering. For a child beyond 5 years, BMI [weight (kg)/ height (m)2] is a better indicator than 'weight for length'. Weight for length/ BMI is also used as a parameter to identify severe acute malnutrition (SAM) as described later.

A well child will have his nutritional parameters (weight for age, length for age, weight for length/ BMI) within ± 2 Z scores of the median expected for the age and sex. If the child's weight, length or weight for length/BMI is less than -2 Z score, it indicates presence of underweight, stunting or wasting respectively. A serial recording of these parameters over time should yield a curve parallel to one of the standard growth curves on the growth chart. When the child's growth parameters falter, serial recordings on a growth chart will no longer be parallel to the standard growth curves.

Regular measurement of weight and height is an essential activity to be undertaken for every HIV infected child. Serial assessment and plotting of weight and height on a growth chart help in early detection of growth faltering. Faltering in growth, especially a weight lower than that expected for child's height often occurs even before opportunistic infections or other symptoms become overt in HIV infection. Early detection of growth faltering allows scope for timely intervention to prevent further deterioration. The weight should be recorded at every visit and height (length for children up-to 2 years of age) once in 3 months for all HIV infected children up-to 5 years of age. For children beyond 5 years of age, height can be taken at 6 monthly interval since the rate of growth is slower. Mid-upper arm circumference (MUAC) is also a good indicator of a child's general nutritional status. At anganwadi & sub-center level where it may not be feasible to measure length or height, MUAC is a useful tool for screening for malnutrition and identifying children at high risk of mortality.

Some children are at a very high risk of malnutrition. These high risk situations include:

- The child's growth curve shows flattening (no weight gain)
- The child's growth curve is dropping downwards (weight loss)
- Change in care-giver or home circumstances
- Caretaker's report of poor appetite or not gaining weight in the child

The growth of these children should be monitored carefully and remedial measures instituted before they become severely malnourished. They should be examined for visible signs of malnutrition like loss of subcutaneous fat & muscles and bipedal edema. Children without visible signs of malnutrition should be given nutritional support at home, with early follow-up (5-7 days). They should also be assessed for other medical problems and need for ART.

Based upon the anthropometric measures and presence of visible signs of malnutrition, the nutritional status of HIV infected children can be classified as given in table 40. Determination of the nutritional status will guide the dietary requirements and further management of these children as described later.

Table 40: Classification of nutritional status of HIV infected children

SIGNS	CLASSIFY AS
Signs of severe visible wasting, or Oedema present in both feet, or Weight-for-height (BMI for children > 5years) less than -3 z-score, or MUAC less than: 115 mm in children 6- 60 months 129 mm in children 5-9 years 160 mm in children 10-14 years	SEVERE MALNUTRITION
Reported weight loss, or Very low weight (weight for age less than -3 z-score), or Underweight (weight for age less than -2 z-score), or Confirmed weight loss (>5%) since the last visit, or Growth curve flattening	POOR WEIGHT GAIN
Child is gaining weight (weight for age more than -2SD and gaining weight appropriately)	GROWING APPROPRIATELY
Chronic lung disease, or TB, or Persistent diarrhoea, or Other chronic OI or malignancy	CONDITIONS WITH INCREASED NUTRITIONAL NEEDS

F3: Nutritional needs of HIV infected children 6 months to 14 years of age

Energy and protein needs of HIV infected children depend upon their age, growth pattern and presence of associated complications. As mentioned earlier, these children have higher energy needs as compared to healthy children due to increased metabolic demands placed by HIV infection. Presence of associated opportunistic infections and other chronic conditions like chronic lung disease, persistent diarrhoea etc further increases the metabolic demand. Table 41 gives the total energy needs of HIV infected children depending upon their nutritional status. HIV infected children with chronic lung disease, tuberculosis, persistent diarrhoea or other chronic opportunistic infections or malignancy have increased nutritional needs in spite of a good nutritional status. The additional energy requirements for these children are similar to children with poor weight gain (Table 42). Children who are not growing well may require additional medical interventions such as treatment for opportunistic infections or ART. Unless associated complications are appropriately managed, improvement in diet alone may not result in normal growth, weight recovery or improvement in clinical status.

Table 41: Total energy needs of HIV Infected Children

	Daily energy needs of HIV uninfected children*	HIV infected and asymptomatic 10% additional energy	HIV infected and poor weight gain or other symptoms 20% additional energy	Severely malnourished and HIV infected (post-stabilisation) 50-100% additional energy**
6-11 mo	690	760	830	150-220 kcal/kg/day
12-23 mo	900	990	1080	150-220 kcal/kg/day
2-5 yrs	1260	1390	1510	150-220 kcal/kg/day
6-9 yrs	1650	1815	1980	75-100 kcal/kg/day
10-14 yrs	2020	2220	2420	60-90 kcal/kg/day

* *Based on average of total energy requirements for light and moderate habitual physical activity levels for girls and boys by ago group. Joint FAO/WHO/UNU Expert Consultation, October 2001. ftp://fao.org/docrop/fao/007/y5686e00.pdf*

** *Management of severe Mainutrition: a manual for physicans and other senior health workers WHO. 1999.*

F4: Nutritional management of HIV infected children: practical guidelines

In general, feeding guidelines for HIV infected infants and children are same as those for healthy children apart from the need for meeting increased energy needs. If an infant is confirmed to be HIV infected, the mother should be strongly encouraged to breast feed exclusively for 6 months and continue breast-feeding up-to 2 years or beyond as per the norm for general population. This will ensure optimum growth for the infant to provide protection from infections. All infants diagnosed to be HIV infected are started on ART as per national recommendations. Complementary foods are introduced at 6 months of age as recommended for all infants. The quantity and frequency of food is increased as the child grows older. The food consistency is also gradually made thicker and variety introduced adapting to the child's requirement and abilities. The IMNCI guidelines for feeding healthy children of different age groups are annexed.

Nutritional management of a HIV infected child growing well

HIV infected children who are growing well and are asymptomatic need about 10 percent extra energy as compared to uninfected children of their age to maintain normal growth, development and activities. The additional energy is best given as additional household foods as part of a balanced diet.

Nutritional management of a HIV infected child growing poorly or having conditions with increased nutritional needs

Children with poor weight gain should have a complete assessment including a detailed dietary history and evaluation for co-morbidities like opportunistic infections that may have an impact upon the nutritional status. These children, along with those with increased energy needs like chronic lung disease, TB, persistent diarrhoea etc require an extra 20-30 percent energy each day. These are also best given through additional household foods. If this is not possible, specific nutritional supplements may be given till the underlying condition is effectively managed. Mother or caretaker should be given dietary counselling about meeting these increased nutritional needs at home. Table 3 shows the additional energy requirements for children with different nutritional status and examples of dietary modification that would meet these increased needs.

Management of children with SAM

Children with severe acute malnutrition i.e. signs of visible wasting, bilateral oedema or severely impaired growth irrespective of whether taking ART or not must be identified and managed correctly since they are at a very high risk of mortality. Children with SAM require 50-100 percent extra energy each by every day after the period for stabilization till nutritional recovery (usual duration 6-10 weeks). They should be treated with therapeutic feeding. Children with no medical complications may be managed at home if they still have a good appetite. They can receive good supervision at home and therapeutic feeds can be provided. Children who are sick and have associated complications like infections, have a poor appetite or are unable to eat, must be referred for inpatient care by trained staff with experience in nutritional rehabilitation. The nutritional management of HIV-infected severely malnourished children is largely the same as for any other severely malnourished child. For details on management of children with SAM refer to the WHO/NACO nutrition guidelines for HIV infected children. In addition, these children should be evaluated at the ART Center for exclusion of opportunistic infections including TB and assessed for ART if they are not receiving it already. If a child already on ART is found to have SAM, he should be evaluated for treatment adherence, treatment failure or development of new OIs.

Table 42: Additional energy requirements of HIV infected children and means of providing them

Additional Energy Requirement in HIV Infected Children			
	Asymptomatic with adequate growth (10% additional energy)	**Poor weight gain or increased nutritional needs (20 -30 % additional energy)**	**Severely malnourished (50 – 100% additional energy)**
6 - 11 months			
Calories required in addition to usual requirement*	60-70 kcal/day	120-150 kcal/day	-
Examples of ways to increase energy intake in addition to meals and snacks appropriate to age	Add 2 tsp of edible oil and 1 tsp of sugar to porridge in addition to normal diet	Add 2 tsp of edible oil and 1-2 tsp of sugar to porridge or other foods. Aim to add 2 times daily.	Therapeutic feeding as per National guidelines to provide 150-220 kcal/kg/day based upon the actual weight
12 - 23 months			
Calories required in additional to usual requirement*	80-90 kcal/day	160-190 kcal/day	-
Examples of ways to increase energy intake in addition to meals and snacks appropriate to age	Add 2 tsp of edible oil and 2 sugar to porridge ,or a medium banana.	Extra cup (200ml) of full cream milk with 1 tsp sugar or 2 big idlis or bread butter (2 slice)	Therapeutic feeding as per National guidelines to provide 150-220 kcal/kg/day based upon the actual weight
2 - 5 years			
Additional Calories*	100-140 kcal/day	200 – 280 kcal/day	Based on actual weight 150-220 kcal/kg/day
Examples of ways to increase energy intake in addition to meals and snacks appropriate to age	Extra cup of milk or sweetened curd or 1 extra roti with vegetables or 1 paratha	2 puris with vegetables or 1 cup porridge or chikki 2 pieces	Therapeutic feeding as per National guidelines to provide 150-220 kcal/kg/day based upon the actual weight
6 - 9 years			
Additional Calories*	130-190 kcal/day total ≅ 1815 kcal/day	260 – 380 kcal/day	Based on actual weight
Examples of ways to increase energy intake in addition to meals and snacks appropriate to age	Extra cup (200 ml) of full cream milk or 1 egg omlette or 1 extra roti with vegetables	Extra cup of full cream milk and one vegetable stuffed parantha, or 2 parathas with curd or halwa 100 gm (1/2 cup) or poha11/2 cups	Therapeutic feeding as per National guidelines to provide 75-100 kcal/kg/day based upon the actual weight
10 - 14 years			
Additional Calories*	170-230 kcal/day	340 – 400 kcal/day	Based on actual weight
Examples of ways to increase energy intake in addition to meals and snacks appropriate to age	Extra one roti in lunch and dinner with vegetable or one dosa with sambhar or one stuffed parantha	1 Egg omlette with 2 slices of bread or 1 stuffed paratha and 1 cup milk	Therapeutic feeding as per National guidelines to provide 60-90 kcal/kg/day based upon the actual weight

* *Calories in addition to that recommended for normal children in the same age group*

5. Supportive measures:

The following measures support the improvement of nutritional status and health of HIV infected children and should be provided to all children:

- Micro-nutrient supplements: Micro-nutrient intake at recommended level should be ensured through balanced diet. If the child's diet does not contain a variety of fruits, vegetables and food from animal sources give, a daily supplement that provides 1 RDA of vitamins and other micro-nutrients. Investigate for presence of anemia and give iron supplements if deficiency is confirmed.
- Give vitamin A supplements every 6 months for children up-to 5 years of age in the following dose:
  * 6-12 months: 1,00,000 IU orally
  * 1-5 years: 2,00,000 IU orally
  * For children beyond 5 years of age vitamin A should be provided through daily micro-nutrient supplement.
- De-worm every 6 months (albendazole 400 mg single dose orally every 6 months after 1st year of life)
- Continue co-trimoxazole prophylaxis as indicated
- In patients with recent history of diarrhoea, give zinc 20 mg daily for 2 weeks
- Encourage regular play and age appropriate activities: Play helps maintain appetite and build muscles. Children who play are healthier and happier. Parents or caretakers should be encouraged to participate in age appropriate activities with the children. This promotes child-caretaker interaction and is a source of happiness for both.
- Administer routine childhood immunization

F5: Nutritional counselling

Nutritional counselling of caretakers is essential for maintenance of a good nutritional status and nutritional rehabilitation. The mother or caretaker should be counselled about need for additional food, dietary modifications required to meet the increased needs, safe food preparation, safe food and water storage methods and hygiene issues.

F6: Follow-up

Nutritional status is assessed at every follow-up visit for an HIV infected child. The frequency and interval between visits depends upon the condition and needs of the child (table 4).

Table 4: Follow up of nutritional status of HIV infected children

CONDITION	NUTRITIONAL FOLLOW UP	REMARKS
The child who is well and growing appropriately.	2-3 months	May be monthly if receiving routine cotrimoxazole/micronutrient or other support/ treatment, including ART.
The child on ART.	3 months	If gaining weight and no other problems.
	2-4 weeks	If not gaining weight.
The child who has chronic increased nutritional needs but investigated and no other active problems.	2-3 months	Tell caregiver to return earlier if problems arise.

Child with poor weight gain.	First visit 1-2 weeks Then 1-2 months	Tell caregiver to return earlier if problems arise.
The child who is unwell and/or showing signs of growth faltering or has had recent diarrhoeal illness.	2-4 weeks	May require more frequent visits depending on clinical status and support offered or being provided.
When the child is malnourished +/- other signs of disease progression e.g. history of recent severe weight loss or recent diarrhoea illness.	Weekly	Only if fulfils criteria for management at home and no immediate need of other investigations that require hospitalisation.
When a child is severely malnourished with medical complications or no appetite.	Refer for hospitalization	

Note: HIV infected children who are followed up by the ART programme monthly should have their normal measurements done as per ART guidelines e.g. weight. Follow up of their nutritional status is as per above.

F7: Nutritional care of HIV infected children with special needs:

HIV-infected children commonly experience poor appetite and suffer from mouth sores and diarrhoea. Sick children need extra drinks and food during illness, for example if they have fever or diarrhoea. It is often difficult to feed such children. During these acute illnesses, they are likely to lose weight.

In the recovery period it is important to:

- increase energy and protein consumed in everyday foods by adding one meal per day (refer to Suggestion sheet 1);
- Feed the child on demand day and night ; and
- Encourage the child in simple and loving ways.
- Some of the ways to encourage a child to eat include the following:
- Make the child comfortable.
- Be patient and feed slowly.
- Feed small amounts frequently. Children may tire easily while eating, making it difficult to eat sufficient food at a sitting. Offering feeds frequently may be needed to increase food intake.
- Give foods that the child likes.
- Give a variety of foods and extra fluids.
- If the child is thirsty give fluids that have some energy e.g. milk. Avoid commercial juices or fizzy drinks that have very little nutritional value.
- Pay attention to the child and make feeding a happy time.

For younger infants and children continue breast feeding. A sick young child may prefer breastfeeding to eating other foods. All sick children should be offered appropriate foods unless there is a medical reason. Nutritional management of children with diarrhoea, mouth ulcers or poor appetite is given in detail in WHO or NACO nutrition guidelines for HIV infected children.

SECTION

G

Issues Related to Pediatric Counselling

While any person living with HIV or AIDS needs psychosocial support in living with the illness and managing treatment, chronic illness in children throws up special challenges. Both the child client and his or her caregivers must be supported through sensitive and caring counselling. The counselling needs are also likely to change as the child grows older and progresses through various stages of child development. So, counselling should adapt to these changing needs. Further, the counsellor and other members of the clinical team must judiciously decide whether a particular counselling message is better addressed to the primary client (that is the child) or to her care giver.

While the counsellor will carry the major responsibility for counselling both sides, it is also important for other members of the clinical team to develop a child-sensitive attitude and create an atmosphere where children will feel comfortable. The ART team must make efforts to procure the special tools prepared by NACO such as the ART Adherence Colouring Books (called My ART Calendar), the NACO Snakes and Ladders Health Education games and the Visual Analogue Scale. They must educate themselves in the use of these aids. Further, efforts should be made to create a child-friendly corner using some portion of the contingency funds. Simple and cost-effective items that are also durable could be purchased such as wall cut-outs of Disney characters or a plastic play house. A simple blackboard supplied with chalk may be placed at the child's eye level in a corner of the waiting area so that they may express their creativity. Simple and cheap chalks or crayons may be purchased for the purpose of counselling and may be placed with the counsellor. A display board may be set up to display drawings and craft work made by the children.

Who Needs Counselling?

The ART counsellor will focus on two types of counselling:

(a) counselling the child client himself / herself, and

(b) counselling about the child's issues. The latter is directed towards the caregivers.

Key Counselling Issues for Child Clients:

G1: Taking medicine regularly

The key challenge for child clients is to help them develop good habits towards taking medicine on a daily basis. Though the parent or caregiver is primarily responsible for ensuring that the child takes treatment, it is necessary to make the child client a willing partner in managing their own health through regularly treatment. Even the most tractable or obedient child will have days of poor compliance to medicine.

With very small children, it is important to emphasize that taking medicine on time will keep them safe from falling ill (or in case they are ill, to improve quickly) so that they can be free to play. Freedom to play is not only the right of the child but also the most potent incentive you can offer to a very young client. For slightly older children, the message will be altered to also include emphasis on being responsible for health, and being fit to attend school like other children of their ages. As they become cognitively capable of understanding medical facts, they can be introduced initially to concepts related to viral infection in general, and later to more specific information on HIV. It is important to link the medicine with keeping the viral infection in check.

The clinical team can ensure adherence through the use of the ART Adherence Colouring Books such as My ART Calendar published by NACO.

G2: Learning about being infected

Helping a child to understand the nature of their infection is an important issue which affects their willingness to take medicines, and a large research literature on disclosure of HIV status to children exists. We highly recommend that children should be informed about the nature of their illness because knowing one's HIV status is likely to encourage compliance to treatment – even in child clients. However, the second part of the recommendation is that the timing of disclosure to the child cannot be a universal date or age.

Counselling the child client in this context is not an all-or-none phenomenon. Children should be prepared gradually for accepting the full and complete knowledge of having HIV infection. A parallel example in the physical world is how we introduce children to solid foods from an initial, exclusive diet of milk. Initially, soft easily digestible foods are introduced such as small pieces of banana. Later we, graduate to foods which require more effort for chewing and digestion – especially as the number of teeth increase. In a similar manner, telling a child about HIV status will be done against the context of their ability to understand and digest the news of their HIV status. For young children, it is sufficient to say that there are germs in the body which can make them very sick. Older children will not be satisfied with such a simplistic answer and may demand more details. Counsellors and caregivers should be prepared for such questions. One useful tool is The Story of the Bam-Bam Virus.

Understanding and acceptance of the child client may wax and wane in response to the individual's stage of development, and also in response to changes in her or his life. For instance, a child of 12 years who displays acceptance about HIV status could display resentment when they reach the age of 17years if they recognise the potential of HIV to limit their life choices such as finding a life partner or to enjoy free sex from worry of infecting the sexual partner. Similarly, the child who physically moves from school to college may face challenges in maintaining the monthly visit to the ART centre, or may find it awkward to take medicines in the presence of new friends. Counsellors should be alert to these changes and should support the client when needed.

G3: Learning to live with a chronic illness

With advances in HIV medicine, this infection has become a chronic manageable illness. For the individual this introduces the challenge of living with illness on a daily basis and factoring this into all life decisions. The monthly visit to the ART centre offers the counsellors an opportunity to explore these challenges with the pediatric client.

G4: Specific Issues of Adolescent Clients

In addition to all the issues mentioned above, adolescent clients face the following challenges:

- Developmental delays – that is delayed growth and development, often resulting in late puberty and, in girls, delayed or irregular menstrual cycles. These may be further worsened by progressing HIV illness and malnutrition.
- Transition from pediatric to adult care, including the choice of appropriate ARV regimens; and adherence.

Counsellors should prepare their clients for these transitions using appropriate anticipatory guidance. They should also be ready for when clients raise these issues, or when they appear to be facing these challenges.

G5: Key Counselling Issues for Parents or Caregivers:

G1.1 Acceptance of Infection in Child

This is a very emotive topic for family members. In most instances, the transmission has occurred from the parent to the child. So acceptance of HIV infection in the child is complicated with guilt on the part of the parent, and worry about being blamed by the child. Counselling for the parent must help him or her deal with personal guilt and worry as well as acknowledge that the emotional needs of the parent cannot be a reason to ignore or subsume the needs and rights of the child.

A particularly difficult situation to navigate is that of a child who is going through the recommended tests that are part of the Early Infant Diagnosis Programme. The emotions of the caregiver may see-saw between hope and dejection as the test dates approach and recede.

G1.2 Disclosure Issues

Parents and caregivers must be supported through the process of disclosure of status to the child client. Counselling is required to enable them to break the news gently to the child. Some caregivers may request counsellor support to break the news. In such cases, it is strongly recommended to include caregivers in the counselling sessions with the child. Caregivers' feedback on the preparedness of the child to receive such disclosure counselling should be considered. However, the counsellor should also gently offer her or his own assessment of the readiness of the child to hear this message.

One common fear of caregivers (and also of counsellors) is that child clients who learn their status may inadvertently blurt out this fact with other people, and thus increase the chances of being stigmatized. The counsellor and other team members should address this issue by suggesting disclosure in stages based on the capacity of the child to absorb the impact of the diagnosis. Further, the team can normalise the situation by comparing HIV to a chronic illness like diabetes which also requires constant personal health promoting behaviour from clients.

Parents may also fear that the child may feel suicidal. Suicidal thoughts can be minimized through carefully staggering the explanation of the diagnosis – namely partial disclosure first and then full disclosure.

Caregivers and parents may be unwilling to share the child's HIV status with other people. This concern and worry could cause interruptions in treatment because of unwillingness to fill prescriptions locally, hiding or relabeling medicine bottles to maintain secrecy with the family, and missed doses when the parent is unavailable. These issues should also be discussed during counselling. Counsellors can gain a complete picture of the child's adherence and the caregiver's administration of the medicine by asking both child and caregiver about the process of taking medicine. Discrepancies in the reports of both sides should be discussed in counselling.

G1.3 Preparing for Treatment

Before starting ART, it is essential to assess if the client is ready to begin treatment. This includes his or her ability and commitment to take medicines correctly and consistently for the rest of their life. For infants and young children, the treatment providers will assess the family or caregivers readiness and commitment. For instance, can the family ensure that they will return for regular, reliable follow up visits? Some families may designate an older sibling as the person who ensures that the pediatric client takes medicine. It is critical in such a case to ensure that the sibling is capable and willing to handle such a responsibility. If required, the team may recommend an alternative caregiver.

Adolescents should be involved in their own treatment and care. While initiating ART in adolescents, the following issues must be reviewed:

- Simplifying the treatment regimen (to ensure maximum adherence).
- Maturity of the client.
- 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.

The second and third points should be handled by counsellors while the other aspects are clinical decisions. Clients at ART centre have a long-term engagement with the centre. While waiting in the waiting area for services, it is common for them to compare notes with each other. The treatment team should head off potential questions about why one drug is selected over another (e.g., EFV in adolescent girls). Also, it is important to give advance warning to clients about the minor side-effects of ARV drugs such as nausea, headaches, and abdominal discomfort. Explain how long a client may expect these to persist, if they will lessen over time, how to manage them, etc.

G1.4 Supporting treatment

Counselling should enable the caregivers to support treatment to the child. Common complaints are how to help children to take the same medicine day after day, difficulty in consuming adult-size pills, queries from children about why they should take treatment unlike their peers, and handling situations like telling other family members. Anticipatory guidance is a counselling technique which prepares clients in advance for common difficulties. Apart from this, counsellors can support parents through organising parental support groups and doing group counselling. By harmonising clinic services to ensure that most pediatric patients are seen on a day which is likely to be the most common school holiday in the region, centres can ensure that child clients are seen mostly on one day of the week. This will provide opportunities for group education sessions during morning OPD hours and smaller group sessions in the quieter hours of the afternoon.

G1.5 Planning for the future

When caregivers are parents who are on ART themselves, it is important to alert them to the need to plan for the future of the child in case of their own untimely death. This includes financial and legal planning. It is also important to enable the parent to identify who will be the legal guardian and caregiver in such an eventuality.

How to structure counselling:

It is important for the counsellor to see the child from time to time in order to build a rapport with her or him. This rapport is the basis on which successful disclosure and medication-related counselling can be situated. In some ART centres it is observed that the child's caregiver may come to pick up the medicine refill citing that the child is in school and is not facing any health problems. In such circumstances, it is important to schedule follow-up visits for the school weekly holiday for at least some months, or to schedule a clinic visit for non-school hours.

Regular monthly visits are opportunities to take up individual issues for counselling. The counsellor must prioritise what issue she or he would like to discuss on a particular visit. Introduce the topic by simply saying, "Have you given any thought to the following?" After the topic is initially introduced, the counsellor has the option of exploring this further on subsequent visits. Medical decisions (such as

following the next EID test) should generally be prioritised over non-medical decisions. Each medical decision should always be explored so that the caregiver understands its rationale. When counselling caregivers about their personal issues, it is appropriate to occupy children so that caregivers have privacy and space to share their concerns.

Building rapport and trust with a child is an endeavour that takes time. Counsellors who are accustomed to working with adults have to unlearn many behaviours and expectations about child client. Counselling children is more effective when interactive methodologies such as drawing, story-telling and puppetry are used. ART counsellors who opt out of using such techniques with children cannot claim to be good counsellors. Lack of time is no excuse.

Counsellors should also ensure when following children over the period of time that they raise issues related to change in developmental status – for instance, child moving from crawling to walking, or puberty.

SECTION

Palliative Care in Children

H1: What is palliative care?

H2: Palliative care in Children

H3: Care and support as below is integral to palliative care:

H4: Supporting family and child

H1: What is palliative care?

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 counseling, 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 multidisciplinary.

H2: 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 pediatric chronic disorders:

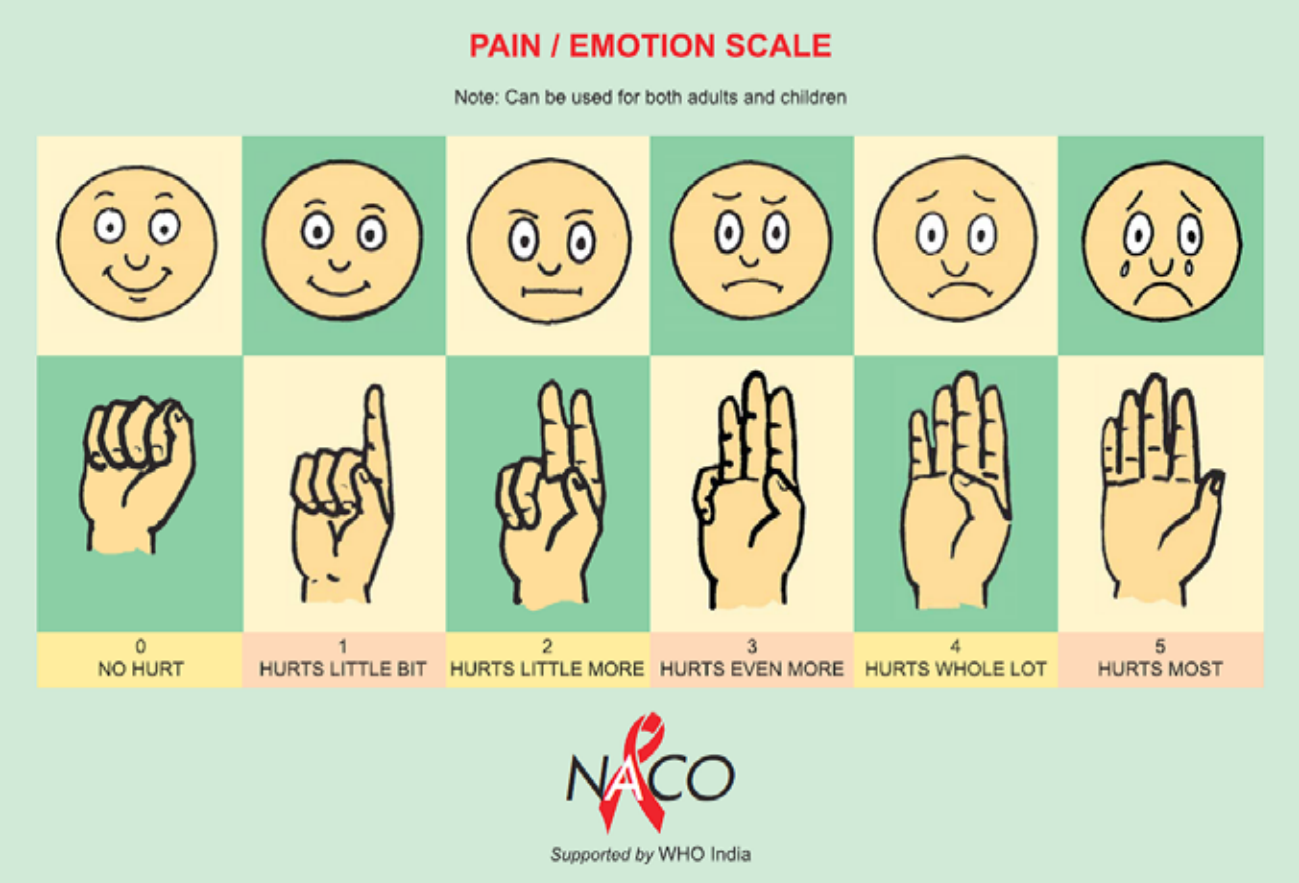
- Palliative care for children is the active total care of the child's body, mind and spirit, and also involves giving support to the family.
- It begins when illness is diagnosed, and continues regardless of whether or not a child receives treatment directed at the disease.
- Health providers must evaluate and alleviate a child's physical, psychological, and social distress.
- Effective palliative care requires a broad multidisciplinary 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.

Essential components in palliative care for children

H3: 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 a possibility to reduce pain, if present.
    - Learn to trust the health care 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 or caregivers. This may be more difficult in preverbal and developmentally delayed children.

Simplified tool for assessing pain in children

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

e) 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.

H4: Supporting family and child

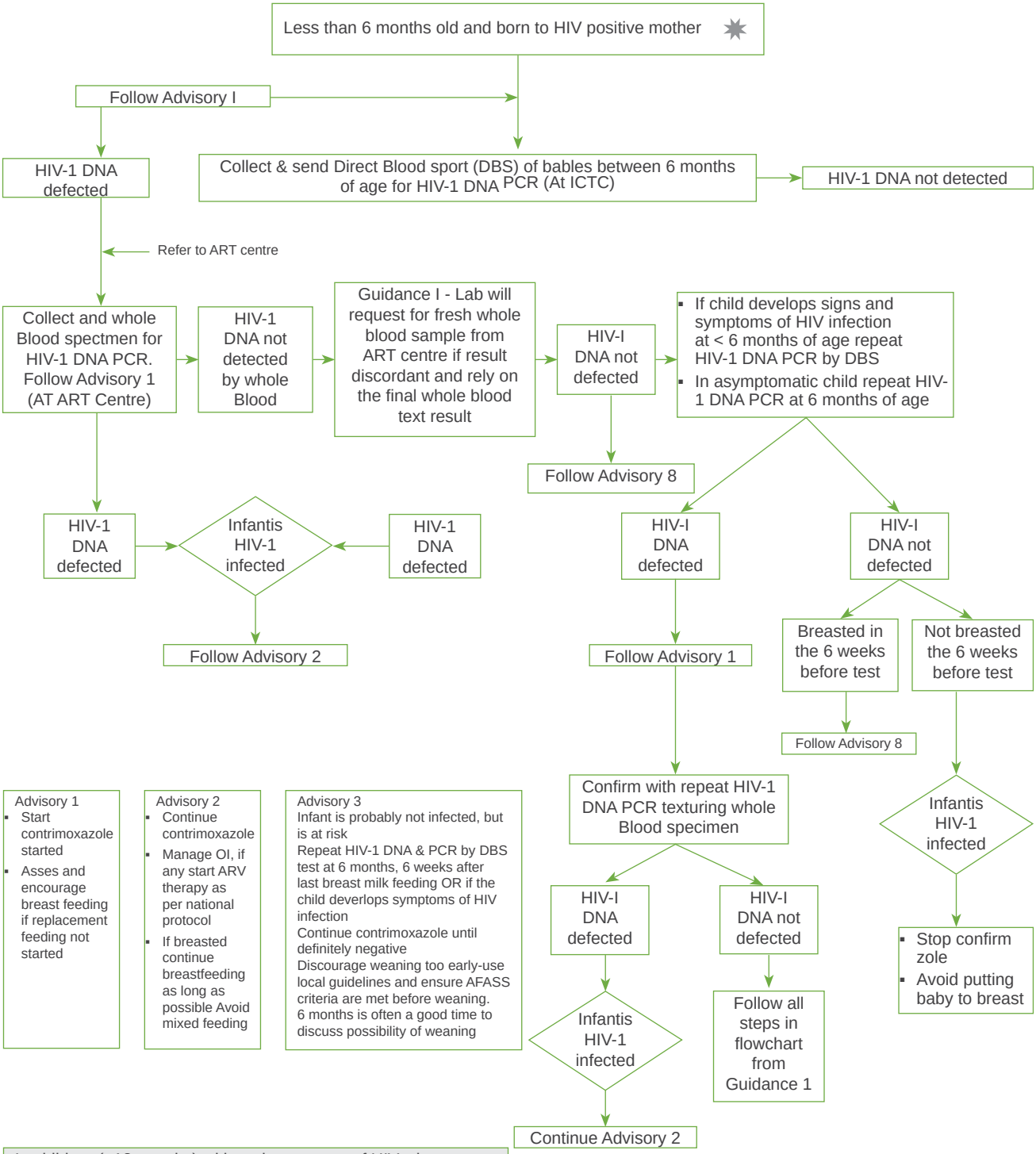
Families need support from the time of diagnosis to treatment and for terminal care (end of life). Each family is unique with different strengths and coping skills. Parents/caregivers go through various emotional difficulties especially for the terminal stage of disease and for issues relating to stopping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

Annexures

Annexure –I Early Infant Diagnosis

Testing algorithm HIV-1 exposed infants and children <18 months

A < 6 months



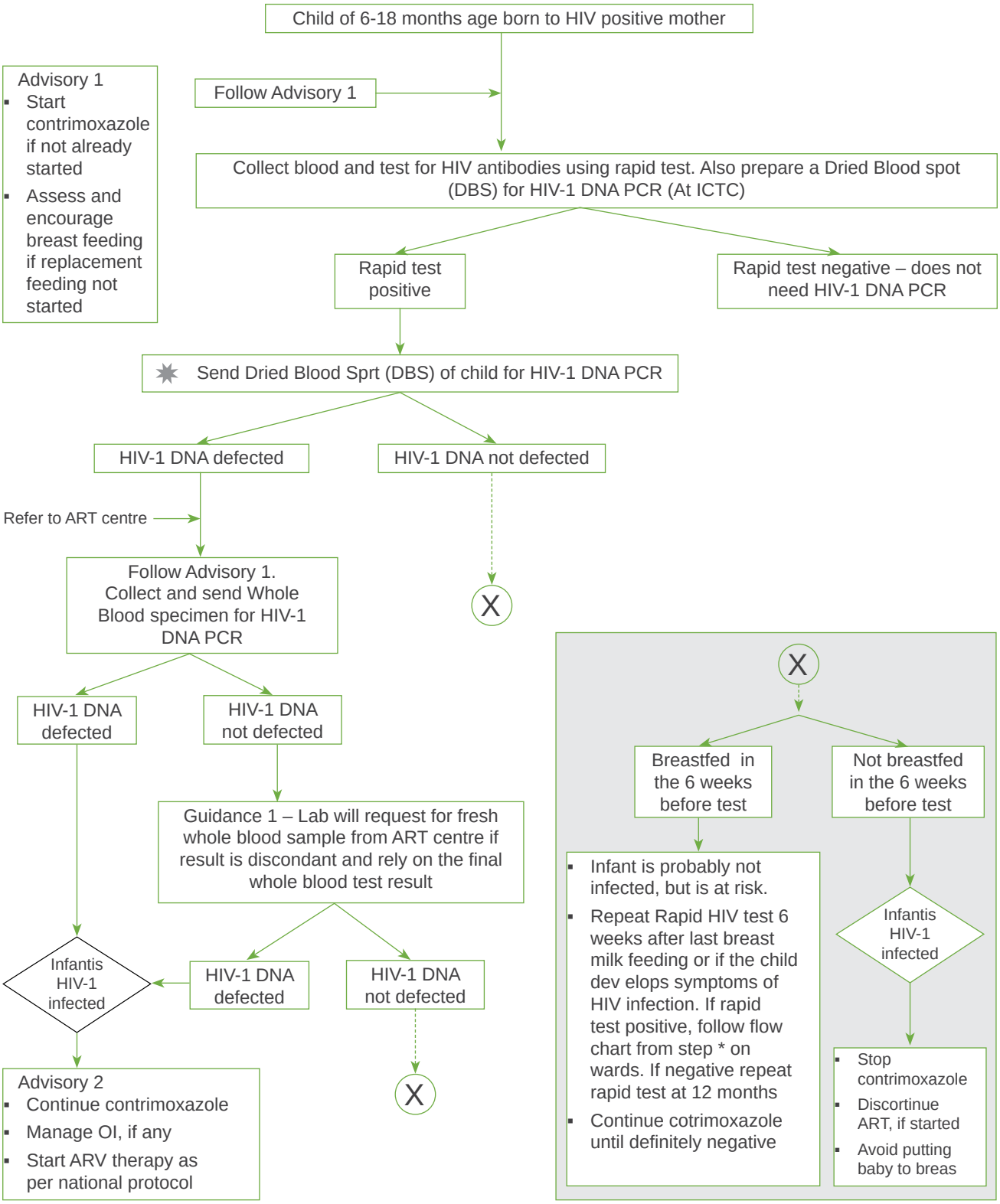
In children (<18 months) with and symptoms of HIV whose exposure status is unknown perform rapid test for HIV antibodies. If negative, label child as uninfected, if positive follow algorithm A or B, depending on age of child. Attempt to determine the HIV infection status of the parents to determine if the child is HIV-exposed; thereafter follow the algorithms to determine the infection status in the child.

Extablish definitive diagnosis at 18 months, by HIV antibody test

- Rapid antibody test not recommended
- if baby is < 6 weeks-HIV-1 DNA PCR not recommended
- 6 weeks and above is the optimal age for a rouline first HIV-1 DNA PCR test

Testing algorithm for HIV -1 exposed infants and children < 18 months

B = 6-18 months



In children (<18 months) with and symptoms of HIV whose exposure status is unknown perform rapid test for HIV antibodies. If negative, label child as uninfected, if positive follow algorithm A or B, depending on age of child. Attempt to determine the HIV infection status of the parents to determine if the child is HIV-exposed; thereafter follow the algorithms to determine the infection status in the child.

Extablish definitive diagnosis at 18 months, by HIV antibody test

Annexure – II

WHO Clinical staging for infants and children with established 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 moderate malnutrition not adequately responding to standard therapy
- Unexplained persistent diarrhoea (14 days or more)
- Unexplained persistent fever (above 37.5 oC, intermittent or constant, for longer than one month)
- Persistent oral Candidiasis (after first 6 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 (<8.0 g/dl), neutropenia (<0.5x109/L3) or chronic thrombocytopenia (<50 x 109/L3)

Clinical stage 4

- 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)
- Extra pulmonary TB
- Kaposi sarcoma
- Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
- Central nervous system toxoplasmosis (after the neonatal period)
- HIV encephalopathy
- Cytomegalovirus (CMV) infection; retinitis or CMV infection affecting another organ, with onset at age more than 1 month
- Extra pulmonary cryptococcosis including meningitis
- Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidioidomycosis, penicilliosis)
- Chronic cryptosporidiosis (with diarrhoea)
- Chronic isosporiasis
- Disseminated non-tuberculous mycobacterial infection
- Cerebral or B cell non-Hodgkin lymphoma
- Progressive multifocal leukoencephalopathy
- HIV-associated cardiomyopathy or nephropathy

Annexure – III

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[b]	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, diarrhea, 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]
Lactic Acidosis (NRTI class, particularly d4T)		

Possible clinical manifestations (Most common ARV drug(s) associated with the toxicity)	Possible laboratory abnormalities[b]	Implications for antiretroviral drug treatment
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 Necrosis	▪ Elevated aminotra-nsferases	▪ 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 readministered 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	▪ Hyper-triglyceridaemia; ▪ Hyper-cholesterolaemia;	▪ Substitution of ABC or AZT for d4T may prevent progression of lipoatrophy

Possible clinical manifestations (Most common ARV drug(s) associated with the toxicity)	Possible laboratory abnormalities[b]	Implications for antiretroviral drug treatment
▪ Fat loss from limbs, buttocks, and face occurs to a variable extent ▪ Insulin resistance, including diabetes mellitus ▪ Potential risk for later coronary artery disease	▪ Low HDL levels ▪ Hyperglycaemia	▪ Substitution of an NNRTI for a PI may decrease serum lipid abnormalities
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:

- *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.*
- *All laboratory abnormalities may not be observed.*
- *See (Section XIII) for recommended antiretroviral drugs substitutions.*

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

Annexure – IV

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 & functional activities[a]: No therapy needed, monitor	Symptoms causing greater than minimal interference with usual social & functional activities: May require minimal intervention and monitoring	Symptoms causing inability to perform usual social & 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
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 schock

PARAMETER	MILD	MODERATE	SEVERE	SEVERE, POTENTIALLY LIFE-THREATENING
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 Angioedema with medical intervention indicated OR symptomatic mild bronchospasm	Acute anaphylaxis OR life-threatening bronchospasm or laryngeal oedema
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, Maculopapular, or morbilliform rash OR target lesions	Diffuse macular, Maculopapular, or morbilliform rash with vesicles or limited number of bullae OR superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic Epidermal Necrosis (TEN)
NEUROLOGIC				
Alteration in personality-behaviour or in moodb	Alteration causing no or minimal interference with usual social & functional activitiesb	Alteration causing greater than minimal interference with usual social & functional activities b	Alteration causing inability to perform usual social & 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 & functional activities b	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities b	Onset of confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities b	Onset of delirium, obtundation, or coma

PARAMETER	MILD	MODERATE	SEVERE	SEVERE, POTENTIALLY LIFE-THREATENING
Neuromuscular weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR minimal muscle weakness causing no or minimal interference with usual social & functional activities b	Muscle weakness causing greater than minimal interference with usual social & functional activities b	Muscle weakness causing inability to perform usual social & 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 & functional activities	Sensory alteration or paraesthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paraesthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paraesthesia causing inability to perform basic self-care functionsc
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 pediatric 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.

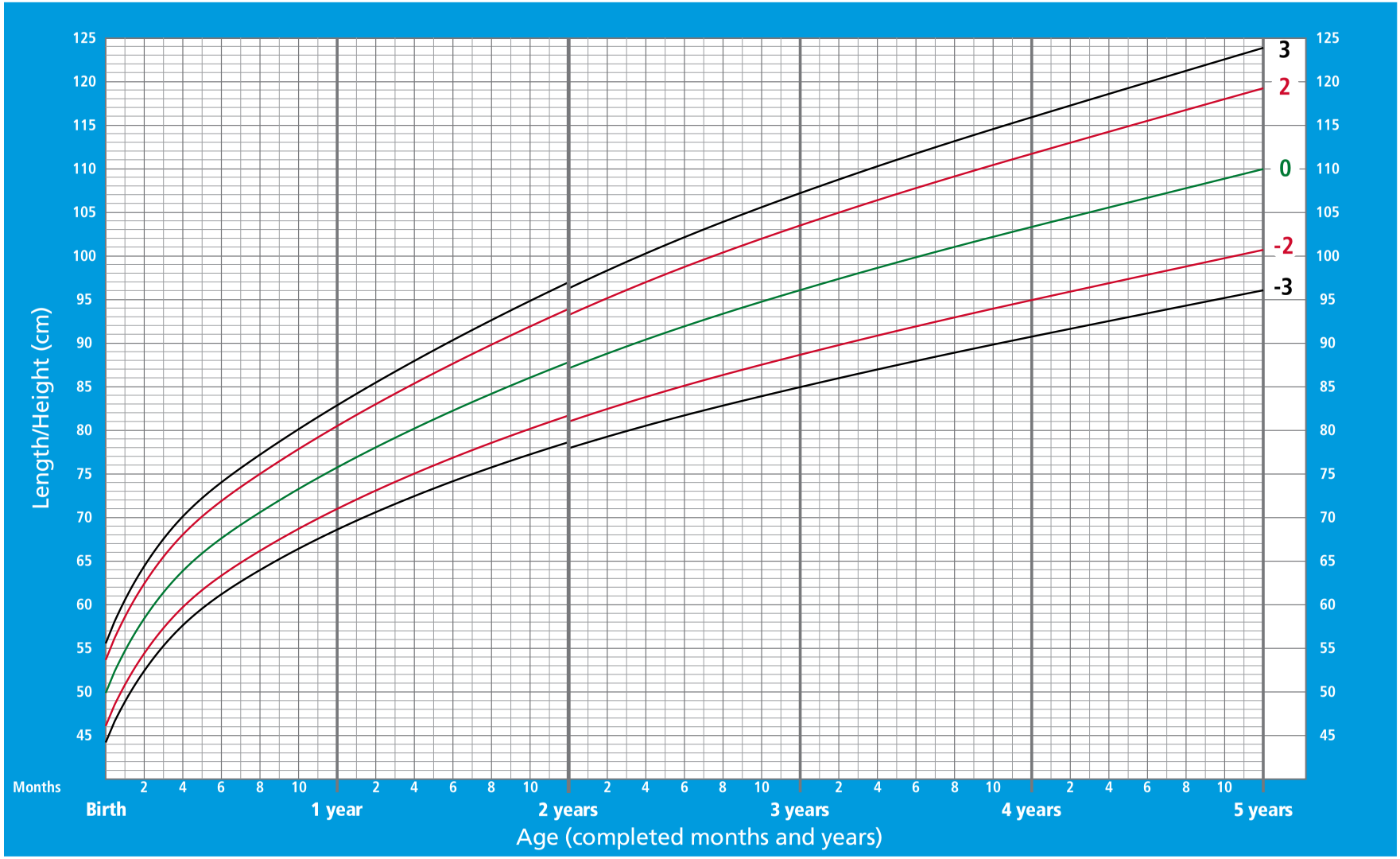
b. Usual social and functional activities in young children include those that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc).

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

Length/height-for-age BOYS

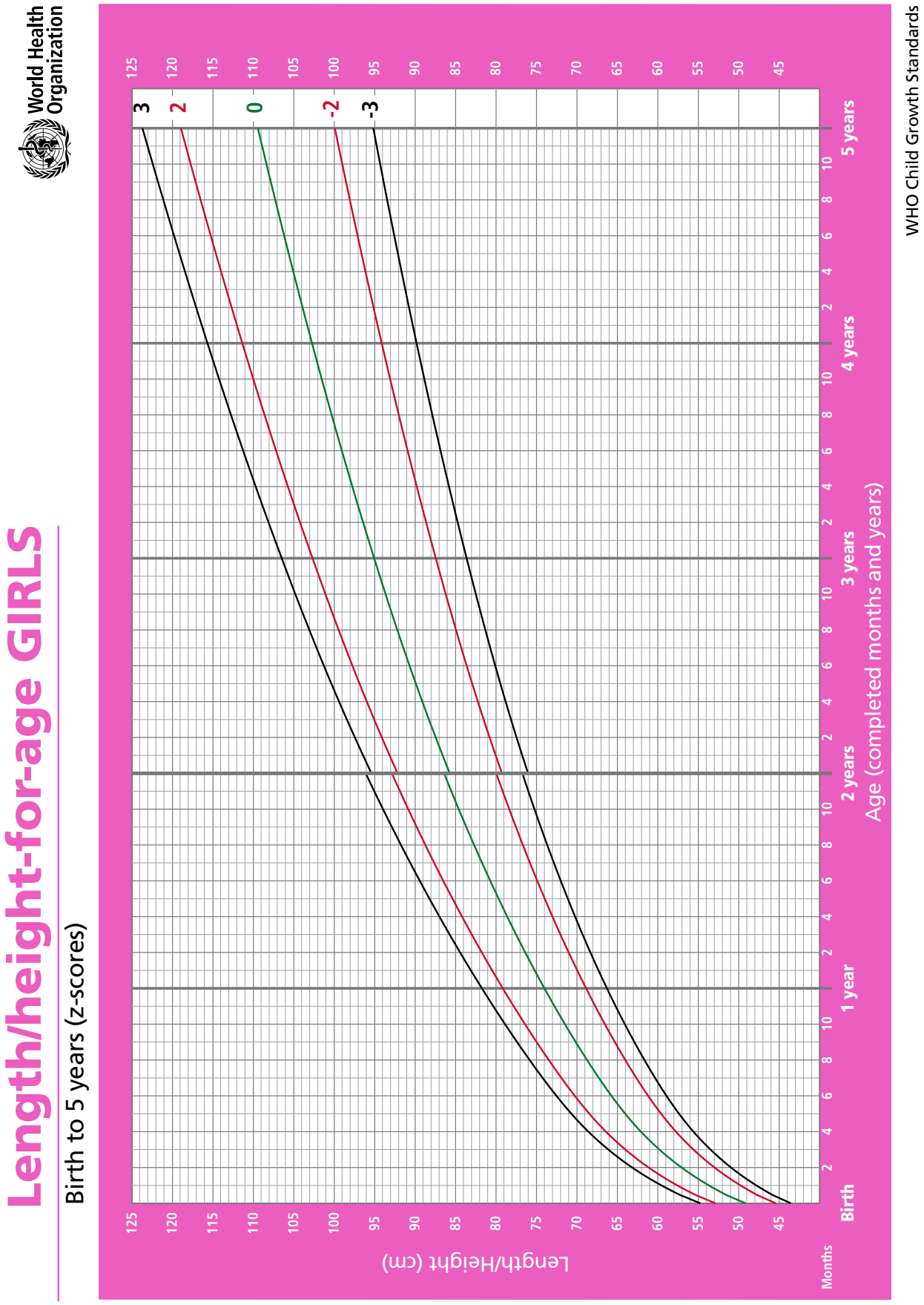
Birth to 5 years (z-scores)

World Health Organization

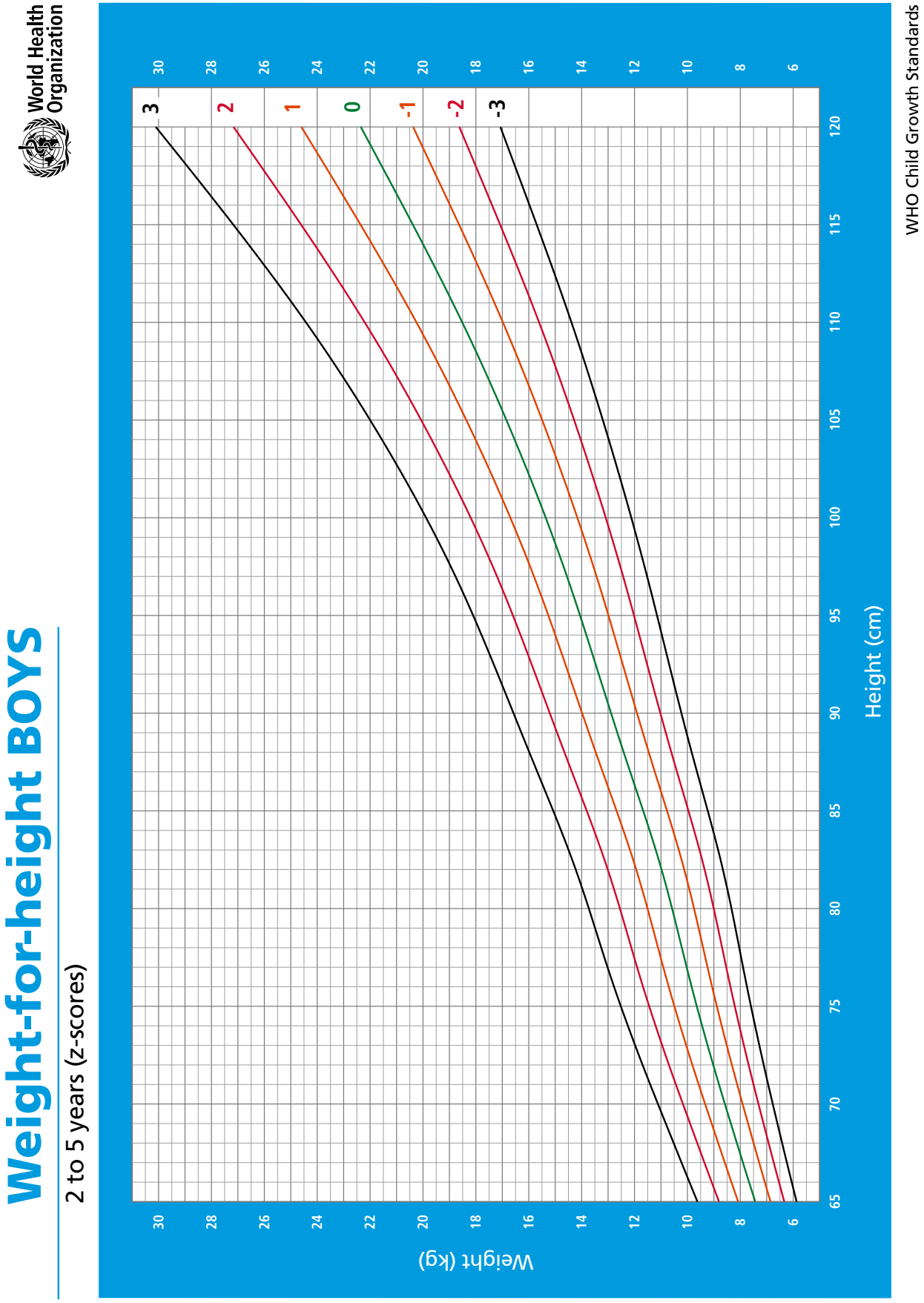


WHO Child Growth Standards

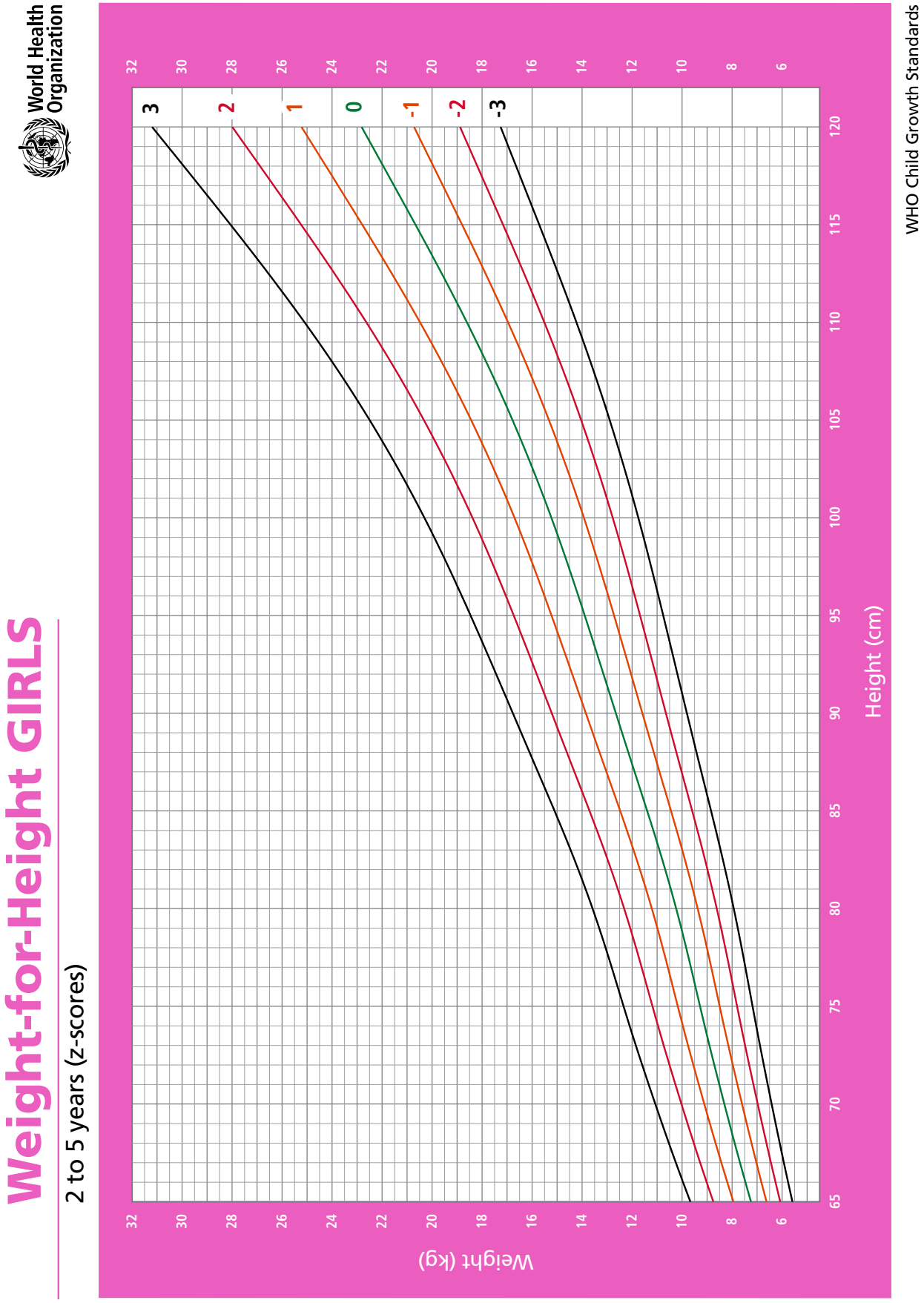
Annexure – VI


World Health Organization
Length/height-for-age GIRLS
Birth to 5 years (z-scores)
3
2
0
-2
-3
Length/Height (cm)
Months
Birth
1 year
2 years
3 years
4 years
5 years
Age (completed months and years)
WHO Child Growth Standards

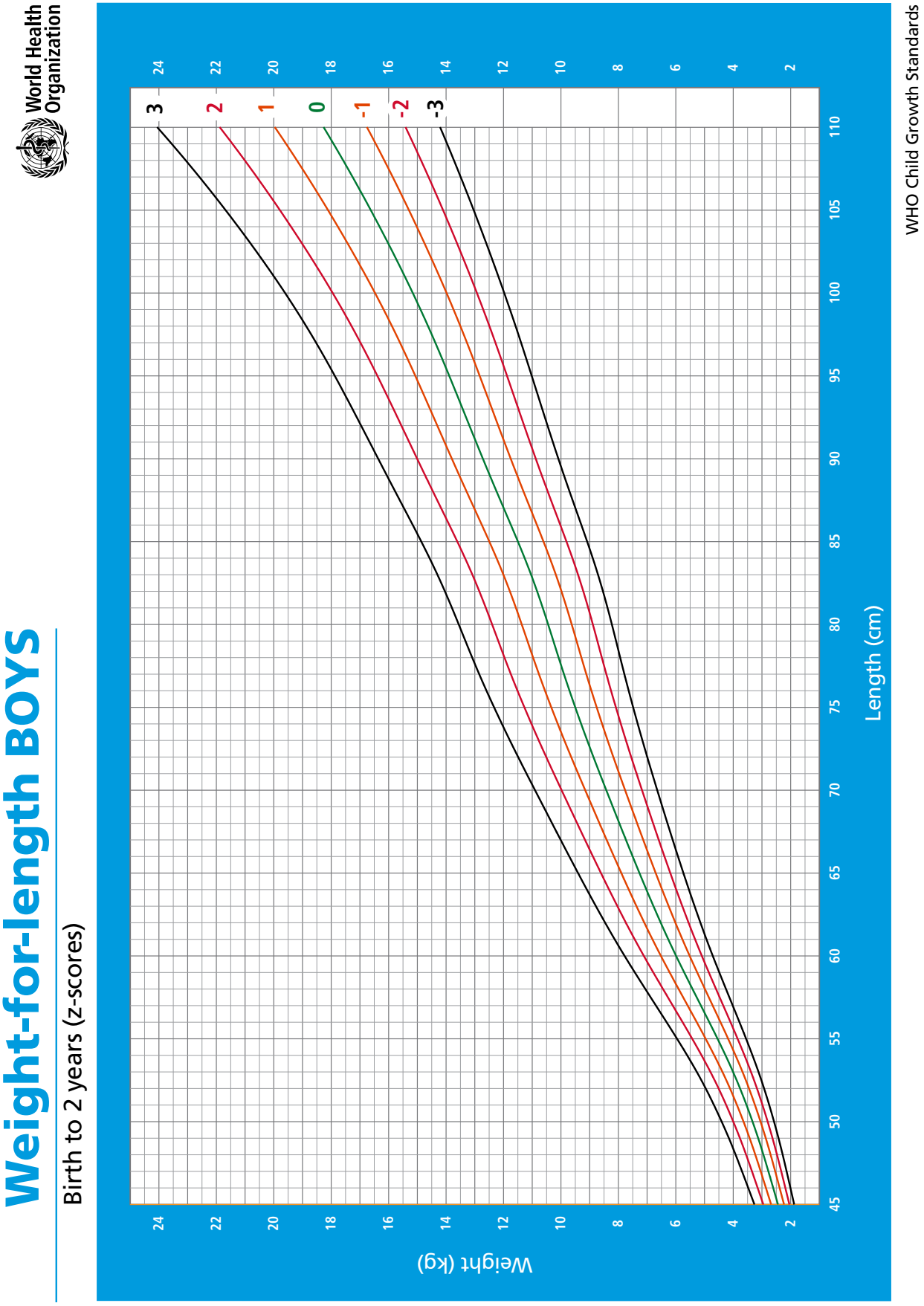
Annexure – VII



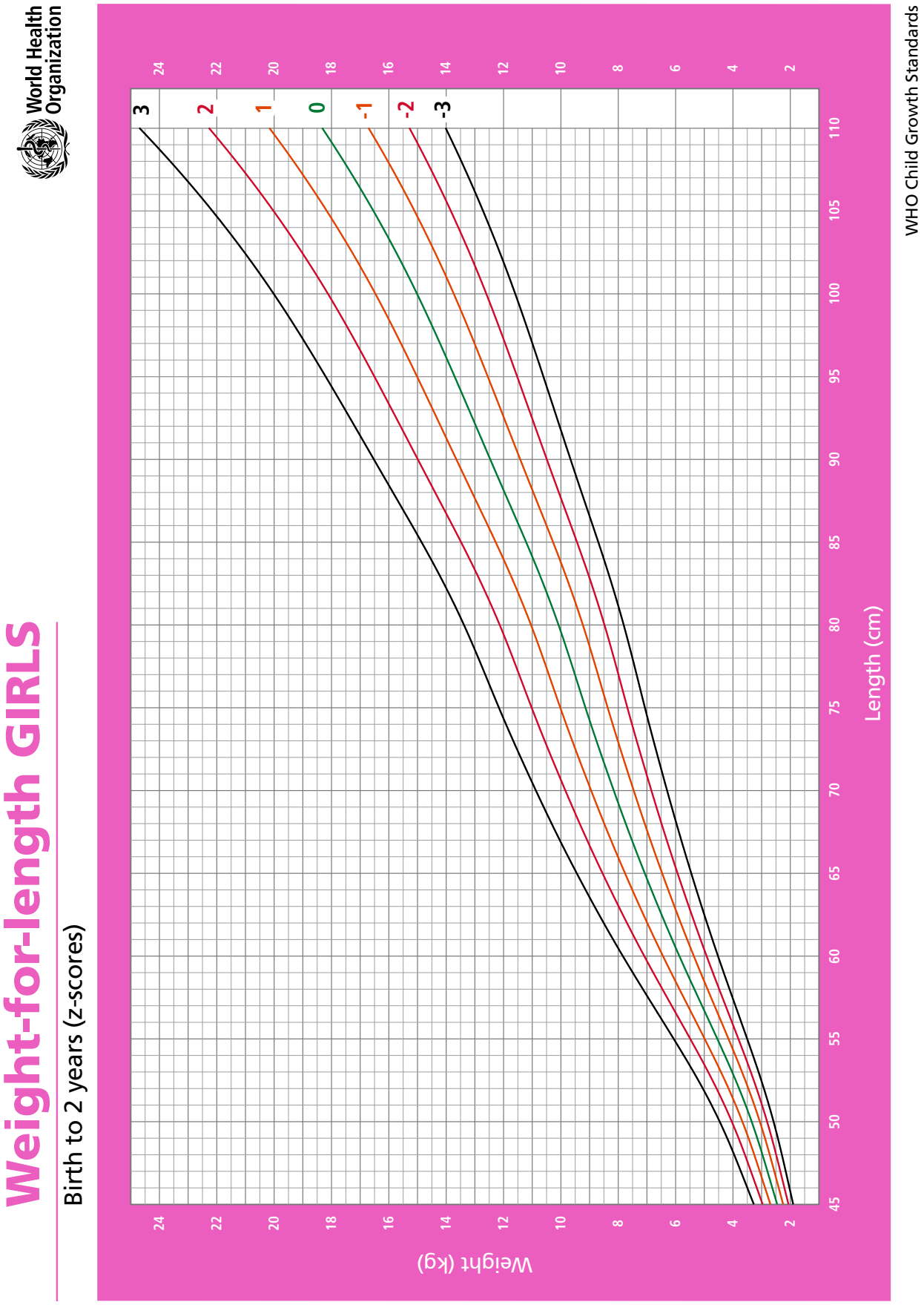
Annexure – VIII



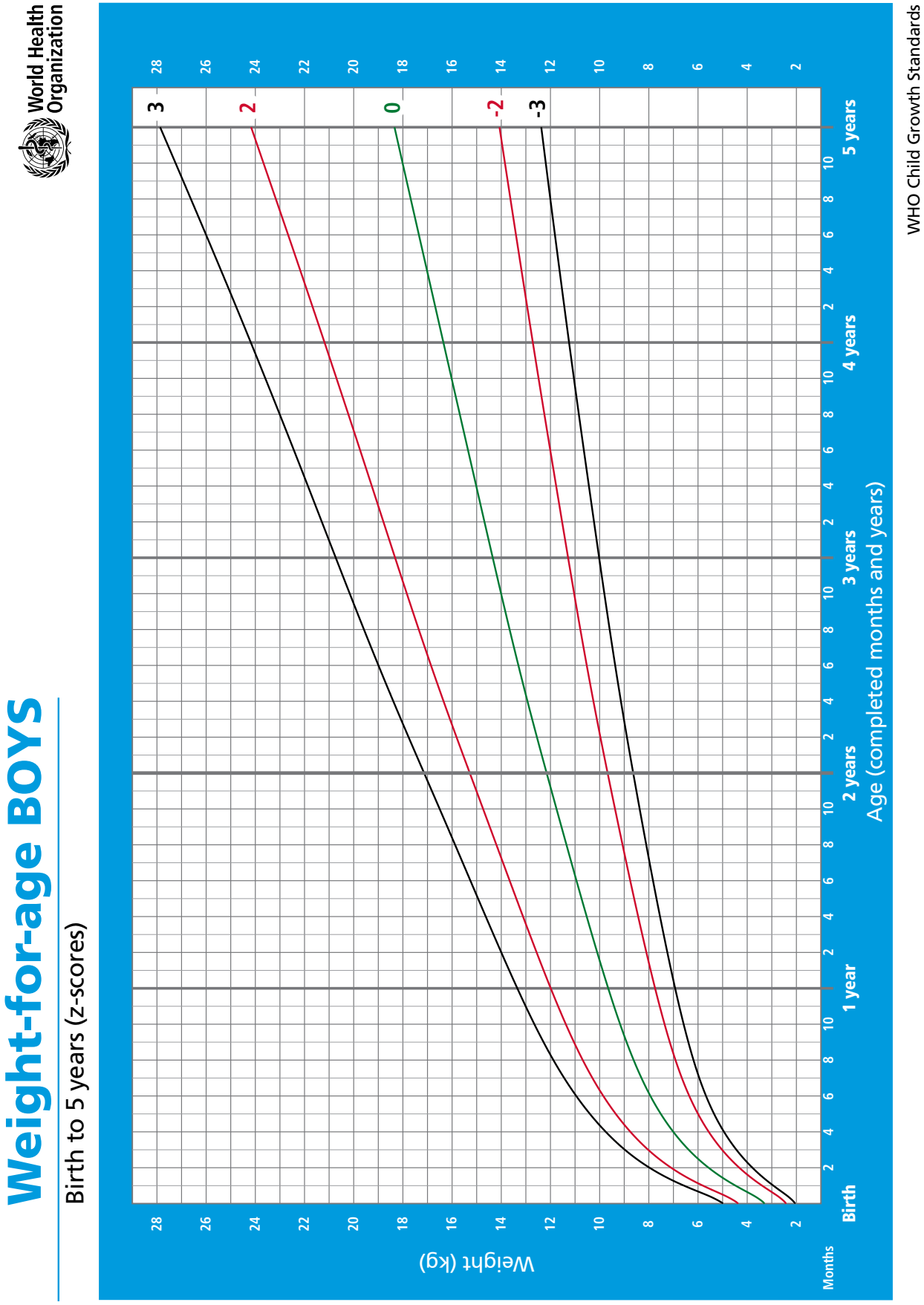
Annexure – IX


World Health Organization
Weight-for-length BOYS
Birth to 2 years (z-scores)
Weight (kg)
Length (cm)
3
2
1
0
-1
-2
-3
WHO Child Growth Standards

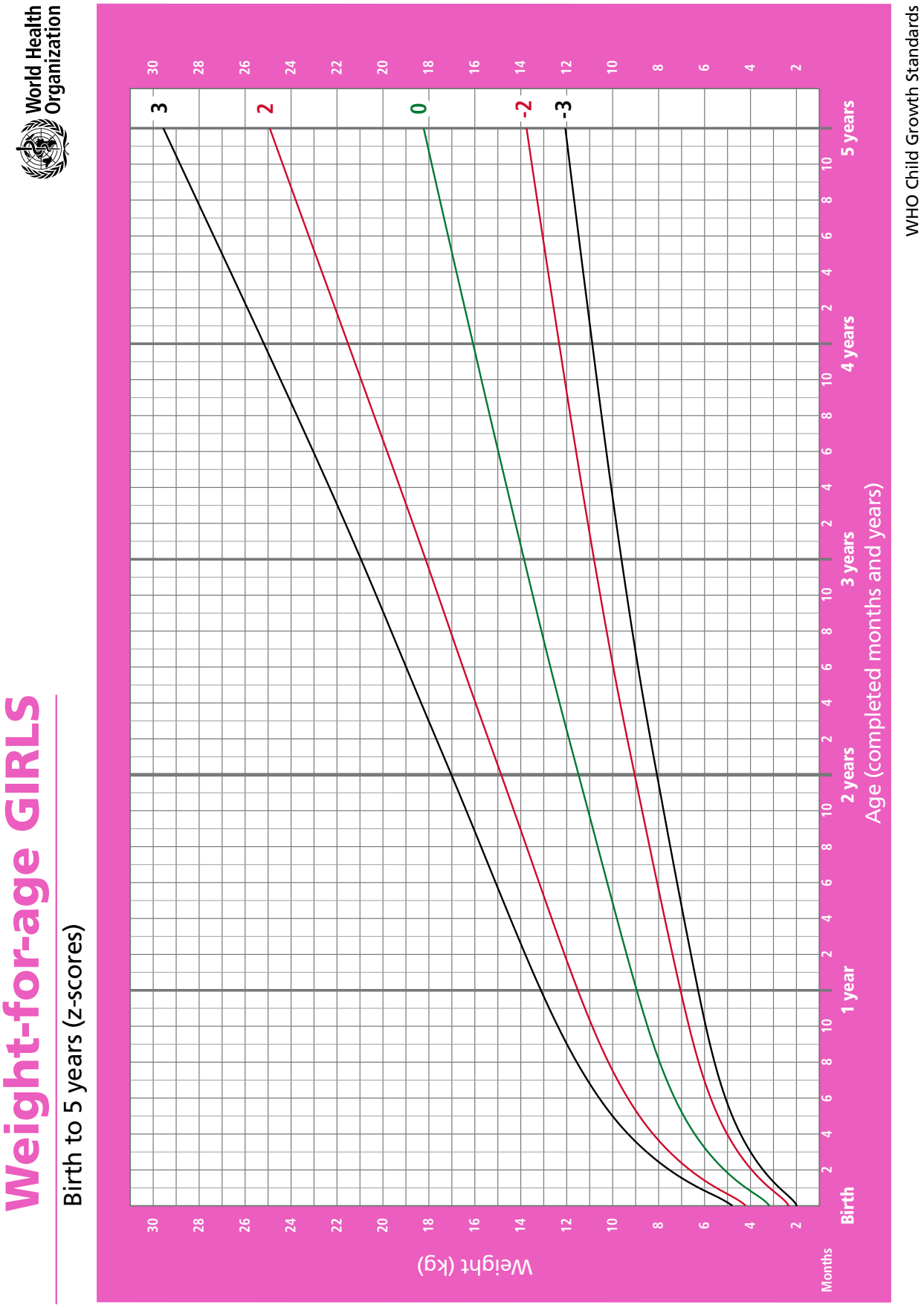
Annexure – X


World Health Organization
Weight-for-length GIRLS
Birth to 2 years (z-scores)
WHO Child Growth Standards
Weight (kg)
Length (cm)
3
2
1
0
-1
-2
-3

Annexure – XI


World Health Organization
Weight-for-age BOYS
Birth to 5 years (z-scores)
Weight (kg)
Months
Birth
1 year
2 years
3 years
4 years
5 years
Age (completed months and years)
3
2
0
-2
-3
WHO Child Growth Standards

Annexure – XII



National AIDS Control Organisation

India's voice against AIDS

Ministry of Health & Family Welfare, Government of India

www.nacoonline.org

National AIDS Control Organisation, India with support from WHO, UNICEF, UNAIDS