The National Guidelines for the
Management of HIV and AIDS in Children in Nepal
2008 (2065)

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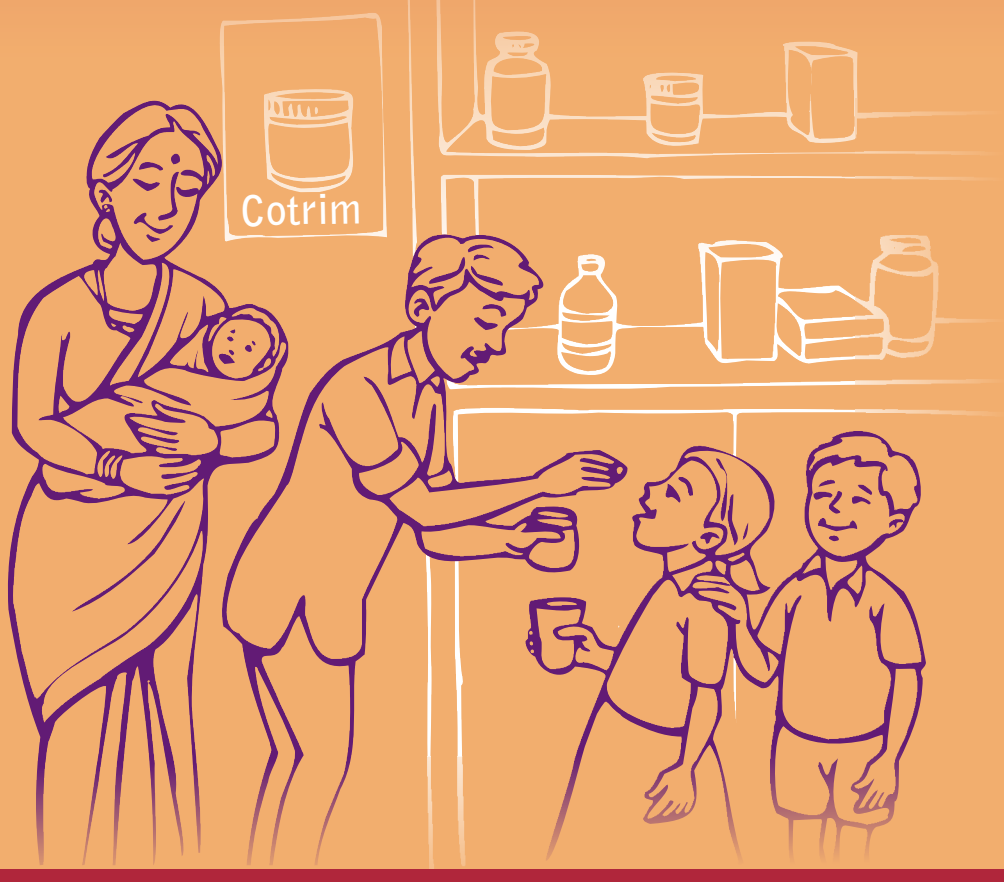
नेपाल



Government of Nepal
Ministry of Health and Population
National Centre for AIDS and STD Control
Kathmandu, Nepal

Government of Nepal
Ministry of Health & Population
NATIONAL CENTRE FOR AIDS AND STD CONTROL

Phone : 4261653
4262753
4258219
Fax: 4261406
Email : ncasc@mos.com.np
Website : www.ncasc.gov.np

TEKU KATHMANDU,
NEPAL

Ref. No .....

Date : .....

FOREWORD

Nepal has the highest prevalence of HIV in South Asia. Current data indicate that HIV Prevalence is around 0.49 percent in the adult population (15-49 years). Nepal has entered in a "concentrated" epidemic with HIV prevalence consistently over 5% in some sub-populations such as injecting drug users and female sex workers. The estimated number of adults and children living with HIV in Nepal at the end of 2007 was around 69,790.

There are 694 cases reported among children age 15 years or less as of August 2008. In Nepal, estimates hold that there are 1,857 children living with HIV and 13,000 under the age of 18 orphaned by AIDS.

Prevention of HIV is a priority of the Government of Nepal. Mother-to-child transmission is one of the critical sources of HIV infection to children in Nepal. Out of an estimated 900,000 annual pregnancies, 1,800 pregnancies are estimated to occur in HIV positive women leading to an annual cohort of about 450-810 new infections per year.

We are pleased to introduce the 2nd Edition of the National Guidelines for the Management of HIV and AIDS in Children in Nepal. These guidelines aim to provide up to date evidence based practical information and knowledge to medical professionals. It aims to aid physicians gain basic knowledge about HIV and AIDS in children and to enhance their ability to make informed decisions on the management of HIV and AIDS in children. . The Guidelines are mainly based on WHO 2006 guidelines on "Antiretroviral Therapy of HIV Infection in Infants and Children in Resource-limited settings" and "Management of HIV infection and antiretroviral therapy in infants and children".

We thank all those who contributed their expertise and experience to development of the 2nd Edition of the National Guidelines for the Management of HIV and AIDS in Children. We would also like to thank UNICEF for supporting us with technical support and subsequent production of this edition. We look forward to seeing that all HIV exposed and infected children are provided with access to timely clinical diagnosis, treatment of HIV and opportunistic infections, and effective care and support. We anticipate that this will ultimately help children exposed to and living with HIV experience a good quality of life.

Dr. Laxmi Raj Pathak
Director
NCASC

Stop AIDS, Keep the Promise.

List of Contributors (2nd Edition)

Name	Designation	Department/Agency
Dr. Laxmi Raj Pathak	Director	National Centre for AIDS and STD Control (NCASC)
Dr. Rajendra Pant	Deputy Director	National Centre for AIDS and STD Control (NCASC)
Ms. Sara Beysolow Nyanti	Chief	HIV and AIDS Section UNICEF
Dr. Laxman Shrestha	Lead-Pediatric Consultant	HIV and AIDS Section, UNICEF
Dr. Lisa Stevens	HIV and AIDS Consultant	Family Health International (FHI)
Mr. Birendra B Pradhan	Program Officer	HIV and AIDS Section UNICEF
Dr. Sushil Shakya	Registrar	Bir Hospital
Prof. Sashi Sharma	Professor of Medicine	TU Teaching Hospital
Dr. Amaya Maw-Naing	Medical Officer HIV and AIDS Unit	WHO
Dr. Ganesh K Shrestha	Pediatrician	Kanti Children's Hospital
Ms Nani Baba	ART Nursing in-charge	Teku Hospital
Ms Dharma Laxmi Shrestha	ART Nursing in-charge	TU Teaching Hospital

Acronyms and Abbreviations

3TC	Lamivudine
ABC	Abacavir
AFASS	Acceptable, Feasible, Affordable, Sustainable, Safe
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
ANC	Antenatal Care
ART	Antiretroviral Therapy
ARV	Antiretroviral
AZT	Zidovudine
CABA	Children Affected by AIDS
CBC	Complete Blood Count
CDC	United States Centers for Disease Control and Prevention
CSF	Cerebrospinal Fluid
CMV	Cytomegalovirus
CNS	Central Nervous System
CRC	Convention for Children's Rights
CTX	Cotrimoxazole
d4T	Stavudine
DBS	Dried Blood Spot
DC	Differential Count
ddI	Didanosine
DNA	Deoxyribonucleic Acid
DOT	Directly Observed Therapy
EVV	Epstein Barr Virus
EFV	Efavirenz
ELISA	Enzyme-Linked Immunosorbent Assay
FNAC	Fine Needle Aspiration Cytology
HAART	Highly Active Antiretroviral Therapy
HCW	Health Care Worker
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HSV	Herpes Simplex Virus
IDU	Injecting Drug User
IMCI	Integrated Management of Childhood Illnesses
INH	Isoniazid
IU	International Units
IRS	Immune Reconstitution Syndrome
KS	Kaposi's Sarcoma
LIP	Lymphoid Interstitial Pneumonitis
LN	Lymph Node
LPV/RTV	Lopinavir/Ritonavir
LRTI	Lower Respiratory Tract Infection
MDR-TB	Multi Drug Resistant Tuberculosis
MOHP	Ministry of Health and Population

MRI	Magnetic Resonance Imaging
MTB	Mycobacterium Tuberculosis
MTCT	Mother-to-Child Transmission
NACO	National AIDS Control Organization (India)
NCASC	National Center for AIDS and STD Control
NFV	Nelfinavir
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitors
NRTI	Nucleoside Reverse Transcriptase Inhibitors
NVP	Nevirapine
OHL	Oral Hairy Leukoplakia
OI	Opportunistic Infection
OVC	Orphans and Vulnerable Children
PCP	Pneumocystis Pneumonia
PCR	Polymerase Chain Reaction
PEP	Post-Exposure Prophylaxis
PGL	Persistent Generalized Lymphadenopathy
PI	Protease Inhibitor
PLHIV	People Living with HIV
PML	Progressive Multifocal Leukoencephalopathy
PMTCT	Prevention of Mother-to-Child Transmission
RNA	Ribonucleic Acid
RSV	Respiratory Syncytial Virus
RT	Reverse Transcriptase
RTV/r	Ritonavir
SMX	Sulfamethoxazole
SQV	Saquinavir
STI	Sexually Transmitted Infection
TB	Tuberculosis
TLC	Total Lymphocyte Count
TMP	Trimethoprim
UNAIDS	United Nations Joint Programme on HIV/AIDS
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
URI	Upper Respiratory Infection
VCT	Voluntary Counselling and Testing
VL	Viral Load
WBC	White Blood Count
WHO	World Health Organization
ZDV	Zidovudine

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Introduction

1.1 Global Epidemic

The global HIV and AIDSepidemic has greatly exceeded earlier predictions and it is now clear that it has the potential to affect all countries and all population groups. About 95% of all HIV infected people are living in developing countries, which have to cope with the huge burden of suffering and death. Although HIV and AIDS can affect people of all ages, about half of new infection occur in young adults under 25 years old who, if untreated, will die within ten years of contracting the infection. By the end of 2007, it was estimated that 33 million people were living with HIV, among them 2.5 million children under 15 years of age, worldwide. In this year alone, approximately 5 million people were newly infected, including 370,000 children under the age of 15 years. Men and women are now almost equally infected and HIV-related deaths continue to increase. Everyday 8,500 children and young people around the world are infected with HIV. Over 90% of HIV-infected babies were born to positive mothers in Sub-Saharan Africa. Worldwide, there is a cumulative total of over 11 million AIDS orphans.

1.2 HIV and AIDS in Asia

National HIV infection levels in Asia are low compared with some other continents, notably Africa. But the populations of many Asian nations are so large that even low national HIV prevalence means, large numbers of people are living with HIV. 2007 estimates show some 4 million people infected in the region, including 1.1 million people who became newly infected in the past year and 2.0 million adult women. AIDS claimed some 520,000 lives in 2005. Adult HIV prevalence was 0.4% for the region at the end of 2005.

With the exception of Cambodia, Myanmar and Thailand, national HIV prevalence levels remain comparatively low in most countries of Asia and the Pacific. Both China and India, are experiencing serious, localized epidemics that are affecting many millions of people. India's national adult HIV prevalence rate of 0.36% offers little indication of the serious situation the country is facing. NACO predicts that 2.5 million Indians are infected with HIV.

1.3 HIV and AIDS in Nepal

The first case of AIDS in Nepal was reported in 1988. By the mid-1990s, Nepal had entered a 'concentrated' epidemic, with HIV prevalence consistently over five percent in some sub-populations such as injecting drug users and female sex workers. Infection rates have increased rapidly in recent years. Nepal has the highest prevalence of HIV in South Asia. Current data indicate that HIV prevalence is around 0.49 percent in the adult population (15-49 years). The estimated number of adults and children living with HIV in Nepal at the end of 2007 was around 69,790. Of these, about half are living in districts along the highways and one quarter are women. There are an estimated 3,000 deaths per year due to AIDS.

As of December 15, 2008, the National Centre for AIDS and STD Control (NCASC) at the Ministry of Health reported 12,933 HIV infections and 2,151 cases of AIDS. There were 763 cases among children less than 15 years of age. In Nepal, estimates hold that there are currently 1,857 children living with HIV and 13,000 under the age of 18 orphaned by AIDS.

Most children acquire the virus around the time of birth or during breastfeeding. Without treatment, most of the children will experience profound reductions in the quality and length of their lives. As the number of infected and affected children is growing, it is necessary to ensure that families and communities prepare to support them. Expert clinical management is an important component of comprehensive care for children living with HIV. The prevention and treatment of opportunistic infections (OI's) and the appropriate use of antiretrovirals are the cornerstones of care for HIV-infected children. HIV infected children may progress more rapidly than adults to full blown disease due to immature immunity. Hence, many children need treatment as early as possible to decrease this rapid progression of disease and to prevent the occurrence of OI's.

Prevention of HIV is a priority of Government of Nepal. Mother-to-child transmission is one of the critical sources of HIV infection to children in Nepal. Out of estimated 900,000 annual pregnancies, 1,800 pregnancies are estimated to occur in HIV positive women leading to an annual cohort of about 450-810 infected newborns. Based on this background, realizing the growing need to start prevention of transmission of HIV infection from mother to child (PMTCT) interventions in Nepal, The Ministry of Health, National Center for AIDS and STD Control (NCASC) has initiated comprehensive PMTCT package services in February 2005 and now this service has expanded to 15 PMTCT sites*(See Annex 5)*.

Children less than 15 years old must also be included in the target group for the "Universal Access by 2010" strategy as supported by WHO and other leading international agencies. It is therefore urgent that strategies and protocols to target and treat these children are developed. Hence the necessity of "National Guidelines for the management of HIV and AIDS in children in Nepal" to regulate the management of this infection among children and to standardize pediatric protocols and procedures countrywide, in all settings including public, private and NGO settings.

These *Guidelines* aim to provide up-to-date, evidence based, practical information and knowledge designed to help health service providers to make informed decisions on the management of HIV and AIDS in children and to gain basic knowledge about HIV and AIDS in the Pediatric age group. The guidelines are mainly based on algorithms with annotations and reflect international best practice. The guidelines do not replace textbooks and publications and do not claim to provide complete information. They give guidance adapted to resource-constrained settings.

chapter 2

PMTCT Programme in Nepal

The objectives of the PMTCT programme include:

- Reduce the number of children born with HIV.
- Increase the life span and quality of life of the children living with HIV by initiating early diagnosis and supportive therapy.
- Allow mothers with HIV to live longer and healthier lives and be better able to nurture and care for their children.
- Referal for care and support for all children affected by AIDS (CABA) and HIV affected households.

A full PMTCT package for mothers, infants and partners contains the following components:

- HIV voluntary counseling and testing.
- Antiretroviral prophylaxis for HIV-infected mother and infant.
- Infant feeding counseling and support.
- Safe obstetrical care.
- Family planning counseling and referral services.
- Referral for care and support of HIV-infected mothers and infants.

2.1 HIV Prevention in Mothers and Young Children

Risk of Mother-to-Child Transmission

- By the end of 2005, an estimated 2.3 million children under the age of 15 years worldwide were infected with HIV. An estimated 530,000 children are newly infected with HIV each year and, among these, the overwhelming majority acquire the infection through MTCT.
- MTCT of HIV can occur during pregnancy, labour, delivery or lactation. In the absence of any intervention, 15-30% of children born to non-breast feeding HIV positive mothers in developing countries will themselves become infected with HIV. Transmission is believed to be uncommon during early pregnancy, but the risk increases sharply in late pregnancy and during labour and delivery.
- Breast feeding contributes further to the overall risk of vertical transmission, and transmission rates may reach 30-45% if breast feeding continues for 18 to 24 months.
- Overall, about 15-20% of those children who acquire HIV infection from their mothers are infected during the antenatal period, 50% during delivery and 33% through breast feeding. Table below summarises estimated rates of transmission during pregnancy and for different durations of breast feeding.

Table 2.1 Estimated risk and Timing of MTCT in the absence of interventions

During pregnancy	5 to 10%
During Labour and Delivary	10 to 15%
During breastfeeding	5 to 20%
Overall without breastfeeding	15 to 25%
Overall with breastfeeding to 6 months	20 to 35%
Overall with breastfeeding to 18 to 24 months	30 to 45%

Source: JAMA, 2000, 283:1175-1182

2.1.1 COMPREHENSIVE PREVENTION OF HIV INFECTION IN MOTHERS INFANTS AND YOUNG CHILDREN

In June 2001, the United Nations General Assembly Special Session (UNGASS) on HIV /AIDS *Declaration of Commitment* undertook to reduce the proportion of infants infected with HIV by 20% by 2005, and by 50% by 2010 through:

- ensuring that 80% of pregnant women accessing antenatal care have information, counselling and other HIV prevention services available to them;
- increasing availability and access for HIV-infected women and babies to effective treatment, especially antiretroviral (ARV) prophylaxis, to reduce MTCT of HIV; and
- effective interventions for women infected with HIV, including voluntary confidential counselling and testing (VCT) and, where appropriate, breast milk substitutes and a continuum of care, treatment and support.

To meet these targets, it is generally agreed that a four-pronged approach to PMTCT should be adopted. This is summarised as follows.

Four-Pronged UN Strategy for PMTCT of HIV

1. Prevent HIV infection in women of reproductive age
2. Prevent unintended pregnancy in HIV-positive women
3. Prevent mother-to-child transmission of HIV by:
   - providing antiretroviral therapy during pregnancy
   - implementing safer delivery practices
   - providing counselling and support on infant feeding methods
4. Provide care, treatment and support to HIV infected and affected parents, infants and families

2.2 Introduction to PMTCT services in Nepal

In February 2005, the NCASC initiated a pilot PMTCT programme in three hospitals; this was extended to additional facilities during 2006 and 2007 with support of UNICEF , WHO and Global Fund. At present there are 15 PMTCT sites. The government chairs a National PMTCT working group which includes UNICEF, WHO, UNFPA, USAID/FHI, National Experts and other partners. This working group provides active support to the program.

2.2.1 CURRENT NATIONAL PMTCT STRATEGIES

TARGETS

- National HIV and AIDS Strategy, 2006-11 seeks to expand and strengthen the PMTCT Program using a more decentralised, community-based model to improve coverage and access.
- The over-arching target is for the proportion of HIV positive pregnant women receiving a complete course of ARV prophylaxis to reduce the risk of MTCT to reach:
  - 80% by 2011

STRATEGIES AND KEY ACTIONS

This target are to be reached through 6 strategic outcomes:

- Reduced transmission of HIV infection to newborn
- Increased decentralised coverage and access to PMTCT at district level in collaboration with private sectors, communities and non-government organisations (NGOs)
- Increased health seeking behaviours among pregnant women and women of child-bearing age and safe sexual practices
- Increased knowledge, acceptance and demands for PMTCT programme among communities, families and targeted pregnant women.
- Strengthened linkage between PMTCT services and HIV CT&S services to ensure that ART programme fast tracks women in PMTCT programmes into ARV treatment plans, followed by care and support services
- Increased capacity of health service providers for effective management and delivery of PMTCT services

2.3 Strengthening HIV Detection in Pregnancy through Counselling and Testing

Confidential voluntary counselling and testing provides an important link between programmes for HIV prevention, STI prevention and treatment, obstetric and neonatal care, and the detection and treatment of tuberculosis and other opportunistic infec-tions. By "normalising" HIV screening and awareness, it may also reduce stigma and discrimination against PLHA.

- Traditionally, HIV testing and counselling has operated on a client-initiated basis – i.e. the individual presents to a health facility requesting a test for HIV infection or "for AIDS".
- Under these circumstances, it is important to provide counselling and risk assessment, as well as to offer (or refer for) HIV testing according to the national VCT Guidelines and the standards summarised as follows:

MINIMUM STANDARDS FOR HIV COUNSELLING AND TESTING

- HIV counselling and testing should be voluntary. Individuals should have sufficient information, understanding and freedom of choice to be able to give informed consent to testing.
- Pre-test information should describe the purpose and procedure of HIV testing and the treatment and support that are available after testing.
- There should be appropriate post-test information counselling and/or referral.
- There should be consistent commitment and ethical support to encourage partner participation and disclosure to significant others.
- Persons whose test result is positive should receive counselling and referral to care support and treatment where available.
- HIV test results and counselling records should be treated confidentially and only those health workers with a direct role in the management of patients should have access to this information.
- Persons whose test results are negative should receive counselling to enable them to remain free of HIV.

2.4 Guiding Principles for VCT in Antenatal Settings

2.4.1 ANTENATAL VCT AND EDUCATION AS A MINIMUM STANDARD OF CARE

All MCH settings that provide

a) family planning services for women of childbearing age and
b) antenatal, labour and delivery, postnatal and other reproductive health care for pregnant women, must be able to provide a basic package of HIV counselling- and testing-related services.

This will include:

- as a minimum, non-test dependent counselling and individual risk assessment,
- pre-test information,
- testing (or referral for testing) where indicated, and
- post-test counselling (regardless of whether the test result is positive or negative).

As part of their counselling and pre-test information, all pregnant women presenting to ANC must receive information on the following:

- safer sex practices,
- prevention and treatment of STIs,
- prevention of HIV in unborn babies, infants and young children, including available PMTCT inter-ventions, and
- HIV testing, post-test counselling and follow-up services (including access to ART).

There should also be a strong emphasis on counselling for partners or as a couple. This is particularly important where there is discussion about whether to continue or terminate the pregnancy, and for sero-discordant couples.

2.5 Prevention of HIV Transmission from HIV Infected Mothers to their Infants

2.5.1 AVAILABLE INTERVENTIONS AND THEIR TIMING

The three elements of PMTCT during pregnancy, labour and post-partum are:

- providing ARV prophylaxis (or therapy) during pregnancy, labour and in some cases post-partum to the mother, and to the baby following delivery
- implementing safer delivery practices
- providing ongoing counselling and support on infant feeding methods

2.5.2 ANTIRETROVIRAL PROPHYLAXIS AND ITS EFFECTIVENESS

The reason for providing antenatal ARV prophylaxis (or treatment) to the mother is to reduce viral replication in order to reduce the risk of transmission to the fetus during pregnancy, labour and delivery.

WOMEN WITH INDICATIONS FOR HAART

To reduce HIV infection in infants and young children, all pregnant women eligible for HAART must be started on treatment.

WOMEN WITHOUT INDICATIONS FOR HAART

- Pregnant women who do not yet need HAART must be given highly effective ARV prophylaxis to prevent MTCT. The most commonly used drugs are the nucleoside reverse transcriptase inhibitors (NRTIs) zidovudine (ZDV) and lamivudine (3TC), and the NNRTI, NVP, prescribed either alone or in combinations of two or three drugs.
- Many different prophylactic regimens have been trialled and evaluated. In resource limited settings, they have been shown to reduce MTCT from around 30% to around 12-14% for the simplest, single-drug approaches, e.g. single-dose nevirapine (sdNVP) at the onset of labour; to around 6% for multi-drug protocols starting during the last 4-8 weeks of pregnancy; and to around 2% for multi-drug protocols commencing no later than the start of the third trimester.

ARV PROPHYLAXIS FOR THE NEWBORN INFANT

- Providing additional ARV prophylaxis for the newborn infant is intended to "mop up" circulating virus that may have been transmitted in spite of maternal ARV prophylaxis or treatment.
- The simplest prophylaxis for the baby is sdNVP given no later than 72 hours following delivery.
- The recommended protocol by WHO include ZDV for 1 to 4 weeks in combination with sdNVP.

RISK OF ARV DRUG RESISTANCE

- Viral drug resistance is potentially a problem for HIV positive women following short-term exposure to ARVs for PMTCT especially single and two-drug regimen and for infants who become infected. This is a particular risk for NVP and 3TC, where a single mutation can lead to high-level resistance; multiple mutations are needed to confer resistance to ZDV.
- WHO now recommends that, where feasible, two NRTI drugs should be given intrapartum and for a short period postnatally (to suppress viral replication) when sdNVP is also used.
- A study in South Africa showed that the giving of ZDV + 3TC during labour (at the same time as sdNVP) and for 4-7 days postpartum reduces the incidence of NVP resistance from 60% to about 10%.

2.5.3 INDICATIONS FOR COMMENCING HAART

CRITERIA FOR COMMENCING HAART

The criteria for commencing HAART in pregnant women are:

- WHO Stage IV disease, irrespective of CD4 cell count or TLC; or
- WHO Stage III disease with CD4 < 350/mm3 (or, if CD4 cell count not available, treat irrespective of TLC);or
- WHO Stage I or II disease with CD4 < 250/mm3 (but don't treat if CD4 cell count not available, irrespective of TLC)

Table 2.2 Recommended First-Line HAART Regimen for treating Pregnant Women and Prophylactic Regimen for Infants

RECIPIENT	TIMING	ARV (S)
MOTHER	Antepartum	ZDV 300mg + 3TC 150mg twice a day + NVP 200mg once a day for 14 days, If no reaction, increase NVP to 200mg twice a day after 14 days
	Intrapartum	ZDV 300mg + 3TC 150mg + NVP 200mg twice a day
	Postpartum	ZDV 300mg + 3TC 150mg + NVP 200mg twice a day
BABY	Neonatal	Infant ZDV 4 mg/kg twice a day for 7 days. If the mother has received less than 4 weeks of HAART, infant ZDV should be continued for 4 weeks

ANTIRETROVIRAL PROPHYLAXIS TO PREVENT HIV INFECTION IN INFANTS

The Recommended PMTCT Protocol

- Where HIV infection is diagnosed no later than during the second trimester of pregnancy, antenatal follow-up and support are available, and delivery takes place in a hospital or other health facility with trained staff and ARVs available, HIV-infected pregnant women should be offered the WHO recommended regimen from 28 weeks' gestation.

Table 2.3 Hospitals and other Health Facilities with an Established PMTCT Recommended Standard PMTCT Protocol

RECIPIENT	TIMING	ARV (S)
MOTHER	Antepartum	ZDV 300mg twice daily from 28 weeks' gestation
	Intrapartum	ZDV 300mg at the onset of labour and 3-hourly until delivery plus 3TC 150mg at the onset of labour and 12-hourly until delivery plus NVP 200mg once at the onset of labour
	Postpartum	ZDV 300mg + 3TC 150mg twice daily for 7 days
BABY	Neonatal	Infant NVP 2 mg/kg as soon as feasible (preferably within 12 hours, but no later than 72 hours following delivery) plus Infant ZDV 4 mg/kg twice daily for 7 days

SINGLE DOSE NEVIRAPINE:

The minimum standard of perinatal PMTCT Prophylaxis:

- The absolute minimum standard regimen for PMTCT in community settings is sdNVP for mother and baby. Community settings include home delivery and delivery at a primary health care (PHC) facility or Sub-Health Post or where standard PMTCT ART protocol is not available.

Table 2.4 Nevirapine for Mother and Baby where recommended Standard PMTCT Protocol is not available or feasible

RECIPIENT	TIMING	ARV (S)
MOTHER	Intrapartum	NVP 200mg once at the onset of labour. If woman presents in established labour, give NVP as soon as possible in the first stage of labour
BABY	Neonatal	Infant NVP 2 mg/kg as soon as feasible (preferably within 12 hours, but no later than 72 hours following delivery)

chapter 3

Diagnosis of HIV Infection in Children

3.1 Laboratory Diagnosis of Pediatric HIV Infection

There are three types of tests available to confirm HIV infection in children and to monitor the progress of disease.

- **HIV antibody testing** continues to be the backbone, however it is of more limited use in children aged <18 months, who may still be carrying maternal HIV specific antibodies.
  - Enzyme linked immunosorbent assay (ELISA) tests for antibodies against HIV. Sensitivity and specificity approach 100%.
  - Rapid tests are based on immunochromatography/lateral flow membrane to detect HIV antibodies and are nearly 100% sensitive, 99% specific. They provide results in 10 minutes and do not require sophisticated laboratory facilities. Reaction is read by naked eye.
  - All infants born to HIV infected mothers will test antibody positive at birth. Most uninfected infants will lose maternal antibodies between 6 and 12 months of age. A few will continue to test positive until 18 months of age.
  - In an HIV-exposed infant a negative antibody test at less than 6 months of age does not exclude HIV infection due to possible lack of antibody production at this age.
  - Children over 12 months of age have usually lost maternal antibody. If ELISA is positive after 12 months of age, there is a 96% chance the child is HIV-infected.
  - The use of two or more rapid tests based on different test principles (antigens) is recommended as the minimum standard HIV test algorithm to be followed at all levels of health care delivery system

- **Virological tests** are needed to confirm HIV infection in children less than 18 months of age. These are more expensive and difficult to perform.
  - DNA PCR is the most common *virological* test for infant diagnosis (qualitative).
  - RNA PCR (quantitative) also called Viral Load is most commonly used to follow response to ART.
  - Virological tests become positive much earlier than antibody tests.
  - If tested at 6 weeks almost all infants infected intrauterine and peripartum will be positive.
  - Recently, Dried Blood Spot (DBS) has been found to be reliable for DNA PCR and allows finger or heel-stick collection along with ease of transportation of the sample to a central laboratory from other parts of the country.

- **Immunological tests:** (CD4 counts, CD4% and total lymphocyte counts) contribute enormously to care and treatment decisions.
  - CD4 cell count is a good predictor of progression of HIV disease.
  - CD4% is the percent of total lymphocytes that are made up of CD4 cells. This is more useful for children under 5 years of age than the absolute CD4 count, because as compared to the CD4 percentage, the CD4 absolute count varies greatly among children. CD4 is also variable depending on the time of day the sample is obtained.
  - For WHO Immunological Classification by CD4 count see Chapter 4 Table 4.3
  - In cases where the CD4 cell count cannot be assessed, the total lymphocyte count may be used to substitute as an indication for treatment in infants and children with documented HIV infection in the presence of WHO Clinical Stage II Disease. (See Table 6.3 Chapter 6)

Note: *Breastfeeding further complicates diagnosis in children. Antibody and virological tests must be performed at least 6 weeks after the cessation of breastfeeding for accurate diagnosis.*

Combining clinical and laboratory criteria to stage HIV disease ensures timely and rational initiation of care, treatment, and appropriate counseling.

3.2 Diagnosis of HIV infection in children less than 18 months of age

1. Timing of testing of HIV-Exposed Infant: (See Figure 1 and 2)

- PCR testing where available:
  - Exposed infants should be tested at 6 weeks of age at the time of first postnatal visit or later when first seen.
  - In children who were diagnosed either as HIV-positive or HIV-negative based on only one virological test, HIV antibody testing should be performed after 18 months of age to confirm status. (See Figure 1).
- Antibody Testing (ELISA or Rapid Tests) where PCR test has not been done or is not available:
  - All HIV-exposed infants should be tested at 9 months of age at the time of measles immunization, for presence of antibodies to HIV. A negative antibody test at this age rules out HIV infection, if the child was not breastfed in the previous 6 weeks.
  - A positive antibody test in children less than 18 months does not distinguish between HIV-infection and continued presence of maternal antibodies.

2. Diagnosing HIV infection in breastfeeding infants

- If an infant is breastfeeding, the infant remains at risk of acquiring infection throughout the breastfeeding period, and therefore, a negative virological test in an infant who is continuing to breastfeed does not rule-out infection.
- Diagnostic testing using viral assays in these situations should be conducted at least 6 weeks or longer after complete cessation of breastfeeding.
- If the child is between 9-18 months of age, HIV antibody testing can be performed prior to virological testing as a cost saving measure. Children who no longer have HIV antibody at this age, do not need virological testing. If breast feeding continues in previous six weeks, further test are needed.
- Negative PCR results should always be confirmed at age 18 months with an antibody test.
- Positive PCR results at any stage indicate HIV infection.

3. Diagnosing HIV infection where mother or infant has received antiretroviral prophylaxis of MTCT

- Infant PCR diagnostic testing is done by HIV DNA assays, which are not affected by the use of antiretroviral prophylaxis of MTCT by the mother or infant.

4. Diagnosing infection when the mother is on ART

- Infant PCR diagnostic testing is done by HIV DNA assays, which are not affected by the use of antiretroviral therapy by the mother.

3.3. Diagnosis of HIV infection in children ≥ 18 months of age

- Definitive HIV diagnosis in children >18 months can be performed with antibody tests, following standard testing algorithms as used for adults. (Figure 3)
- A positive antibody test should be confirmed by duplicate testing (testing the same specimen twice) using a different HIV antibody test.

3.4. Presumptive clinical diagnosis of HIV infection

No single clinical diagnostic algorithm has proved to be highly sensitive or specific for diagnosis of HIV infection. Clinical algorithms are rarely more than 70% sensitive for diagnosis of infection and vary considerably with age, in particular in children aged less than 12 months. However, there are situations where the use of a clinical algorithm may be required to initiate appropriate, life-saving treatment of a seriously ill child.

For infants and children aged less than 18 months where access to laboratory testing is not available but a child has symptoms that are suggestive of HIV infection, a presumptive clinical diagnosis of HIV infection may need to be made as follows:

TABLE 3.1:

1. Criteria for presumptive clinical diagnosis of severe HIV disease in infants and chlidren aged under 18 months in situations where virological testing is not available

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

- Infant is confirmed HIV-antibody positive; *and*
- Diagnosis of AIDS-indicator condition(s)[a] can be made

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

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

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

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

a. AIDS indicator conditions include some but not all HIV pediateric clinical stage 4 such as Pneumocystis pneumonia, cryptococcal meningitis, severe wasting or sever malnutiriton, Kaposi sarcoma, extrapulmonary tuberculosis.

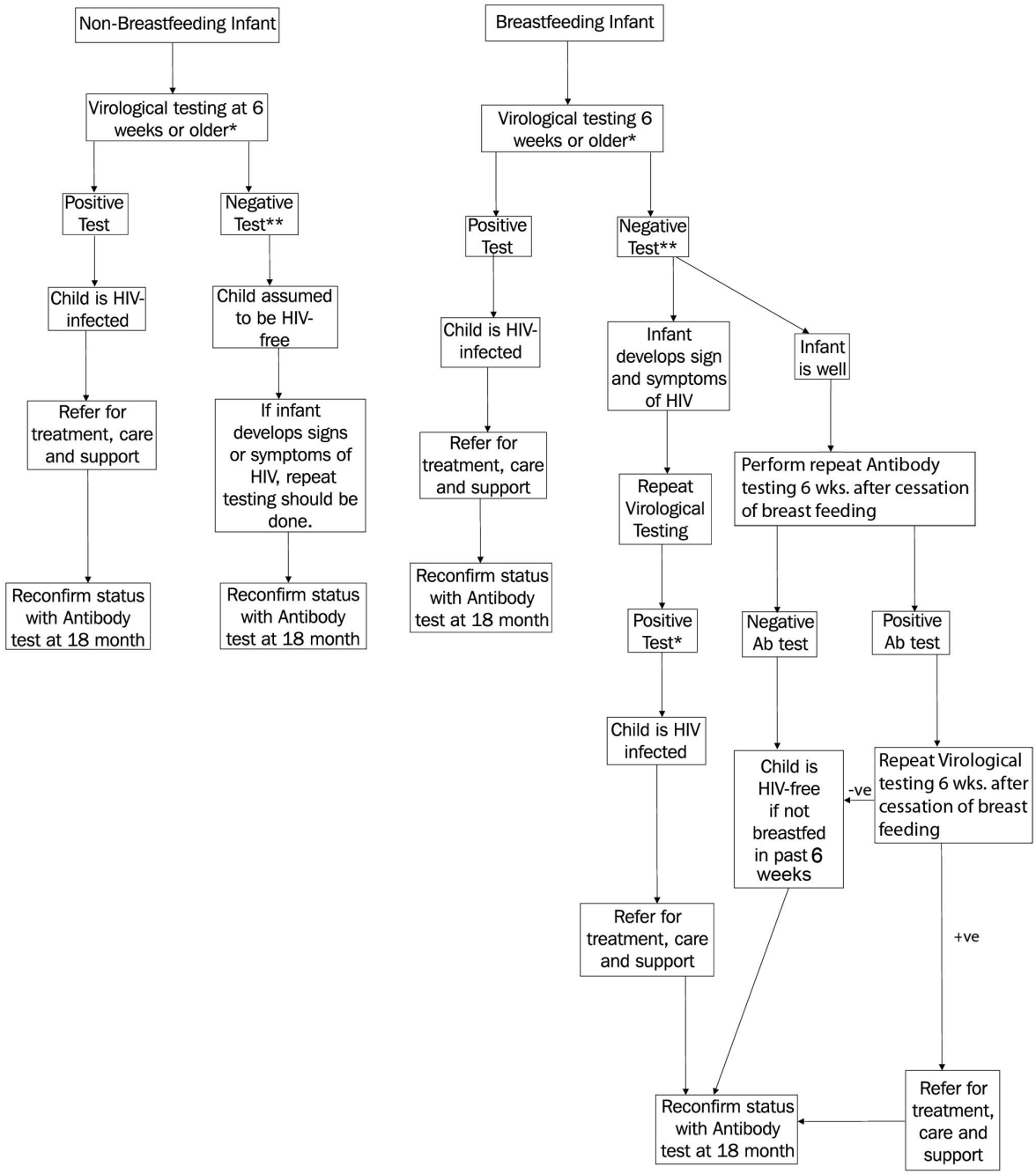
b. As per IMCI definition:

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

2. Children 18 months of age and older

- For children >18 months with signs and symptoms suggestive of HIV, antibody testing should be used for diagnosis.
- Presumptive clinical diagnosis of severe HIV disease is not indicated in this age group.
- Some clinical conditions are very unusual without HIV infection (i.e. pneumocystis pneumonia, esophageal candidiasis, lymphoid interstitial pneumonitis, Kaposi's sarcoma and cryptococcal meningitis), and the diagnosis of these conditions thus suggests HIV infection and indicates the need to perform an HIV antibody test.

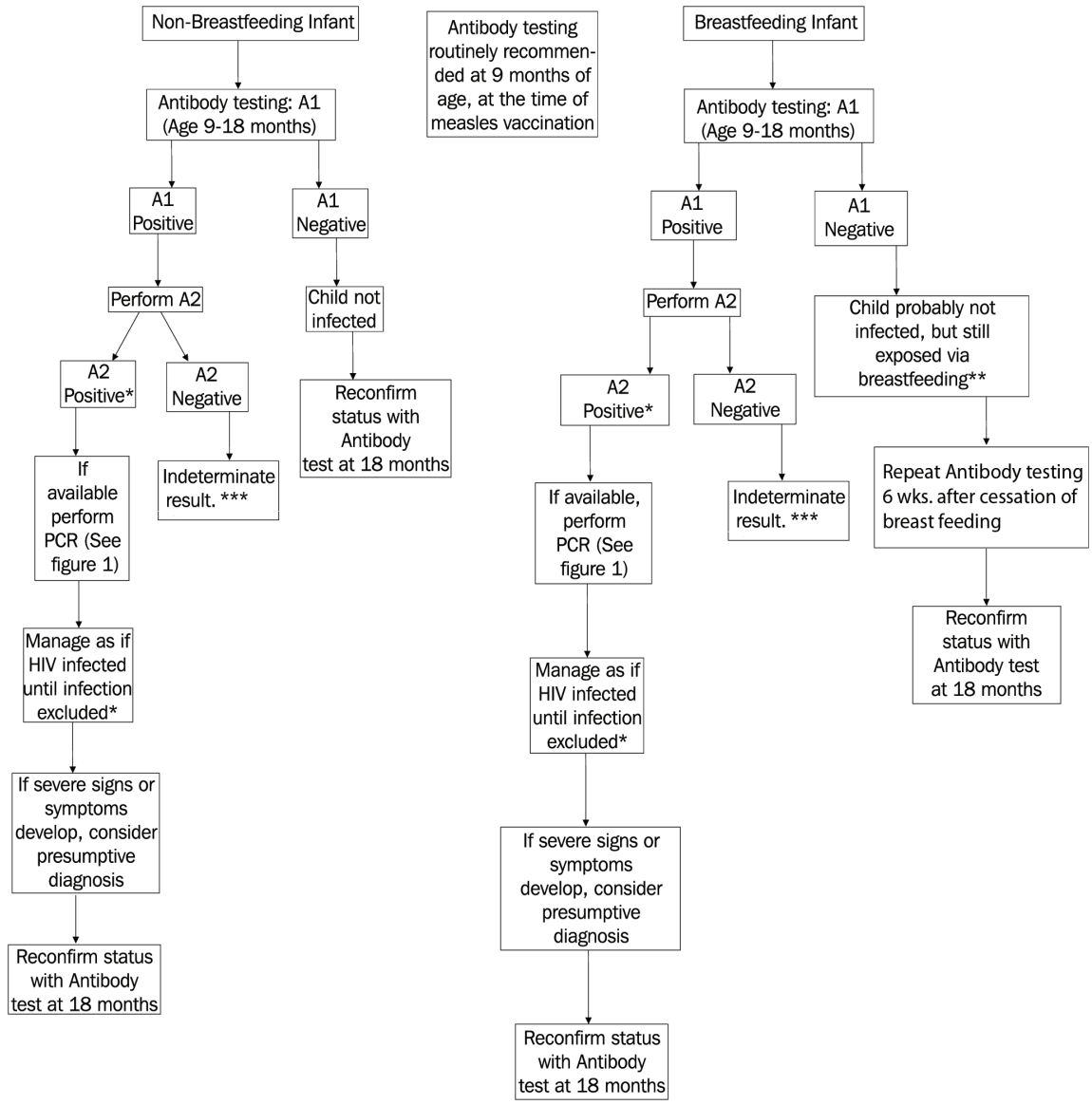
FIGURE 1: HIV diagnosis with virological assay (PCR) in children less than 18 months of age with confirmed HIV exposure



***Note:** If the infant is 9-18 months of age, antibody testing can be performed to identify HIV exposure; virological testing is then only needed if the infant is still antibody positive*

****Note:** Due to window period, both antibody and virological tests are accurate 6 weeks after the last exposure.*

FIGURE 2: HIV diagnosis with Antibody testing in HIV-exposed children < 18 months of age



**A positive Antibody test in a child <18 months of age may be from maternal HIV antibodies or child may be HIV infected*

***If Antibody negative breastfeeding child later becomes ill, consider repeat antibody testing. If repeat is negative, look for other cause of illness.*

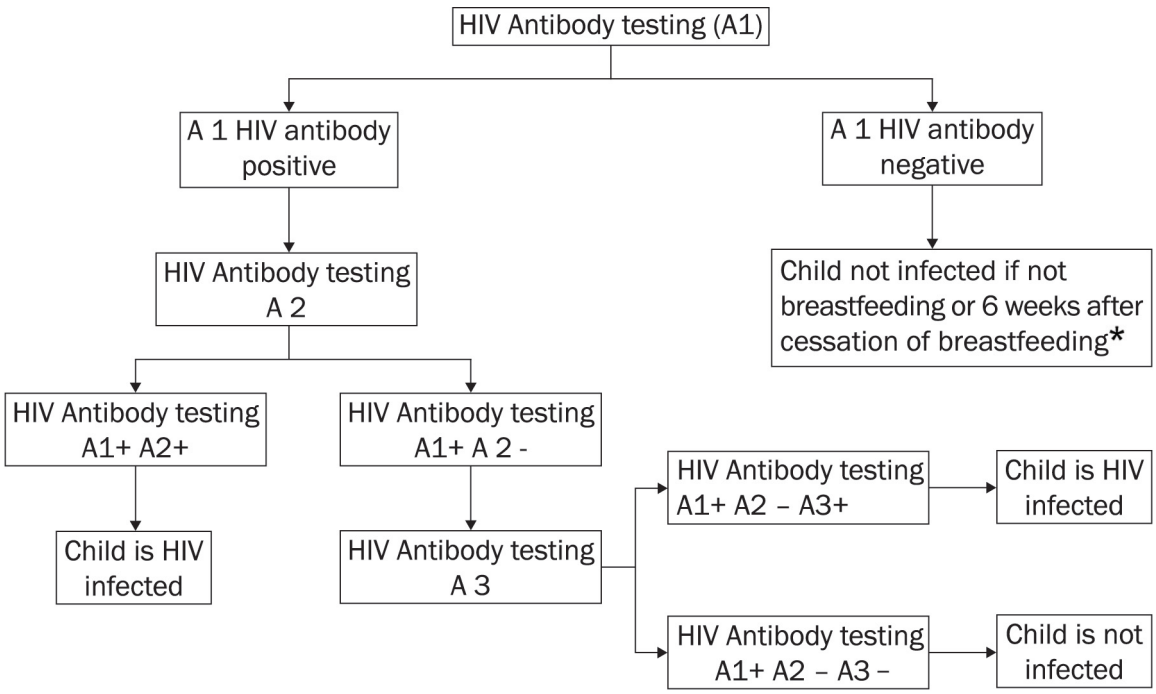
HIV antibody testing is not recommended in children <6 months of age unless ART is being considered and PCR is not available

**** Run through third test as in figure 3*

A1= Highly sensitive Rapid Assay

A2= Highly specific Assay that is based on a different antigen and/or different test principle

FIGURE 3: HIV diagnosis with Antibody testing in HIV-exposed children > 18 months of age*



**For children continuing to breast feed, final antibody testing must be done 6 weeks after breastfeeding cessation to ensure HIV negative status.*
A1 = Highly sensitive Rapid Assay
A2, A3 = Highly specific Assay that is based on a different antigen and/or different test principle

chapter 4

Clinical Features and Staging of HIV Infection in Children

4.1 Introduction

The immunosuppressive effects of HIV are additive to the poor response of the immature immune system at birth, predisposing to an increased frequency of invasive bacterial and opportunistic infections. Common childhood infections and conditions are more frequent in HIV-infected children and have a higher case fatality rate compared to uninfected children. They last longer and are slower to respond to standard treatments. In addition, the virus disseminates throughout the various organs leading to systemic manifestations of HIV infection.

Differences in pediatric and adult HIV infection:

- Overall progression of disease is more rapid in children.
- Immune system is more immature with higher CD4+ counts.
- Recurrent invasive bacterial infections are more common in children.
- Disseminated CMV, candida, herpes simplex and varicella zoster are more common.
- LIP occurs almost exclusively in children.
- CNS infections are common.
- Peripheral neuropathy, myopathy and Kaposi's sarcoma are rare in children.

4.2 Patterns of manifestations

Most infected infants do not have any abnormal findings on clinical examination at birth. The natural history of children perinatally infected with HIV fits into one of three categories:

CATEGORY 1: RAPID PROGRESSORS (ABOUT 25-30% OF CASES)

- Manifestations of HIV-infection may occur within the first few months of life.
- Opportunistic infection and neurological manifestations are usual clinical features.
- Undergo a rapid downhill progression; untreated die within 1 year.
- Are thought to have acquired the infection in-utero or in the early perinatal period.

CATEGORY 2: MAJORITY OF PEDIATRIC INFECTIONS (ABOUT 50-60% OF CASES)

- Develop manifestations early in life.
- Failure to thrive, recurrent bacterial infections and lymphoid interstitial pneumonitis usual presentations.
- Downhill course with death by age 3-5 years.

CATEGORY 3: SLOW PROGRESSORS (ABOUT 5-25% OF CASES)

- Long term survivors.
- These children reveal minor manifestations later in their childhood.
- Live beyond age 8 years.
- May have had late postnatal acquisition (breastfeeding).

High index of suspicion by clinician is important!

Alarming signs and symptoms: "Red flags"

- Failure to thrive
- Persistent cough
- Prolonged fever
- Recurrent infections
- Lymphadenopathy
- Hepatosplenomegaly
- Oral thrush
- Persistent diarrhea
- Unusual infections

4.3 Clinical Manifestations

(For details of clinical entities caused by opportunistic organisms see Chapter VIII. For some diseases not caused by opportunistic infections, a brief mention of diagnostics and management is included below)

1. Failure to thrive

- May manifest as early as 4-6 months of age in perinatally infected infants
- Measured by body weight, length/height and head circumference
- Causes: Decreased energy intake, diarrhea, malabsorption, chronic diseases of the heart, kidney and lungs, micronutrient deficiencies, neuroendocrine abnormalities and repeated episodes of infection.

2. Lymphadenopathy

- Causes:
  - Infiltration of lymph nodes by HIV (may present as persistent generalized lymphadenopathy-PGL).
  - Infections: tuberculosis, disseminated atypical mycobacterial infections, viral infections such as CMV, Epstein-Barr Virus (EBV).
  - Malignancies like lymphoma and lymphosarcoma.
  - Persistent Generalized Lymphadenopathy (PGL) WHO Definition:
    - Swollen or enlarged nodes >1 cm at 2 or more noncontiguous sites.
    - Without known cause.
    - Definitive diagnosis is not required.

3. Respiratory Manifestations

- Pneumonia and chronic lung deseases contribute to the increased morbidity and mortality
- Most children present with recurrent bacterial pneumonias, but in children less than 1 year of age PCP also frequent.
- Other HIV-related chronic lung deseases often have a similar clinical presentation leading to over diagonosis of TB.
- Signs and symptoms: cough, fever, dyspnea, wheezing, ear discharge.
- Recurrent infections: recurrent bacterial pneumonia- Streptococcus pneumonia is the commonest organism.
- Viral causes are common. Other causes include Tuberculosis, Recurrent otitis media and sinusitis and Lymphoid Interstial Pneumonitis
- Opportunistic infections: Pneumocystis jiroveci pneumonia (PCP) causes acute life threatening pneumonitis.

3.1 Lymphoid Interstial Pneumonitis (LIP)

- LIP is common in children occurring in at least 40% of children with perinatal HIV (usually over 2 years of age). It is often mistaken for pulmonary TB (miliary) because of the chronic cough and the *miliary-like* pattern on chest x-ray.
- Etiology: Possibly a co-infection of the lungs by HIV and Epstein Barr Virus (EBV), leading to immune stimulation, lymphoid infiltration and chronic inflammation.
- Clinical symptoms:
  - Patient usually in good general condition despite respiratory distress.
  - Recurrent cough and dyspnoea
  - Usually associated with parotid enlargement, generalized lymphadenopathy, and hepatosplenomegaly.
  - Clubbing of fingers may be present.
  - Poor response to TB therapy
  - Terminally chronic lung disease with hypoxia
- Chest Examination: Normal or minimal rales.
- CXR: Diffuse bilateral reticulonodular or interstitial infiltrates may appear similar to miliary TB, bilateral hilar or mediastinal lymph node enlargement.
- WHO diagnostic criteria: Diagnosed by CXR
  - Bilateral reticulonodular interstitial pulmonary infiltrates present for more than 2 months.
  - No response to antibiotics.
  - No other pathogen found.
  - Oxygen saturation persistently <90%.
  - May present with cor pulmonale and have exercised induced fatigue.
- Management:
  - Steroids for significant respiratory distress (exclude TB first): Prednisone 2mg/kg/day initially for 4 weeks daily, then alternate day maintenance for 2 to 3 months and review.
  - Oxygen therapy during episodes of hypoxia.
  - Bronchodilators (e.g., salbutamol) where wheezing is a problem.
  - Antibiotics during episodes of concurrent super-infection with pneumonia.
  - Chest physiotherapy and postural drainage, if there is secondary bronchiectasis.

3.2 Chronic HIV-associated lung disease (including bronchiectasis)

- Clinical diagnosis: History of cough productive of copious purulent sputum with or without clubbing, halitosis and crepitations and/or wheezes.
- Definitive diagnosis: CXR confirms with honeycomb appearance (small cysts) and/or persistent areas of opacification and /or widespread lung destruction, with fibrosis and loss of volume.

4. Neurological Manifestations

- HIV is a neurotropic virus that invades CNS by infecting monocytes, which cross the blood-brain barrier and establish HIV infection in macrophages and microglial cells.
- Neurological symptoms are widely prevalent, occuning at all stages of HIV infection and affecting any part of the nervous system.
- About 40% to 70% of HIV-infected persons develop symptomatic neurological disturbances, but the brain is most commnly affected in children
- Delay in reaching developmental milestones may be an early indication of HIV infection.
- Encephalopathy and developmental delay are common in HIV-infected children and indicate advanced clinical desease. Encephalopathy may be progressive or static encephalopathy

- Presentation of encephalopathy: Failure to attain or loss of motor and intellectual milestones
- Impaired brain growth: microcephaly
- Motor deficits, abnormal reflexes, spasticity, cerebellar and extra pyramidal signs
- Emotional lability, hyperactivity and lethargy
- Developmental delay is common (esp. gross and fine motor and language skills)
- CT findings: Cerebral atrophy; progressive multifocal leukoencephalopathy
- Causes: CNS infiltration by HIV itself, bacterial infections such as pyogenic meningitis, opportunistic infections like toxoplamosis, CMV, cryptococcal meningitis, TB meningitis, malignancies

- WHO Diagnostic Criteria: At least one of the following, progressing over at least two months in the absence of another illness:
  - failure to attain, or loss of, developmental milestones, loss of intellectual ability; or
  - progressive impaired brain growth demonstrated by stagnation of head circumference; or
  - acquired symmetric motor deficit accompanied by two or more of the following: paresis, pathological reflexes, ataxia, gait disturbances.

- Management:
  - Exclusion of opportunistic infection.
  - ART using anti-retrovirals with good CNS penetration i.e. zidovudine, stavudine or nevirapine.
  - Symptomatic treatment may be needed in addition (ie. physiotherapy, surgery for contractures).
  - Valproate is the drug of choice to treat seizures in children on ART, since it has the least drug interactions.

- Acute neurological episode
  - Meningitis or encephalitis presenting with altered fever, altered sensorium, seizures and focal deficits.
  - See Chapter 8 for specific OI management.

- Peripheral neuropathy (often drug related, can be caused by HIV itself).
  ~ Management:
  - Stop offending agent, if due to drug toxicity.
  - Treat with analgesics (especially NSAIDS), Amitryptiline, Carbamezapine or Lamotrigine

5. Gastrointestinal and Hepatobiliary

A. Diahrrea

- Acute diarrhea is the most common cause of morbidity.
- It is the leading cause of death in HIV–infected children during the 1st year of life.
- Diarrhea tends to be prolonged and is usually complicated by dehydration and malnutrition
- Causes: Common infections, opportunistic infections (bacteria, virus, protozoa, fungi), malabsorption, inflammatory processes, HIV enteropathy.

Management of Acute diarrhea

- Caregivers to administer available home fluids immediately upon onset of diarrhea.
- Start ORS at home for mild to moderate dehydration.
- Consider Resomal ORS for severe malnutrition with acute diarrhea.
- Severe dehydration: Hospitalize and Intravenous fluid therapy.
- Signs of bacterial infection: fever, blood in the stool.
- Stool microscopy and start antibiotics if indicated.
- Provide Zinc supplementation for 10 days (10 mg if < 6 months of age, 20 mg if > 6 months of age)
- Emphasise continued feeding or increased feeding during and after the diarrhoeal episode.

Management of Persistent or Recurrent Diarrhea

- Hospitalization.
- History: Frequency and nature of stools, urination, nutrition history including mode of feed preparation and administration, other illnesses.
- Physical examination: Signs of dehydration, malnutrition and other illnesses.
- Investigations: Stool microscopy and culture, full septic screen if possible with blood, urine and stool cultures, CBC, electrolytes, blood sugar, urea and chest x-ray.
- Examine and investigate child for non-intestinal infections and treat appropriately.
- Give empiric broad spectrum antibiotics, antipyretics for fever, treat specific aetiological agent if found.
- Management of dehydration: As for acute diarrhea, with oral/IV fluids. Correct electrolyte imbalance.
- Management of malnutrition: Emphasize continued feeding with locally available food during and after the diarrhoeal episode
- Prevent hypothermia.
- Prevent/treat hypoglycemia.
- Counseling mothers/caregivers regarding food hygiene and dietary management.

B. Hepatomegaly:

- Hepatomegaly within 3 months of age in perinatally acquired infection is associated with rapid progression of disease.
- Causes: HIV replication in reticulo-endothelial tissue, fatty infiltration, malnutrition, viral hepatitis: Hepatitis A, Hepatitis B, Hepatitis C (rare in pediatrics), CMV.
- Drug toxicity.

Other HIV-Related Conditions (for Opportunistic Infections see Chapter 8)

NUTRITIONAL CARE

Malnutrition and cachexia are characteristic signs of HIV infection. Malnutrition in turn aggravates the disease and increases susceptibility to opportunistic infections, thus starting a vicious cycle. See Chapter 7 for detailed feeding information.

MANAGEMENT OF MALNUTRITION

1. Detection of malnutrition.
   - Deviations in linear growth and weight may be apparent as early as 3 months of age.
   - Marasmus is more common than kwashiorkor in HIV-infected children.
   - Hence maintenance of growth charts during follow-up is important.

2. Evaluate and treat the underlying causes:
   - Decreased food intake: Due to anorexia, illness, oral ulcers and thrush.
   - Increased nutrient loss: Due to malabsorption, diarrhea, HIV enteropathy.
   - Increased metabolic rate: Due to OI , esp. TB, other infections and HIV infection itself.
   - Chronic systemic diseases.
   - Poverty and lack of knowledge of the caregiver regarding nutrition.

3. Dietary management:
   - Ensure high calorie and protein intake. Child should be fed at least five times per day, with the usual home foods modified to contain 2-3 gm/kg/day of protein.
   - Ensure adequate supplementation of micronutrients like vitamins, potassium, magnesium, zinc, copper, selenium, and iodide.
   - Initiate iron supplementation after the child's appetite improves and infections have been treated.

4. Children with severe malnutrition may need hospitalization for management of:
   - Hypoglycemia with IV 10% Dextrose followed by 3 hourly high calorie liquid diet.
   - Follow WHO Guidelines for Management of Severe Malnutrition.
   - Dehydration-IV fluids / ORS.
   - Hypothermia.
   - Infections.
   - After successful treatment for severe malnutrition consider ART initiation. See Chapter 6.

C. PAROTITIS

- Recurrent or chronic painless unilateral or bilateral parotid swelling.
- Causes: HIV infiltration, lymphocytic infiltration.
- Parotitis is associated with a more favorable outcome.

D. ORAL MANIFESTATIONS

- Thrush (Candidiasis).
- Periodontitis.
- Ulcerative gingivitis.
- Oral hairy leukoplakia.
- Oral or oesophageal ulcerations.

6. Skin Manifestations

INFECTIOUS DISORDERS AND LESIONS	NON-INFECTIOUS DISORDERS AND LESIONS
Viral Infections: Herpes simplex, Herpes zoster, Molluscum contagiosum, Warts	Seborrheic dermatitis Atopic dermatitis Generalized dermatitis Nutritional deficiency Eczema Psoriasis Drug eruptions Vasculitis Alopecia
Fungal Infections: Candida Tinea Onychomycosis	
Bacterial: Impetigo	
Other: Scabies	

7. Haematological Manifestations

a. Anemia

- Etiology: Nutritional, bone marrow suppression by HIV virus or other opportunistic infection (ie. TB), drug side effect (ie. most commonly ZDV).
- Management.
  - Iron, Vitamin B_{12} and folic acid supplementation for nutritional anemia.
  - ZDV induced anemia treated with drug substitution (ie. d4T).
  - Erythropoietin for impaired reticulocyte response, where available and affordable.

b. Thrombocytopenia

- Etiology: Most commonly from bone marrow suppression by HIV itself.
- Management.
  - ART
  - Corticosteroids for platelet counts < 20,000/mm^3 or active bleeding
  - IVIG may be helpful, where available and affordable.

c. Neutropenia common side effect of ZDV (bone marrow suppression).

d. Lymphopenia with CD4, CD8 Depletion

e. Eosinophilia

8. Cardiovascular Manifestations

- Subclinical persistent disease common.
- Cardiomegaly, cardiomyopathy, conduction disturbances, pericardial effusion, endocarditis seen.
- Hemodynamic instability due to autonomic neuropathy.
- Causes: TB related disease (ie. pericarditis) most common followed by HIV itself other possibilities include immune-mediated causes, other intercurrent infections or drug toxicity.
- Diagnosis: CXR, EKG, Echocardiography.
- Management:
  - Vasodilators (ACE inhibitors), diuretics and digoxin used in that order.
  - Other measures include restriction of activity, fluid and salt restriction, correction of anemia.
  - Some patients improve with ART.

9. Nephropathy

- More often seen in older children with symptomatic disease.
- Most common presentation-Nephrotic syndrome-proteinuria, oedema, oliguria with normal blood pressure.
- Others: haematuria, hypertension, renal tubular acidosis, acute renal failure, end stage renal disease.
- Various underlying renal pathology eg. minimal lesion glomerulonephritis, focal segmental glomerulosclerosis, IgA nephropathy.
- Causes: Immune-mediated, direct viral infection, drug-induced.

10. Malignancy

- Less frequent and different from than those in adult AIDS.
- Most common: Non Hodgkin's lymphoma, CNS lymphoma, leiomyoma, EBV associated leiomyosarcoma and leukemia.
- Kaposi's sarcoma very rare in children.

TABLE: 4.1 **WHO CLINICAL STAGING OF HIV FOR INFANTS AND CHILDREN WITH ESTABLISHED HIV INFECTION (Details of definitions are given in annex 3)**

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 respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis)
Fungal nail infections
Angular cheilitis

Clinical Stage 3
Moderate unexplained malnutrition not adequately responding to standard therapy
Unexplained persistent diarrhoea (14 days or more)
Unexplained persistent fever (above 37.5 intermittent or constant, for longer than one month)
Persistent oral candida (after first 6 weeks of life)
Oral hairy leukoplakia
Acute necrotizing ulcerative gingivitis/periodontitis
TB lymphadenitis
Pulmonary tuberculosis
Severe recurrent presumed bacterial pneumonia
Symptomatic lymphoid interstitial pneumonitis
Chronic HIV-associated lung disease including bronchiectasis
Unexplained anaemia (<8g/dl), neutropenia (<500/mm^3) or chronic thrombocytopenia (<50 000/ mm^3)

Clinical Stage 4
Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy
Pneumocystis pneumonia
Recurrent severe presumed bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)
Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration or visceral at any site)
Extrapulmonary tuberculosis
Kaposi sarcoma
Oesophageal candidiasis (or candida of trachea, bronchi or lungs)
Central nervous system toxoplasmosis (outside the neonatal period)
HIV encephalopathy
Cytomegalovirus (CMV) infection; retinitis or CMV infection affecting another organ, with onset at age over 1 month.
Extrapulmonary cryptococcosis (including meningitis)
Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis)
Chronic Cryptosporidiosis (with diarrhea)
Chronic Isosporiasis
Disseminated non-tuberculous mycobacteria infection
Acquired HIV-associated rectal fistula
Cerebral or B cell non-Hodgkin lymphoma
Progressive multifocal leukoencephalopathy
HIV-associated cardiomyopathy or nephropathy

4.4 WHO HIV Staging in Children Using Clinical and Immunological criteria

Staging is a standard method of assessing disease stage/progression and of making treatment decisions. It is important to stage children with HIV infection in order to:

- Predict mortality in HIV-infected chlidren not yet on ART.
- Decide when to start co-trimoxazole and
- Decide when to start ART in combination with CD4 assessment where available.

4.4.1 WHO HIV Staging in Children Using Clinical criteria

TABLE 4.2: WHO Classification of HIV-associated Clinical Disease

CLASSIFICATION OF HIV-ASSOCIATED CLINICAL DISEASES	WHO CLINICAL STAGE
Asymptomatic	1
Mild	2
Advanced	3
Severe	4

4.4.2 Using Immunological Criteria

CD4 COUNTS

- CD4 (absolute count or %) is the best measurement to assess immune deficiency.
- The CD4 count should be used in conjunction with clinical assessment; however, CD4 count allows early detection of worsening of HIV disease, as the CD4 count usually falls before clinical progression takes place.
- Absolute CD4 count counts (and less so CD4%) fluctuate within an individual and values vary with intercurrent illness, physiological changes.
- CD4% is the preferred measurement in children <5 years old, as absolute count is less reliable in young children .
- CD4 monitoring can aid in the decision to initiate ART or switch to another ARV drug.

TABLE 4.3: Immunological Staging: WHO Classification of HIV-associated immunodeficiency

CLASSIFICATION OF HIV-ASSOCIATED IMMUNO DEFICIENCY	AGE-RELATED CD4 VALUES			
	≤ 11 mo (%)	12 - 35 mo (%)	36-59 mo (%)	≥ 5 yrs (/mm³)
Not significant	> 35	> 30	> 25	> 500
Mild	30 - 35	25 - 30	20 - 25	350 - 499
Advanced	25 - 30	20 - 25	15 - 20	200 - 349
Severe	< 25	< 20	< 20	< 200 *or* < 15%

Note: *The TLC is an option that is used only if CD4 measurement is not available in children with WHO clinical stage 2 desease. It cannot be used in asymptomatic children. The TLC is also not useful for monitoring ART.*

chapter 5

Management of HIV-Exposed and infected infants and Children

Introduction

The care of children with HIV is a complex undertaking. Ideally, a comprehensive care team should be available, including physician, nurse, pharmacist, social worker and mental health professional.

- All children born to HIV-infected mothers or exposed to HIV infection by any other route should be managed as HIV-infected until the diagnosis is clarified by appropriate tests
- All aspects of the health of the HIV-infected child must be managed including treatment of HIV infection and its complications, opportunistic infections, preventive therapy, growth and development, immunization, nutrition and counseling.

5.1 Definition of "HIV-exposed"

1. Children born to mothers with HIV until HIV infection in the child is excluded by age appropriate tests.
2. Children breastfeeding from HIV infected mothers until HIV infection in the child is excluded,
   - by negative virological tests (<18 months of age) at least 6 weeks after cessation of all breastfeeding OR
   - by negative antibody tests (beyond 18 months of age) at least 6 weeks after cessation of all breastfeeding

All HIV- exposed children should be managed as if HIV infected until the HIV status of the baby is determined by age- appropriate tests.

5.2 Immediate newborn care of all babies born to HIV-infected mothers

- Clamp cord immediately after birth and do not milk the cord.
- Clean injection site well before infant injections or invasive procedures are performed (ie. Vitamin K injection or IV line placement).
- Maintain universal precautions: Wear gloves to handle the baby. Dispose of all needles properly. Avoid mouth operated suction devices.

5.3 Antiretroviral prophylaxis

- Must be provided to all babies born to HIV-infected women.
- For more details refer to the latest Nepal National PMTCT Guidelines (Chapter 2)

5.4 Cotrimoxazole prophylaxis

OI prevention alone has proven to considerably reduce HIV-related mortality and morbidity associated with malaria, bacterial diarrheal diseases and pneumonia, in addition to the prevention of PCP and toxoplasmosis, particularly in children below 1 year of age.

5.4.1 Timing of Initiation of CTX in Relation to Initiation of ART

Since the most common initial side effect of CTX and ART (especially nevirapine and efavirenz) is rash, it is recommended to start CTX prophylaxis first and initiate ART two weeks later if the individual is stable on CTX and has no rash.

TABLE 5.1 Initiation of Co-trimoxazole prophylaxis in HIV exposed children

HIV – EXPOSED INFANT AND CHILDREN

CTX prophylaxis is universally indicated, starting at 6 weeks after birth and maintained until cessation of risk of HIV transmission and exclusion of HIV infection.

TABLE 5.2: Cotrimoxazole Prophylaxis for HIV infected children: When to start and stop

SITUATION	START	DISCONTINUE
All HIV-infected infants < 12 mo of age	Regardless of CD4 count or clinical status	Until age 5 yrs and then reassess as below
1-5 years.	1. All Symptomatic (WHO Stage 2, 3 or 4) regardless of CD4 count 2. Any WHO stage and CD4 <25%	Until age 5 yrs and then reassess as below
When CD4 count not available ≥ 5 years.	All Symptomatic (WHO Stage 2, 3 or 4)	If not on ART, Do not discontinue If on ART:* - Absence of clinical symptoms after at least 1 year of ART - With good adherence and secure access to ART
When CD4 count available ≥ 5 years.	Any WHO clinical stage and CD4 <350/mm^3 Or WHO clinical stage 3 or 4, irrespective of CD4 level	If not on ART, Do not discontinue If on ART:* - CD4 > 350 cells /mm^3 after at least 6 months of ART*
If history of PCP (secondary prophylaxis)	At initial visit	Do not discontinue
Presumptive symptomatic HIV disease	At any age	Until HIV infection can be excluded

**Recommence Cotrim prophylaxis if the CD4 count falls below the initial threshold or if new or recurrent WHO clinical stage 2, 3, or 4 conditions occur*

TABLE 5.3 CTX formulations & dosage for HIV-infected/exposed infants and children

RECOMMENDED DAILY DOSAGE	SUSPENSION SYRUP (5 ml 200 mg /40 mg)	PAEDIATRIC TABLET (100 mg/20 mg)	SINGLE STRENGTH ADULT TABLET(400 mg/ 80 mg)	DOUBLE STRENGTH ADULT TABLET(800 mg/ 160 mg)
< 6 months	2.5 ml	One tablet	¼ tablet, possibly mixed with feeding	——
6 months – 5 years	5 ml	Two tablets	Half tablet	——
> 6 – 14 years	10 ml	Four tablets	One tablet	Half tablet
> 14 years	——	——	Two tablets	One tablet

Frequency - once a day

5.4.2 Adverse Reactions to Cotrimoxazole

- Hypersensitivity: Most common form is maculopapular rash. Severe form manifests as Stevens Johnson syndrome. This is very rare in children. Enquire about mucosal and eye symptoms. Mild to moderate rashes need only symptomatic treatment like antihistamines and repeated observation.
- Dapsone is the best alternative for prophylaxis at 2mg/kg/day orally, maximum dose 100mg/day. Ideally, screen for G6PD deficiency. Dapsone is less effective in the prevention of toxoplasmosis and also lacks the broad antibacterial activity of cotrimoxazole.
- Hematological toxicity (bone marrow suppression)
- Renal toxicity
- Hepatic toxicity

5.4.3 Monitoring of CTX prophylaxis

- Clinical monitoring of children on CTX should be performed by health staff at the site of CTX provision at three monthly intervals, followed by laboratory investigations or referral, as required.
- Caregivers should be provided with information on how to recognize common CTX reactions such as jaundice and rash and to stop the drug and report to the nearest clinic, should they occur.
- For those children who are already under laboratory monitoring for HIV care or ART, no additional laboratory tests are needed.

5.5 Early Confirmation of Diagnosis

- HIV infection status should be confirmed with the best age-appropriate test that is available as early as possible.
- The diagnostic criteria differ for children below and above 18 months of age due to the placental transfer of maternal HIV antibodies. See Chapter III.

5.6 Clinical and immunological staging

5.6.1 Clinical staging

Once the diagnosis of HIV infection is confirmed, staging according to WHO Pediatric Staging guidelines, and assessment of the baseline health status must be done.

a) History

- Mode of HIV acquisition.
- History of past illnesses and treatments .
- Symptoms related to HIV infection and its complications.
- Family history including socio-economic status, HIV status of family members and assessment of the possible level of care from the family or other caregivers.

b) Physical Examination

- At the initial presentation, thorough general and systemic examination to assess signs of HIV infection and its complications must be completed.
- Nutritional status and growth and development must be followed closely.

c) Screening

For TB, other co-infections and treatable HIV-related diseases and opportunistic infections as clinically indicated.

5.6.2 Immunological Staging

a) CD4 absolute count and CD4 % if available.

b) TLC if CD4 is unavailable.

c) At the time of initiation of antiretroviral therapy, a baseline Viral Load, if available, is helpful to monitor future response to therapy. However, it should not be used as criteria for ART initiation decisions.

d) Clinical and /or immunological staging are necessary for evaluating the present and future course of HIV disease, decisions regarding CTX prophylaxis, ART initiation and changes and imunization.

5.7 Feeding advice

- Parents / Caregivers need to decide the best method of feeding their HIV-exposed child.
- See chapter 7 on Infant feeding policy and nutrition for details.

5.8 Immunization advice

- See chapter 9 Immunization of children exposed/infected with HIV for details.

5.9 Nutritional advice

- Malnutrition and cachexia are characteristic signs of HIV infection. Malnutrition in turn aggravates the disease and increases susceptibility to opportunistic infections, thus starting a vicious cycle. See Chapter 7 for detailed feeding information and Chapter 4 for management of malnutrition.

5.10 Regular monitoring

- Early detection and management of onset of symptoms suggestive of AIDS allows for timely initiation of anti-retroviral therapy
- Monitoring adherence and toxicity of Cotrimoxazole prophylaxis.
- Feeding and immunization advice
- Growth and development monitoring

Table 5.4: Recommended schedule of follow-up visits for HIV exposed and HIV infected children

Birth	Infant feeding counseling
6 - 14 weeks of age	At 6, 10 and 14 weeks at the time of immunizations (reinforce infant feeding counseling)
14 weeks to 1 year of age	Monthly
1 year of age and older	Every 3 months
18 months of age	Confirmatory HIV Antibody test
Child is sick	Anytime

5.10.1 History Taking

- Birth history.
- Mode of feeding including method of preparation .
- Enquire about parents' health and what HIV care and support they are receiving.
- Ask about history of tuberculosis in the family
- Enquire about symptoms suggestive of HIV infection

5.10.2 Physical Examination

- Thorough general and systemic examination
- Growth assessment: Weight, Height / Length
- Head Circumference if less than 2 years old

5.10.3 Ill child

- If child found to be symptomatic at any visit proceed with the best available HIV diagnostic evaluation (Chapter 3.).
- If found or suspected to be HIV-infected, see management plan in Chapter 5
- Investigate and treat current illnesses: See Chapter 4 and 8

5.10.4 Counseling

- Counsel caregivers on follow-up and testing plan for HIV exposed infants as described above
- Counsel caregivers on Cotrimoxazole prophylaxis including reasons for medication, proper administration

and dosing, potential side-effects and length of continuation of prophylaxis.
- Counsel caregivers on early warning signs of illness in HIV exposed children with a plan on how to seek appropriate care
- Ongoing feeding counseling is necessary for all, regardless of which feeding option was initially chosen.

5.11 Growth and development

- Assess growth and development in the initial evaluation
- Growth and development monitoring in subsequent follow-up is essential
- Growth failure is one of the most sensitive indicators of disease progression
- Linear growth failure occurs before clinical wasting.
- Growth and development charts with recording of anthropometric measurements must be maintained meticulously.
- Neurological state should also be assessed

Table 5.5: Develpomental Red Flags signs

Age	Development problems
Birth to 3 months	Failure to alert to environmental stimuli Rolling over before 3 months (indicative of hypertonia), Persistent fisting at 3 months
4 – 6 months	Poor head control, failure to smile, failure to reach object by 5 months
6 – 12 months	No babbling sounds, inability to localize sounds by 10 months
12 – 24 months	Lack of consonant production, hand dominance prior to 18 months (indicates contralateral weakness)
Any age months	No imitation of speech and activities by 16 months Loss of previously attained milestones

5.12 Management of common infections

Provide early and vigorous therapy for common Paediatric infections

- All infants with HIV antibodies should be treated vigorously for common Paediatric infections such as pneumonia, otitis media and diarrhea
- These diseases may be more persistent, severe, poorly responsive to therapy and severe complications may develop.
- All HIV-infected children should be taken urgently for examination and treatment whenever symptoms of such infections develop.
- Other HIV-related conditions (for Opportunistic Infections see Chapter 8)

5.13 Antiretroviral Therapy

- If indicated by clinical and immunological stage, ART should be started and the child is then followed up accordingly (see Chapter 6). Child will also need concomitant CTX, see guidelines above.
- If ART is not indicated, CTX prophylaxis is started as per guidelines and child is continued to be monitored as per the schedule below.

5.14 Follow-up of those infected and not on ART

Regular follow-up must be done at each visit:

- for early detection of cases requiring ART.
- for management of HIV related and other intercurrent illnesses.
- to ensure patient compliance with the treatment esp. CTX prophylaxis.
- to monitor treatment outcome and side effects,
- to monitor growth and development and provide other routine care and.
- for counseling
- During the course of follow up whenever indicated by clinical and immunological criteria, ART should be started promptly as per guidelines (see Chapter 6).

TABLE 5.6: Clinical and Laboratory Monitoring Schedule for HIV-infected Children not on ART

PARAMETER	SCHEDULE
Clinical review with history and physical examination[1] (see check list of signs and symptoms below)	Initial visit, Then monthly for children <12 months of age 3 monthly thereafter
HIV Diagnostic tests	Initial visit (baseline); then if and when required for age appropriate confirmatory test
CD4 Counts (If available)	First visit (baseline) Then 6 monthly More frequently, if counts are reducing rapidly or WHO clinical stage 2, 3 or 4 symptoms develops
Complete blood count HB, TLC, Differential count	Baseline Then 3-6 monthly
Urine routine exam	Baseline Then if and as indicated
Liver enzymes	Baseline Then if and as indicated
Renal function tests	If and as indicated
Chest X-Ray	If and as indicated
Cardiological assessment	If and as indicated
Ophthalmological assessment	If and as indicated
Pregnancy test (for adolescent girls)	At baseline Then if and as indicated
Mantoux test	Annually
Dental check up	Annually
Adherence to treatment/CTX prophylaxis	Every visit

1. Medical history and clinical review of (new) symptoms and signs, including medication use, side effects, complications. For each visit assess the clinical stage of HIV infection (WHO clinical stage) and the need for ART and/or prophylaxis

TABLE 5.7: Checklist for taking medical history in children not on ART

- When and where was the diagnosis of HIV made
- What is this child's possible source of HIV infection
- What are the current symptoms and concerns of the child
- Past medical history of symptoms, known diagnoses and treatments given including traditional remedies
- Known allergies to drugs or other substances
- History of past recurrent infections
- History of possible contact with TB
- Current and prior opportunistic infection (OI) prophylaxis
- Previous ART
- Attitude to and readiness to commence ART
- Ability of the caregiver to adhere to OI prophylaxis and other drugs (such as TB therapy) in the past
- Ability to keep scheduled appointments in the past
- Family history (e.g. other immediate family members esp. mother) with known HIV infections and their state of health
- Psychological, financial and family support status
- History of drug and alcohol use in older children

TABLE 5.8: Checklist for symptoms and signs

	SYMPTOMS	SIGNS AND PHYSICAL EXAMINATION
General	Fever Fatigue Appetite changes Failure to thrive	Body weight, height, Head circumference (for infants<2yrs.) Temperature Lymphadenopathy Pallor Parotitis
Cutaneous manifestations	Rash Pruritis	Skin rash, herpes zoster (current or past), papular pruritis eruptions (PPE), diffuse skin dryness, etc
Oropharyngeal manifestations	Pain, odynophagia Dysphagia	Candidiasis Oral hairy leucoplakia (OHL) Mouth sores
Gastrointestinal system	Nausea or vomiting Diarrhoea Abdominal pain	Jaundice Liver and/or spleen enlargement
Respiratory and Cardiovascular systems	Cough Difficulty in breathing Chest pain Dyspnoea	Tachypnoea, respiratoy distress, cyanosis Signs of consolidation, Signs of pleural effusion Cardiomegaly, murmurs
Neurological and musculoskeletal system	Mental and motor developmental abnormalities headache, dizziness, irritability Tingling, numb or painful feet/legs Seizure, Paralysis	Mental state, motor and sensory deficit Microcephaly Signs of raised intracranial pressure
Eye	Any visual changes	Examination of optic fundus: retinitis, papilloedema
Ear, nose, throat	Sore throat Recurrent URTI Discharge from ears	Otitis media Sinusitis Pharyngeal thrush
Functional status: Able to go to school, Ambulatory, Bedridden		

5.15 Pain Management and End of Life Care

- Despite advances in ART and the treatment and prophylaxis of opportunistic infections, some children living with HIV will experience progression of disease.
- As disease advances, the focus of care shifts from preventing disease progression to alleviating symptoms and controlling pain, which is a difficult transition for care providers, especially when caring for children.
- Pain assessment is an important part of caring for children with advanced disease. Chronic pain is often under-treated.
- Concerns about "giving up on" the child, addiction, or diversion of drugs by family members should not interfere with adequate treatment of pain using long acting and potent agents.

5.16 Syndromic approach to common infections

- Clinical management of respiratory problems (Figure 4)
- Clinical management of skin lesions (Figure 5)
- Clinical management lymphadenopathy (Figure 6)
- Clinical management of acute neurological crises (Figure 7)
- Clinical management of oral lesions (Figure 8)
- Clinical management of dysphagia/odynophagia (Figure 9)
- Clinical management of acute diarrhea (Figure 10)
- Clinical management of chronic diarrhea (Figure 11)
- Clinical management of prolonged fever (Figure 12)

Figure 4: Clinical Management of Respiratory Problems

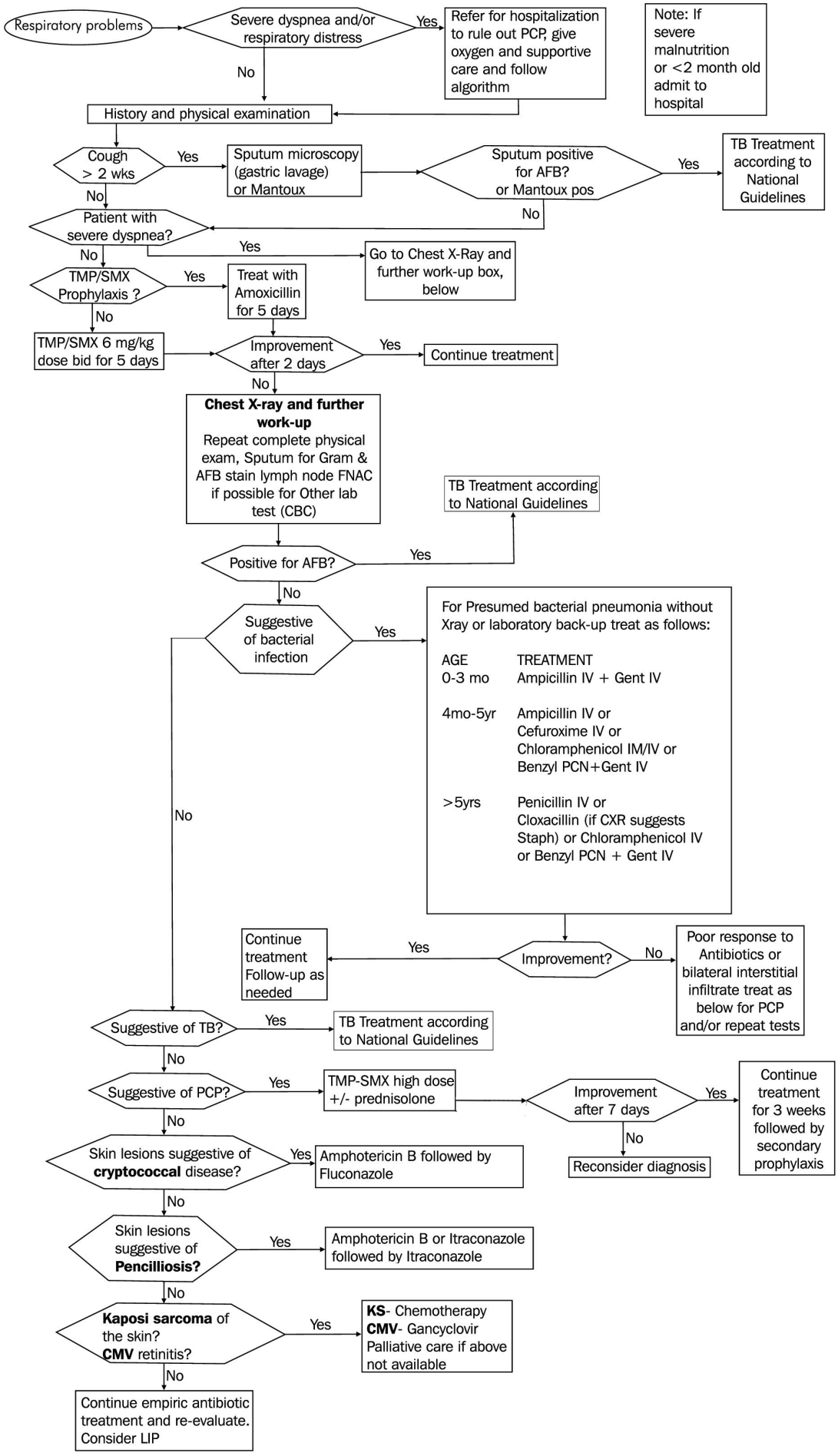


Figure 5: Clinical Management of Skin Lesions

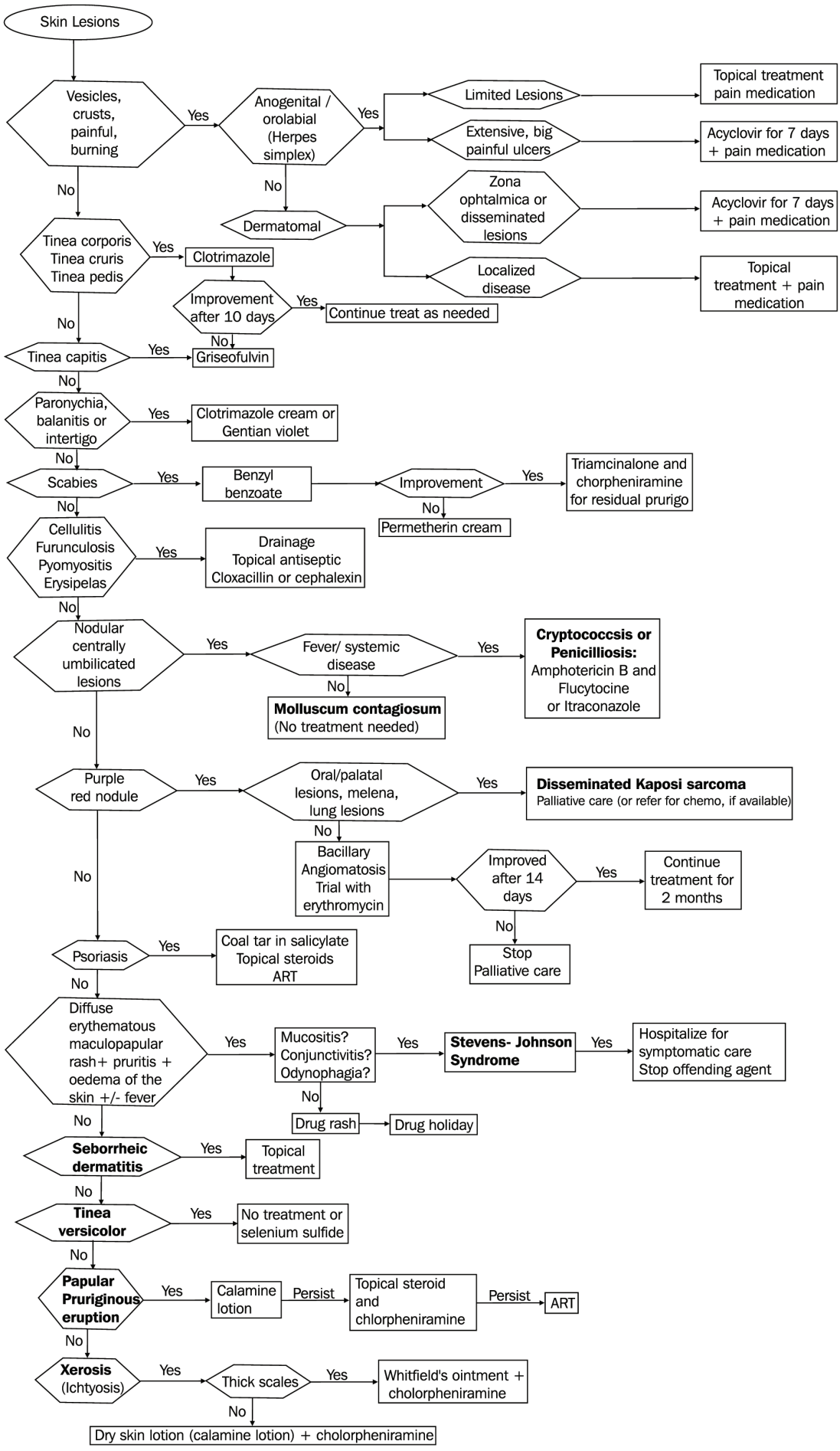


Figure 6: Clinical Management of Lymphadenopathy

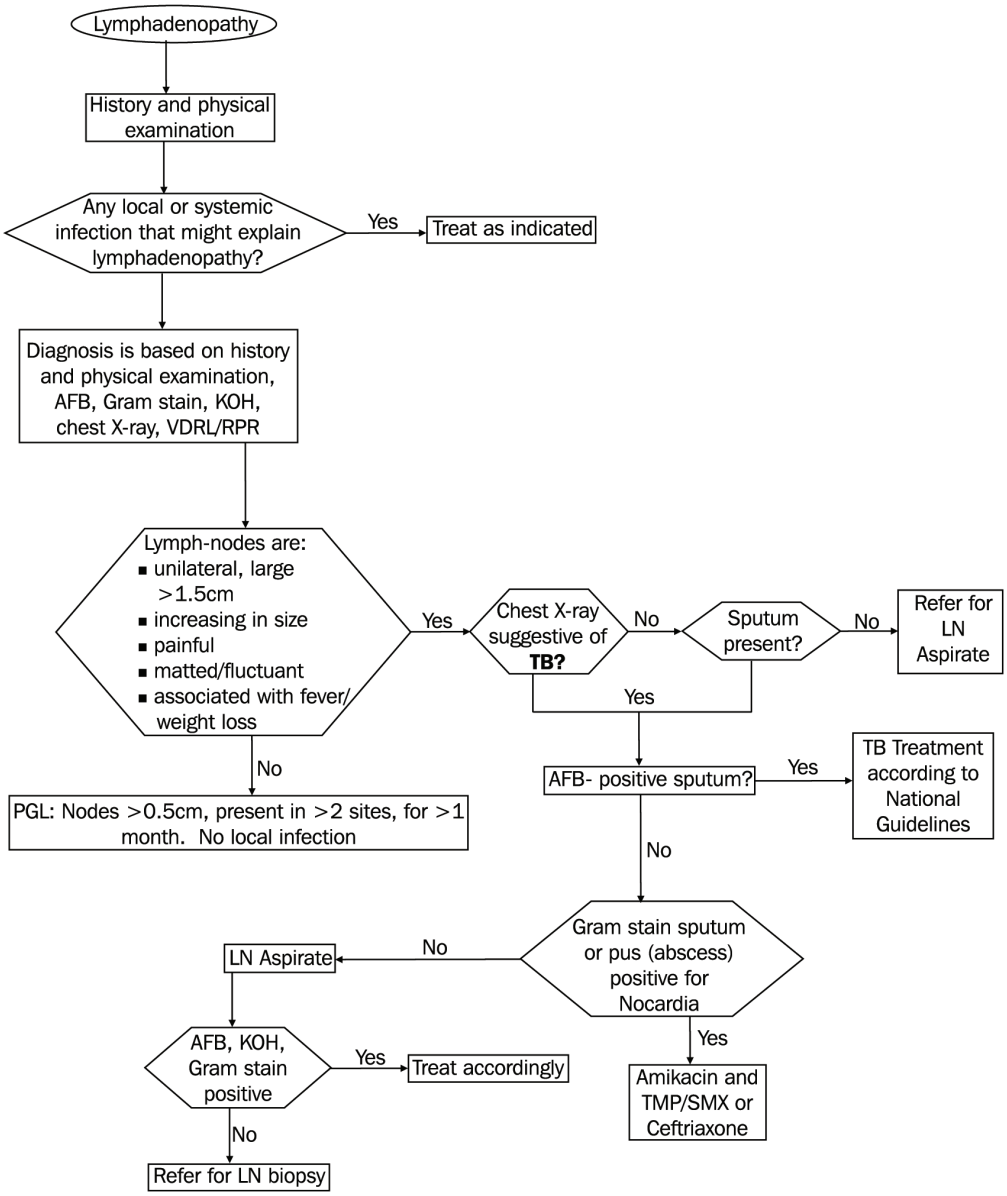


Figure 7: Clinical Management of Acute Neurologic Crises

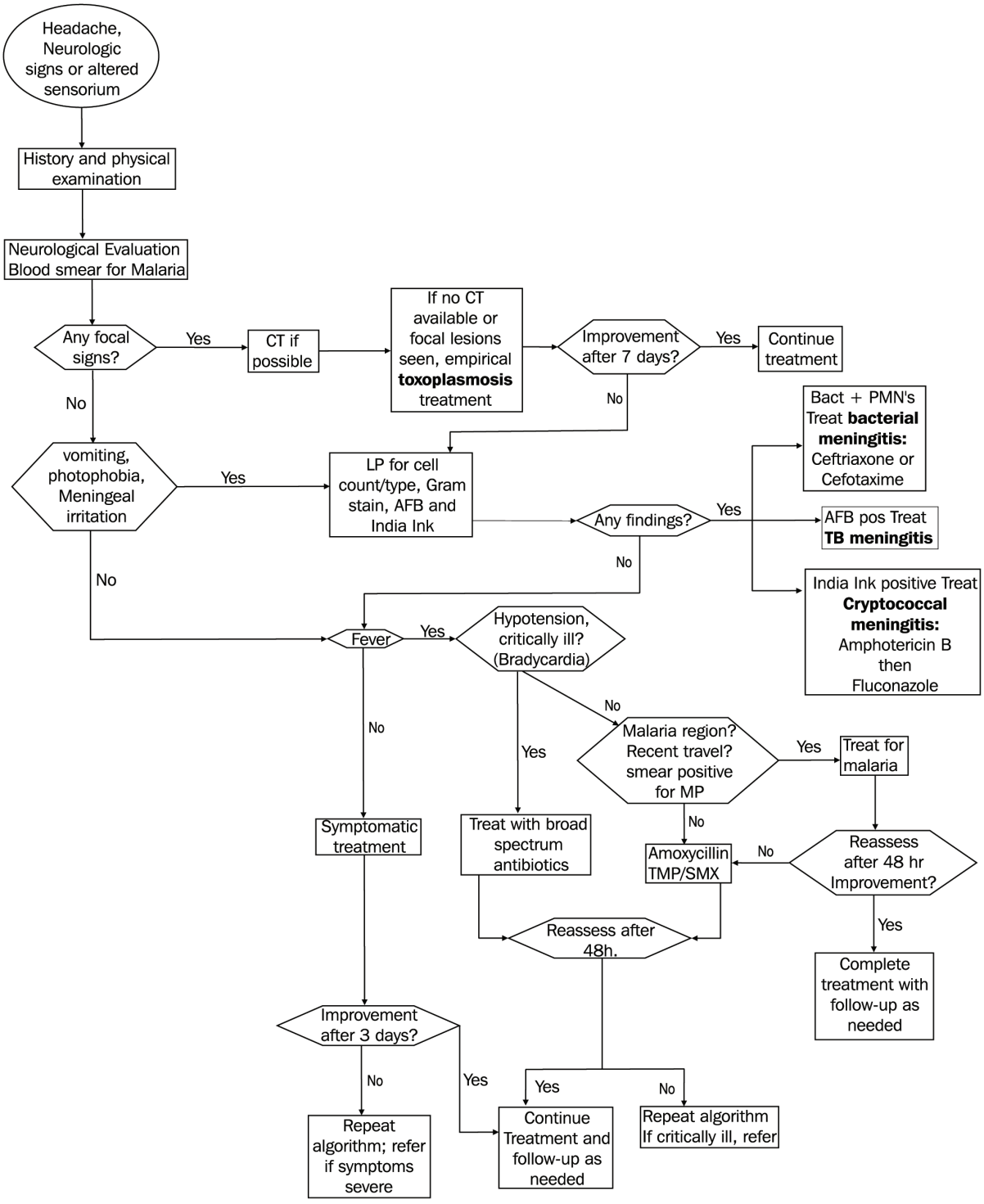


Figure 8: Clinical Management of Oral Lesions

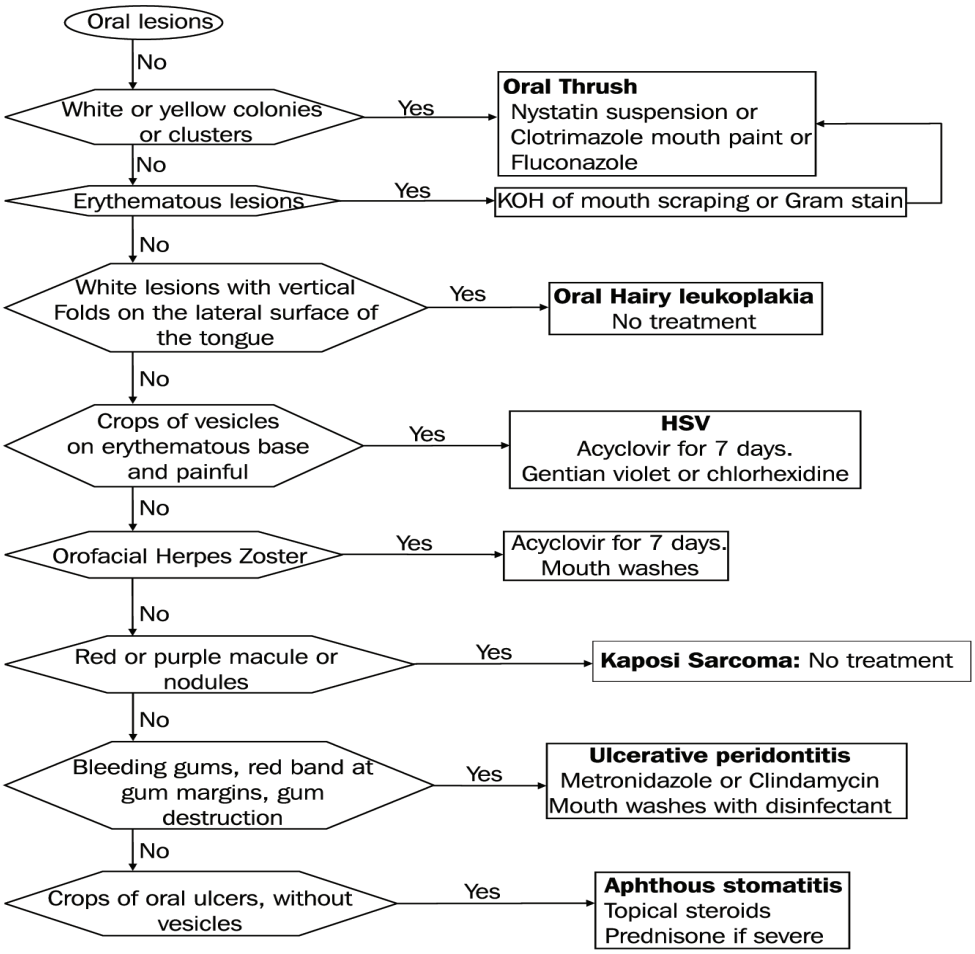


Figure 9: Clinical Management of Dysphagia/ Odynophagia

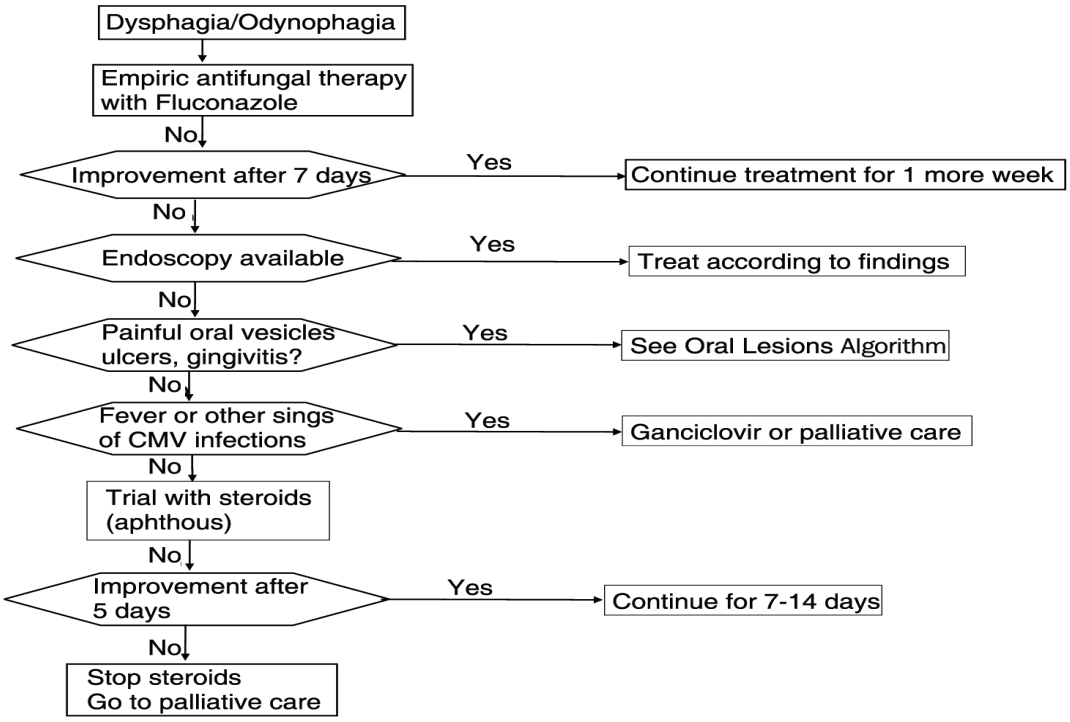


Figure 10: Clinical Management of Acute Diarrhea

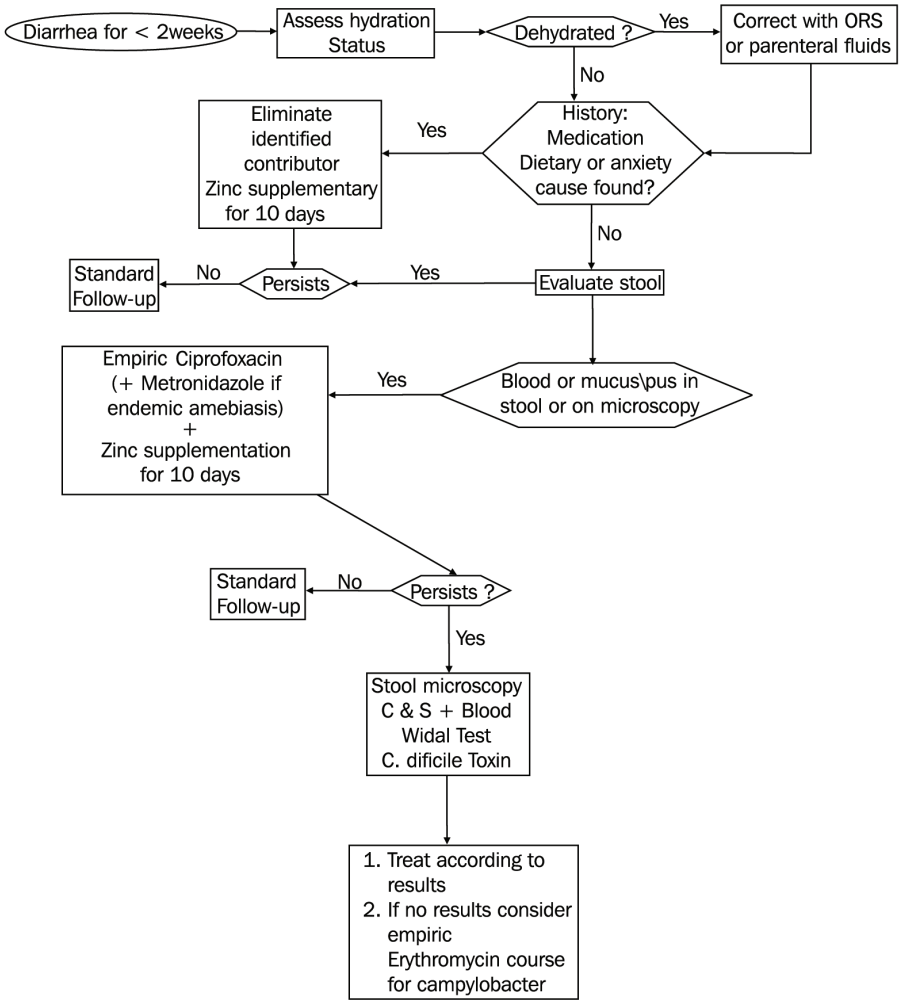


Figure 11: Clinical Management of Chronic Diarrhea

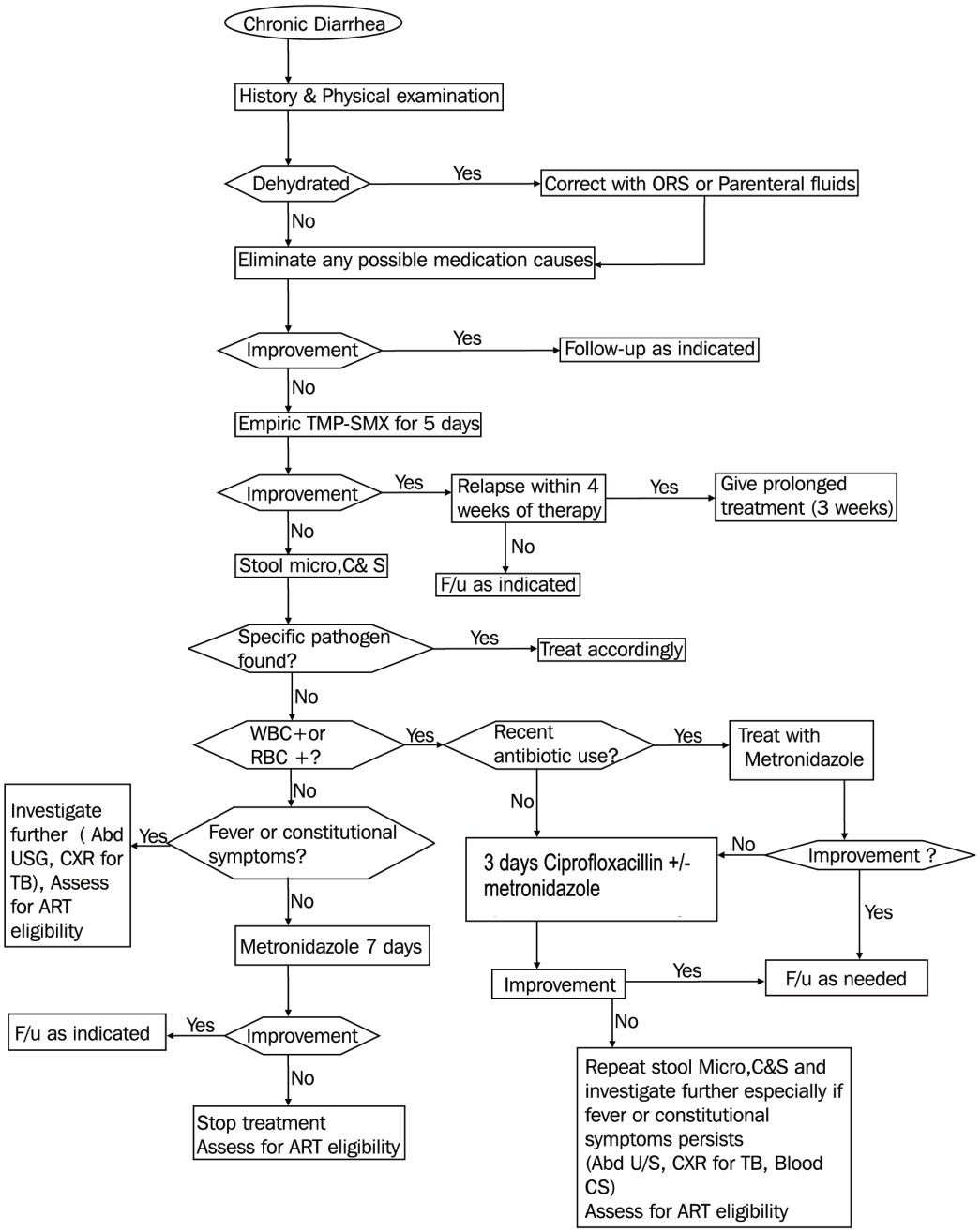
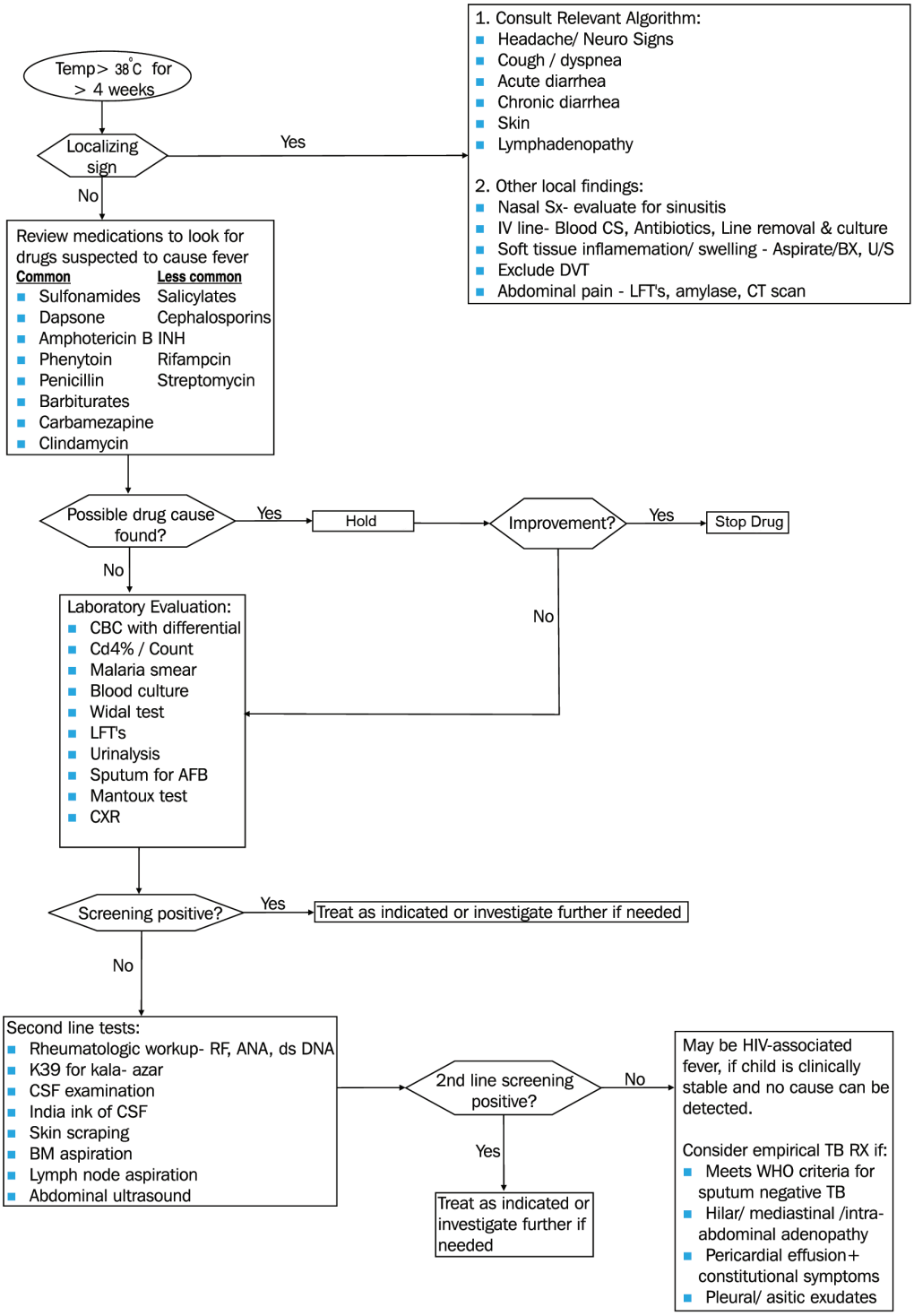


Figure 12: Clinical Management of Prolonged Fever



chapter 6

Anti-Retroviral Therapy (ART) in Infants and Children

6.1 Introduction

The advent of potent antiretroviral therapy has dramatically reduced rates of mortality and morbidity and has improved the quality of life of infants and children living with HIV although it does not provide a cure. As a result HIV/AIDS is now perceived as a manageable chronic illness.

6.2 Indications for starting ART in HIV-Infected Infants / Children:

6.2.1 Under 12 month

- Treat all if DNA PCR is positive, irrespective of clinical or immunological stage.
- Where DNA PCR is not available, ART needs should be based on presumptive clinical diagnosis of severe HIV disease (See Table 6.2)

6.2.2 For Children above 12 months of age

1. Clinical status: Based on WHO Pediatric Clinical Staging
2. Immunological status
   - CD4 Absolute Counts/CD4 %
   - Total Lymphocyte Count in certain clinical situations, where CD4 count is not available
3. For children below 18 months where virological test is not available ART needs should be based on presumptive clinical diagnosis of severe HIV disease

TABLE 6.1: Recommendations for initiating ART in children above 12 months of age

WHO PAEDIATRIC STAGE	AVAILABILITY OF CD4 CELL MEASUREMENTS	TREATMENT RECOMMENDATION
4[a]	CD4[b]	Treat all
	No CD4	
3[a]	CD4[b]	Treat all, CD4 guided in those children with TB[c], LIP, OHL, thrombocytopenia
	No CD4	Treat all[c]
2	CD4[b]	CD4-guided
	No CD4	TLC-guided
1	CD4[b]	CD4-guided
	No CD4[b]	Do not treat

Notes:

LIP - lymphocytic interstitial pneumonia; OHL- Oral hairy leukoplakia; TB - tuberculosis

a. *Stabilize any opportunistic infection prior to initiation of ARV therapy*
b. *CD4 is useful to monitor ART, even if it is not required to initiate therapy*
c. *In children with pulmonary tuberculosis, the CD4 level and clinical status should be used to determine the need for and timing of initiation of ART in relation to tuberculosis treatment*

Presumptive Clinical Severe HIV Disease in Infants/Children <18 months

TABLE 6.2: Criteria for presumptive clinical diagnosis of severe HIV disease in infants and children less than 18 months of age requiring ART in situations where virological testing is not available

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

- The infant is confirmed HIV antibody positive; and
- Diagnosis of any Clinical Stage 4 or AIDS-indicator condition(s) can be made; or
- The infant is symptomatic with two or more of the following:
  - Oral thrush[a];
  - Severe pneumonia[a];
  - Severe sepsis[a].

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

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

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

Notes:

a. As per IMCI definition (See chapter 3, Table 3.2)

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

TABLE 6.3: Recommendations for Initiating ART in children according to age using immunological criteria

IMMUNOLOGICAL MARKER	12-35 MONTHS	36-59 MONTHS	≥ 5 YRS
CD4%*	<20%	<20%	<15%
CD4 Count*	<750 cells/mm3	<350 cells/mm3	<200 cells/mm3
To be used in the absence of CD4:			
Total Lymphocyte Count	<3000cells/mm3	<2500 cells/mm3	<2000 cells/mm3

** Immunologic markers supplement clinical staging. ART should be initiated by these cutoffs, regardless of clinical stage CD4% preferred in children <5 yrs*
All infants less than 12 months of age, should be started on ART regardless of CD4 count or % as there is high risk of death even with high CD4 count or %.
Note: Both CD4 and TLC are subject to considerable variability. If possible obtain two values below threshold before starting ART in Stage 1 or 2.

6.3 Pre-ART assessment

A. Assessment before starting ART

1. HISTORY

- Detailed medical history as per Chapter 5
- Updated information from baseline history
- Socioeconomic status of family
- Caregiver assessment
- Full adherence evaluation with education and counseling is essential. This should be done by a trained counselor prior to writing the first prescription. This often requires 2 or 3 visits to complete well.

2. PHYSICAL EXAMINATION

- Full thorough physical examination (see Chapter 5)
- Growth and nutritional status (weight, height/length, head circumference if <2 years old)
- Neurodevelopmental milestones

3. LABOTORY INVESTIGATION:

- Complete blood count
- Urine examination
- Chest x-ray

- Mantoux test
- Liver enzyme

4. ACUTE INFECTIONS, ESPECIALLY OPPORTUNISTIC INFECTIONS, HIV-RELATED DISEASES AND TUBERCULOSIS SHOULD BE LOOKED FOR AND TREATED BEFORE STARTING ART.

6.4. Classes of antiretroviral drugs

TABLE 6.4:

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTI)	NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTI)	PROTEASE INHIBITORS (PI)	FUSION INHIBITORS	INTEGRASE INHIBITORS	ENTRY INHIBITORS
Zidovudine (ZDV /AZT) Stavudine (d4T) Lamivudine (3TC) Didanosine (ddI) Abacavir (ABC) Emtricitabine (FTC) Tenofovir (TDF)	Nevirapine (NVP) Delavirdine (DLV) Efavirenz (EFV) Etraverine	Saquinavir (SQV) Ritonavir (RTV) Nelfinavir (NFV) Amprenavir (APV) Indinavir (IDV) Lopinavir (LPV) Atazanavir (ATV) Fosamprenavir (f-APV) Darunavir Tipranavir	Enfurvirtide (T-20)	Raltegravir	Maraviroc

Antiretroviral Drugs and their mechanism of action:

Approved antiretroviral drugs are grouped into four categories:

- Nucleoside analog reverse transcriptase inhibitors (NRTI) block the reverse transcriptase enzyme by incorporation into the growing DNA strand during replication.
- Non-nucleoside analog reverse transcriptase inhibitors (NNRTIs) bind noncompetitively to the reverse transcriptase enzyme.
- Protease inhibitors (PIs) block the action of the viral protease required for protein processing late in the viral cycle.
- Fusion Inhibitors inhibit viral binding or fusion to host target cells
- Integrase inhibitors block integration of viral genetic materials in host DNA.
- Entry Inhibitors block - CCR5 receptors which prevent viral entry into host target cells

6.5 Recommended first-line ART regimen drugs

TABLE 6.5: Select 1 NRTI to be used in combination with Lamivudine (3TC)

NNRTI	Pros	Cons
Zidovudine (AZT) (preferred NRTI if Hb $\geq$ 7.5 g/dl)	▪ AZT causes less lipodystrophy and lactic acidosis than d4T. ▪ AZT liquid formulation does not need refrigeration.	▪ AZT has more initial gastrointestinal side-effects. ▪ A large volume of AZT liquid formulation is often poorly tolerated. ▪ Severe anemia and neutropenia can occur. ▪ AZT liquid formulation comes in glass bottles and is sensitive to light.
Abacavir (ABC)	▪ ABC is less likely to cause lipodystrophy and lactic acidosis than AZT and d4T. ▪ ABC has little hematological toxicity and is well tolerated. ▪ ABC does not need refrigeration. ▪ ABC has good efficacy.	▪ ABC is associated with potentially fatal hypersensitivity in 3% of children. ▪ ABC is more expensive than AZT and d4T, and is not widely available in generic form.
Stavudine (d4T)	▪ d4T is usually very well tolerated. ▪ d4T causes less GI side-effects and anemia than AZT and ABC. ▪ d4T is available in pediatric fixed dose tablet with 3TC and NVP	▪ d4T causes more lipodystrophy, lactic acidosis and peripheral neuropathy than AZT and ABC. ▪ d4T liquid formulation needs refrigeration.

TABLE 6.6: Choose 1 NNRTI

1NNRTI	Pros	Cons
Nevirapine (NVP)	■ NVP can be given to children at any age. ■ NVP does not have a teratogenic effect. ■ NVP is available in both pill and liquid formulations, and neither requires refrigeration.	■ NVP causes rash more often than EFV. The rash may be severe and life-threatening. Also there is life-threatening risk of hepatoxicity (rare) ■ For adolescent girls, the risk of NVP-associated hepatotoxicity or severe rash increases with a CD4 count >250 cells/mm^3. ■ Rifampicin lowers the NVP level more than EFV.
Efavirenz (EFV)	■ EFV causes less rash and hepatotoxicity than NVP. ■ EFV levels are less affected by rifampicin and can be considered the NNRTI of choice in children receiving rifampicin-based anti-TB treatment. ■ For children unable to swallow pills, an EFV capsule can be opened and added to liquids or a small amount of food.	■ EFV can only be used in children ≥ 3 years of age. ■ Transient CNS disturbances can occur in 26-36 % of children; EFV should be avoided in children with a history of severe psychiatric illness. ■ EFV has a teratotogenic effect and should be avoided in adolescent girls with the potential for pregnancy. ■ EFV is not available in liquid formulation in most countries in the region. ■ EFV is more expensive than NVP

- Lamivudine (3TC) is used in all 3 combinations as it has an excellent record of efficacy, safety and tolerability. However, it has a low threshold for the development of drug resistance if full adherence is not ensured.
- AZT is the drug of choice. However, should the child have an Hb <7.5 g/dl, ABC or d4T should be considered. Because of the risk of lipodystrophy with the long-term use of d4T, consider switching from d4T to AZT.

TABLE 6.7: NRTI drug combinations to be avoided

d4T + AZT
d4T + ddI

6.6 ART regimen

6.6.1 Recommended first-line Regimen

2 nucleoside reverse transcriptase inhibitors (NRTIs) + 1 non-nucleoside reverse transcriptase inhibitor (NNRTI)

1. ZDV + 3TC + NVP < 3 years or 10 kg

2. ZDV + 3TC + EFV > 3 years and 10 kg

3. d4T + 3TC + NVP / EFV for Anemic Children

(Note: For HIV infected infants with a history of exposure to single dose nevirapine or non-nucleoside reverse transcriptase inhibitor containing maternal antiretroviral therapy or preventive antiretroviral regimens, a 2 NRTIs + PI regimen could be considered. Where PIs are not available, affordable or feasible use above regimen.)

6.6.2 Recommended Second line Regimen in the event of treatment failuer of first-line regimens

If the first-line regimen is 2 NRTI + 1 NNRTI = 2 new NRTIs + 1 PI

TABLE 6.8:

First-line NRTI	Second-line NRTI	PI
AZT or d4T + 3TC	ddI + ABC	LPV/r
ABC + 3TC	ddI + AZT	

DOSAGE

- Dosage of individual ARVs (see Annex 1)
- Where possible, fixed dose combinations (FDCs) should be used (see Annex 1)

6.7 ART regimen for HIV infected children with TB

If possible, ART should be deferred until completion of anti-tuberculous treatment in order to minimize drug interactions with rifampicin, to decrease pill burden and to enhance adherence.

The following table from WHO Pediatric ART Guidelines helps with various scenarios of HIV and TB co-infections:

TABLE 6.9: Recommendations for the timing of ART following initiation of TB treatment with rifampicin-containing regimen in HIV infected infants and children

CLINICAL STAGE OF CHILD WITH TB (AS AN EVENT INDICATING NEED FOR ART)	TIMING OF ART FOLLOWING INITIATION OF TB TREATMENT (RIFAMPICIN-CONTAINING REGIMEN)[a]	RECOMMENDED ARV REGIMEN[c]
WHO paediatric clinical stage 4[b]	**Start ART soon after TB treatment** (between 2 and 8 weeks following start TB treatment)	<u>In children < 3 years[d]:</u> ■ Triple NRTI first-line regimen (d4T or AZT + 3TC + ABC) or ■ Standard first-line regimen of two NRTIs + NVP[c] <u>In children >3 years:</u> ■ Triple NRTI first-line regimen (d4T or AZT + 3TC + ABC) or ■ Standard first-line regimen of two NRTIs + EFV[d] Following completion of TB treatment it is preferable to remain on the ART regimen if well tolerated except for triple NRTI's regimen
WHO paediatric clinical stage 3[c]	**With clinical management alone:** ■ **Start ART soon after TB treatment** (between 2 and 8 weeks following start TB treatment) ■ If excellent clinical response to TB treatment in first 2 to 8 weeks of TB therapy, and child is stable and on co-trimoxazole preventive therapy (CPT),[a] it may be reasonable to delay initiation of ART	
	Where CD4 available: ■ Evaluate possibility of delaying initiation of ART depending on assessment of clinical status and CD4, and clinical and immunological response to TB therapy: ■ <u>Severe and advanced immunodeficiency:</u> initiate ART soon after TB treatment (between 2-8 weeks following start TB treatment) ■ <u>Mild or no immunodeficiency:</u> Initiation of ART may be delayed until after the completion of TB therapy; closely monitor response to TB therapy and reassess need for ART after TB therapy; if no improvement, consider starting ART	■ Regimens as recommended above ■ Where ART can be delayed until after completion of TB treatment, initiation with a standard two NRTIs + NNRTI first-line regimen is recommended

Notes:

a Administration of CPT is important in children with TB/HIV coinfection.

b All children with paediatric clinical stage 4 should be initiated on ART regardless of CD4 criteria.

c Careful clinical monitoring with laboratory support, if available, is recommended where NVP is administered concurrently with rifampicin.

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

- Rifampicin lowers the drug level of NVP by 20-80% & that of EFV by 25%.
- Apart from rifampicin, other anti-TB drugs do not interact with ARV drugs.
- Anti-TB drugs and NNRTIs (esp. NVP) can have overlapping hepatoxicity, closely monitor LFT.
- Non-rifampicin based ATT has shown to have lower efficacy.

TABLE 6.10: Recommendation for Co-Management of TB and HIV in Infants and Children Diagnosed with TB while receiving First-Line or Second-Line ARV Regimens

Time of TB diagnosis in relation to ART	Underlying cause of TB	Considerations for ART following initiation of TB treatment (rifampicin containing regimen)[a]	ARV regimen
Child on standard two NRTIs + NNRTI **first-line** regimen diagnosed with TB	TB attributable to primary infection (consider at any time during ART, depending on exposure to TB)	Continue ART but assess for need to change ART regimen - response to TB therapy should be used to evaluate need for change	■ Continue on standard two NRTIs + NNRTI first-line; if on NVP,[b] substitute to EFV[c] if the child is aged 3 years or above or ■ Substitute NNRTI to triple NRTI first-line regimen
	TB as part of IRIS (consider in first 6 months of ART)		
	TB as a sign of treatment failure of first-line regimen (consider only after at least 24 weeks of ART)		■ Consider consultation with experts for construction of second-line regimen
Child on standard **second-line** regimen (NRTI+ boosted PI) diagnosed with TB	TB attributable to primary infection (consider at any time during ART, depending on exposure to TB)	Assess for need to change regimen- response to TB therapy should be used to evaluate need for changing or stopping	■ Continue same regimen, consider adding RTV to achieve full therapeutic RTV dose (increase RTV until same dose as LPV in mg)
	TB as a sign of treatment failure of second-line regimen		■ Consider consultation with experts for construction of salvage regimen

a Administration of co-trimoxazole preventive therapy (CPT) is important in children with TB/HIV coinfection.

b Careful clinical and laboratory monitoring should be ensured where NVP is administered concurrently with rifampicin.

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

6.8 FOLLOW-UP OF CHILDREN ON ART

A. AIMS

- To monitor side effects of ART
- History and physical exam for growth and development
- Immunization
- Nutrition assessment
- To monitor treatment adherence
- Labotory Tests including CD4 count/%
- Monitor dose of ART as child grows. Switch formulations as child crosses weight or age related thresholds.

B. Adherence monitoring

Adherence is the cornerstone of successful ART and can be especially challenging with children

- Often the family unit is disrupted as a consequence of adverse health or economic conditions
- Lack of disclosure of HIV status to the child may interfere with adherence
- ART success relies on the commitment and involvement of a responsible caretaker
- Lack of pediatric formulations, poor palatability, frequent dosing, dietary restrictions and side effects are barriers to good adherence.
- Attention to understanding of medication dosing, importance of almost 100% adherence, and queries about barriers to adherence are essential at each visit
- The development of an adherence plan and education of patients and caregivers are important steps.
- Continuous assessment and support of adherence is a vital component of treatment success.
- Discuss potential side effects of ART prior to initiation and during the early stages and offer patient support during minor or moderate adverse events.

C. Clinical monitoring

I. IMPORTANT CLINICAL SIGNS OF RESPONSE TO ART INCLUDE:

- Improvement in growth, if previously failing to grow
- Improvement in neurological symptoms and development, if previous delay in developmental milestones or encephalopathy
- Decreased frequency of infection (both bacterial infections and opportunistic infections)

II HISTORY

- Drug intake
- Symptoms suggestive of any illness, drug toxicities or immune reconstitution syndrome

III. PHYSICAL EXAMINATION

- Growth: weight, height, head circumference if <2yrs
- Developmental milestones
- General and systemic examination

Monitoring and Follow-Up Schedule

TABLE 6.11: Clinical monitoring after ART

Items	Baseline	2wks.	1m	2m	3m	4m	5m	6m	Every 2-3m	Symptom-directed
Clinical evaluation	x	x	x	x	x	x	x	x	x	x
Wt, Ht	x	x	x	x	x	x	x	x	x	x
ART dose calculation	x	x	x	x	x	x	x	x	x	
Other medications	x	x	x	x	x	x	x	x	x	
Adherence to ART		x	x	x	x	x	x	x	x	

TABLE 6.12: Laboratory monitoring (Post ART initiation)

Items	Baseline	2 wks	1m	2m	3m	6m	Every 6m	Symptom-directed
Hb, WBC	x		x AZT	x AZT	x AZT	x	x	x
ALT/AST	x	x NVP	x NVP	x NVP	x NVP	x	Every 6 months	x
Pregnancy test in adolescent girl	x							x
CD4% or count	x					x	Every 6 months	x

- If ALT/AST is abnormal, follow-up with full LFT is required.
- For patients on second line drugs draw full chemistry panel (LFT's, RFT's, glucose, amylase, electrolytes and lipids every 6 months)
- For a patients not responding to treatment, a viral load test may be requested if feasible.
- If viral load testing becomes readily available, ideal testing is baseline, every 6 months and with suspicion of virological failure.

6.9 Managing side effects of ART

TABLE 6.13 Guiding principles in the management of ARV drug toxicity

1. Determine the seriousness of the toxicity.
2. Evaluate concurrent medications, and establish whether the toxicity is due to (an) ARV drug(s) or due to another non-ARV medication taken at the same time.
3. Consider other disease processes (e.g., viral hepatitis in a child who develops jaundice on ARV drugs) because not all problems that arise during treatment are due to ARV drugs.
4. Manage the adverse event according to severity. In general:
   - Severe life-threatening reactions (Table 6.16): Immediately discontinue all ARV drugs, manage the medical event (i.e. symptomatic and supportive therapy); reintroduce ARV drugs using a modified regimen (i.e. with an ARV substitute for the offending drug) when patient is stabilized
   - Severe reactions: Substitute the offending drug without stopping ART
   - Moderate reactions: Consider continuation of ART as long as feasible; if patient does not improve on symptomatic therapy, consider single drug substitutions. For a few moderate toxicities (e.g. peripheral neuropathy or lipodystrophy) single drug substitution needs to be considered earlier.
   - Mild reactions are bothersome but they do not require change in therapy.
5. Stress maintaining adherence despite toxicity for mild and moderate reactions
6. If there is a need to discontinue ART because of life-threatening toxicity, all ARV drugs should be stopped until the patient is stabilized.

Note: *The NNRTI drugs have a long half-life, and if a child is on an NNRTI-based regimen and drugs are discontinued for non-life-threatening reasons, some clinicians may want to continue the NRTI dual backbone for 7 days after discontinuation of the NNRTI drug. However, in situations of life-threatening toxicity, it is more advisable to discontinue all ARV drugs at once.*

TABLE 6.14: When do side-effects and toxicities occur with ARVs ?

Time	Side-effects and toxicities
Within the first few weeks	■ GI toxicities include nausea, vomiting and diarrhoea. These side-effects are usually self-limiting and require symptomatic treatment only. ■ Rash and liver toxicity are more common with the NNRTI drugs but are also seen with certain NRTI drugs such as ABC and some protease inhibitors (PIs).
From 4 weeks onward	■ Drug-induced bone-marrow suppression such as anaemia and neutropenia are most commonly seen with AZT. ■ Other causes of anaemia should be looked for and treated. ■ Asymptomatic mild anaemia is common.
	■ If there is severe anaemia (Hb <7.5 g/dl) and neutropenia (neutrophil count $<500/mm^3$) AZT should be stopped and either ABC or d4T given.
6 – 18 months	■ Mitochondrial dysfunction is primarily seen with the NRTI drugs; these include lactic acidosis, hepatic toxicity, pancreatitis, peripheral neuropathy, lipoatrophy and myopathy. ■ Lipodystrophy is frequently associated with d4T use and can cause permanent disfigurement ■ Lactic acidosis is rare and can occur at any time. It is particularly associated with d4T use. Severe lactic acidosis can be life-threatening. ■ Metabolic disorders are more common with PIs and include hyperlipidaemia, fat accumulation, insulin resistance, diabetes and osteopenia.
	■ Stop the NRTI and switch to another drug with a different toxicity profile
After 1 year	■ Nephrolithiasis is commonly seen with indinavir (IDV). ■ Renal tubular dysfunction is associated with tenofovir disoproxil fumarate (TDF).
	■ Stop the PI and switch to another drug with a different toxity profile.

TABLE 6.15: Serious acute and chronic toxicities due to ARV drugs that may require therapy modification: Clinical presentation, laboratory abnormalities, and implications for ART management (See Annex 4)

POSSIBLE CLINICAL MANIFESTATIONS (MOST COMMON ARV DRUG(S) ASSOCIATED WITH THE TOXICITY)	POSSIBLE LABORATORY ABNORMALITIES[a]	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)
▪ May have accompanying lactic acidosis (see below) if secondary to NRTI drug
	▪ Elevated transaminases
	▪ Elevated bilirubin
		▪ D/C all ARV until symptoms resolve
		▪ If possible, monitor transaminases, bilirubin
		▪ If receiving NVP, It 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[b]

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	▪ D/C 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[b]
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 ▪ *NVP:* Systemic symptoms of fever, myalgia, arthralgia, hepatitis, with or without rash	▪ Elevated transaminases ▪ Elevated eosinophil count	▪ Immediately D/C 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[b]
Lactic Acidosis (NRTI class, particularly d4T)		
▪ Generalized fatigue and weakness ▪ Gastrointestinal features (nausea, vomiting, diarrhoea, abdominal pain, hepatomegaly, anorexia, 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	▪ D/C 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)[b]
Severe Rash/Stevens Johnson Syndrome (NNRTI class, particularly NVP, less common EFV)		
▪ Rash usually occurs during first 6-8 weeks of treatment ▪ *Mild to moderate rash:* erythematous, maculopapular, confluent, most often on the body and arms, with no systemic symptoms ▪ *Severe rash:* extensive rash with moist desquamation, angioedema, or serum sickness-like reaction; or a rash with constitutional findings such as fever, oral lesions, blistering, facial edema, conjunctivitis ▪ Life-threatening Stevens Johnson Syndrome or toxic epidermal necrolysis (rare, approximately 0.3% individuals receiving NVP)	▪ Elevated aminotransferases.	▪ If mild or moderate rash, can continue ART without interruption but close observation ▪ For severe or life-threatening rash, discontinue all ARVs until symptoms resolve ▪ NVP should NOT be 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)nemia (AZT)		
■ Severe pallor, tachycardia ■ Significant fatigue ■ Congestive heart failure	■ Low hemoglobin	■ If refractory to symptomatic treatment (e.g., transfusion), discontinue AZT only and substitute an alternative NRTI[b]
Severe neutropenia (AZT)		
■ Sepsis / infection	■ Low neutrophil count	■ If refractory to symptomatic treatment (e.g., transfusion), discontinue AZT only and substitute an alternative NRTI[b]
Chronic Late Serious Adverse Reactions		
Lipodystrophy/Metabolic Syndrome (d4T; PIs)		
■ Fat loss and/or fat accumulation in distinct regions of the body: ■ Increased fat around the abdomen, buffalo hump, breast hypertrophy ■ Fat loss from limbs, buttocks, and face occurs to a variable extent ■ Insulin resistance, including diabetes mellitus ■ Potential risk for later coronary artery disease.	■ Hyper-triglyceridaemia; ■ Hyper-cholesterolaemia; ■ Low HDL levels ■ Hyperglycemia	■ Substitution of ABC or AZT for d4T may prevent progression of lipoatrophy ■ 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; child refuses 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[b] ■ Symptoms may take several weeks to resolve

a. All laboratory abnormalities may not be observed.
b. See Table 6.16 for recommended antiretroviral drugs substitutions.

6.10. Immune Reconstitution Syndrome (IRS)

Clinical disease progression should be differentiated from the immune reconstitution syndrome (IRS), an entity that has been observed in adults and less frequently in children starting ART with very low CD4 values.

- IRS is defined as paradoxical clinical deterioration after starting ART, resulting from improving immune system interaction with organisms that have colonized the body during the early stages of HIV infection.
- They occur within the first 3 months after the start of potent ART, concurrent with a rapid rise of CD4 values and are usually self-limiting lasting 10 to 40 days.
- A wide range of pathogens can cause IRS. These include Mycobacterium tuberculosis (MTB), Mycobacterium avium complex, Cryptococcus neoformans, Aspergilla, Candida albicans, Pneumocystis jiroveci (PCP), CMV, human herpes viruses, and hepatitis B.
- May have atypical presentations of some opportunistic infections. Such as, IRS caused by MTB may present with high fever, lymphadenopathy, worsening of the original lesion, and/or deteriorating chest radiographic manifestations, including the development of a miliary pattern or pleural effusion.
- Managing IRS includes specific antimicrobial therapy (e.g. TB treatment for IRS caused by MTB). In severe reactions, glucocortisteroids may help.

6.11 Changing Antiretroviral therapy

REASONS FOR CHANGING THERAPY

Drug toxicity

See table below Ideally, single drug substitutions should be used as much as possible in the case of drug toxicity to help preserve limited future ART options.

TABLE 6.16: Severe toxicities in infants and children associated with specific first-line antiretroviral drugs and potential first-line drug substitutions

CLINICAL STAGE (WITH TB AS ART INDICATING EVENT)	TIMING OF ART FOLLOWING INITIATION OF TB TREATMENT (RIFAMPICIN-CONTAINING REGIMEN)	RECOMMENDED ARV REGIMEN
ABC	Hypersensitivity reaction	AZT
AZT	Severe anaemia or neutropaenia	d4T or ABC
	Lactic acidosis	ABC
	Severe gastrointestinal intolerance	d4T or ABC
d4T	Lactic acidosis	ABC
	Peripheral neuropathy	AZT or ABC
	Pancreatitis	
	Lipoatrophy/metabolic syndrome	
EFV	Persistent and severe central nervous system toxicity	NVP
	Potential teratogenicity (adolescent girl in 1st trimester pregnancy or of childbearing potential not receiving adequate contraception)	
NVP	Acute symptomatic hepatitis	EFV
	Hypersensitivity reaction Severe or life-threatening rash (Stevens-Johnson syndrome)	Preferred substitution by NVP to: ■ a third NRTI (disadvantage, may be less potent) or ■ PI (disadvantage, premature start of class usually reserved for second line)

6.12 Treatment Failure

Before changing therapy due to presumed treatment failure adherence to treatment must be confirmed.

Signs of drug failure

A. CLINICAL SIGNS

If after receiving the regimen for at least 24 weeks and adherence to therapy has been assessed and considered to be adequate, there is development of a more severe (new or recurrent) Clinical Stage III or IV condition presenting as:

- Lack of or decline in growth in children who show an initial response to treatment (after ensuring adequate nutrition)
- Loss of neurodevelopmental milestones or the development of encephalopathy
- Occurrence of new OI's or malignancies or recurrence of infections.
- Clinical failure MUST be differentiated from immune reconstitution syndrome (see note above).
- The detection of new or recurrent clinical events classified within the WHO clinical staging may also reflect progression of disease when a child is on ART. Treatment failure should be considered when either new or recurrent stage 3 or 4 clinical events develop in a child on therapy (Table 6.18).

B. IMMUNOLOGIC FAILURE (AFTER AT LEAST 24 WEEKS ON ART)

- Immunological treatment failure can be identified by examining baseline CD4 and the initial immunological response to ART.
- Switching a regimen should particularly be considered if CD4 values fall to below 15% (12-35 months of age), 10% (36-59 months of age), or 100 cells/mm3 (>5 years of age). Immunological criteria for recognizing treatment failure are supplemental to clinical criteria .
- Total lymphocyte counts (TLC), while useful in the absence of CD4 assays to guide when to initiate therapy, should not be used for the evaluation of response to ARV therapy as change in TLC is a poor predictor of treatment success.

TABLE 6.17: CD4 criteria to guide decision making on switching to a second-line regimen in children with clinical signs of treatment failure on a first-line regimen[a,b]

- Development of age-related severe immunodeficiency after initial immune recovery[c]
- Development of new age-related severe immunodeficiency, confirmed with two measurements[c]
- Rapid rate of decline to at or below threshold of age-related severe immunodeficiency[c]

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

b. At least two CD4 measurements should be available

c. Age-related severe immunodeficiency values as defined in Table 6.3; %CD4 is preferred in children <5 years of age; at least two measurements should be available and the same parameter should be compared i.e. count with count. If serial CD4 values are available, the rate of decline should be taken into consideration.

Use of Clinical and immunological markers for switching ART

- Where CD4 values are not available a simplified approach is needed to guide decisions on the need to switch to a second-line regimen.
- CD4 values supplement clinical findings when decisions are being made on switching therapy (Tables 6.17 and 6.18).

TABLE 6.18: DECISION-MAKING ON SWITCHING TO SECOND-LINE THERAPY FOR TREATMENT FAILURE BASED ON AVAILABILITY OF CD4 MEASUREMENT

NEW OR RECURRENT CLINICAL EVENT ON ART[a]	AVAILABILITY OF CD4 MEASUREMENTS[b]	MANAGEMENT OPTIONS[c]
T1 **OR T2** **EVENT(S)**	NO CD4	■ Do not switch regimen
	CD4	■ Consider switching regimen only if two or more values below the age-related threshold for severe immunodeficiency[d] are avalable ■ Increase clinical and CD4 follow-up if CD4 approaches the age-related threshold for severe immunodeficiency[e]
T3 event(s)	No CD4	■ Consider switching regimen[e,f]
	CD4	■ Switching regimen is recommended if CD4 is below the age-related threshold for severe immunodeficiency[d,f] and particularly if the child initially had a good immune response to ART ■ Increase clinical and CD4 follow-up if CD4 approaches age related threshold for severe immunodificiency
T4 event(s)	No CD4	■ Recommended switching regimen
	CD4	■ Switching is generally recommended but it may not be necessary where CD4 is above age related threshold for severe immunodeficiency

Note:

a Clinical events refer to new or recurrent events presenting while the child is on ART.

b Consideration of previous CD4 is useful.

c Any intercurrent infections should be treated according to national treatment guidelines and it is necessary to ensure that the child had at least 24 weeks of ART, adherence to therapy has been assessed and considered adequate before considering switching to a second-line regimen. Additionally, in considering changing treatment because of growth failure, it should be ensured that the child has adequate nutrition.

d Age-related severe immunodeficiency values as defined in Table 6.3; switching should particularly be considered if values are <15% (12 - 35 months of age), <10%(36 - 59 months of age), <100 cells/mm3 (≤5 years of age); use of %CD4 in children aged under 5 years and absolute CD4 counts after 5 years of age is preferred; if serial CD4 values are available the rate of decline should be taken into consideration.

e Some T3 conditions (i.e. pulmonary or lymph node tuberculosis and severe bacterial pneumonia) do not always indicate the need to switch regimens.

f Viral load determination may be useful to support recognition of treatment failure.

C.VIROLOGIC FAILURE

- Virological failure is diagnosed with the use of viral load testing (HIV RNA levels)
- Where CD4 and clinical criteria for recognizing treatment failure are conflicting then viral load may be a useful adjuvant to guide decision on the need for switch therapy.
- In adults a viral load greater than 10,000 copies is proposed to reflect viral replication suggestive of treatment failure, thresholds for children are not yet defined

WHO RECOMMENDS

- At first line treatment failure, change the entire regimen to second-line combination.
- Second-line should ideally include at least three new drugs with at least one of them from a new class.
- This increases the likelihood of treatment success and minimizes the risk of cross-resistance.

6.13 Differential diagnosis of common clinical events that develop during first six months of ART

TABLE 6.19:

SYMPTOMS	SIDE EFFECTS OF ARV OR OI PROPHYLAXIS	IRIS
Nausea, Vomiting	**ART** ■ AZT, usually self limiting after 2 weeks **OI prophylaxis** ■ Cotrim or INH	■ Hepatitis B or C can occur with IRIS ■ Suspect if nausea, vomiting plus jaundice
Abdominal or flank pain, &/or jaundice	**ART** ■ d4T or ddI may cause pancreatitis ■ NVP (less with EFV) may cause liver dysfunction which require stopping the drug **OI prophylaxis** ■ Cotrim or INH	■ Hepatitis B or C can occur with IRIS ■ Suspect if nausea, vomiting plus jaundice
Diarrhea	**ART** ■ NFV	■ IRIS from MAC or CMV
Headache	**ART** ■ AZT or EFV usually self limiting but can last 4-8 weeks	■ Assess for toxoplasmosis and cryptococcal meningitis
Fever	**ART** ■ Hypersensitivity reaction to ABC or adverse drug reaction of NVP	■ IRIS due to several organism, e.g. MAC, TB, CMV, Cryptococcus neoformans, herpes zoster
Cough, difficulty in breathing	**ART** ■ NRTI-associated lactic acidosis	■ IRIS can be associated with PCP, TB, fungal and anemia
Fatigue, pallor	**ART** ■ AZT, which usually develops 4-6 weeks after initiation	■ Suspect MAC IRIS if there is fever, fatigue and anemia
Skin rash, itching	**ART** ■ NVP or ABC ■ Should asses carefully and consider stopping drug in case of severe reaction. Rash due to EFV is often self-limiting **OI prophylaxis** ■ Cotrim or INH	■ Skin condition which can flare up due to IRIS in the first 3 months of ART - Herpes simplex and zoster - Papillomavirus (wart) - Fungal infection - Atopic dermatitis

chapter 7

Infant Feeding Policy and Nutrition

7.1 Introduction

Breastfeeding, in particular exclusive breastfeeding, is the ideal way to feed infants and it should be protected, promoted and supported. Beyond sound nutrition, it protects against common childhood infections. However, as it is one of the routes for mother-to-child HIV transmission, HIV-infected women need to consider carefully the following information about relative risks and benefits to their babies of breastfeeding, compared with alternatives.

- Most children with HIV are infected as a result of transmission of HIV infection from their mothers.
- Mother-to-child (vertical) transmission can occur before or during birth, or after birth through breast feeding. The risk of transmission of HIV through breastfeeding varies in relation to maternal clinical and immunological status, plasma and breast milk viral load and possibly breast health (subclinical or clinical mastitis, cracked nipples etc)
- The rate of mother-to-child transmission of HIV in the absence of preventive interventions is about 15-25% without breastfeeding and 25-40% with breastfeeding.
- Mother-to-child transmission can occur late in breastfeeding.
- Acute HIV infection during breastfeeding increases the risk of transmission.
- Mixed feeding (defined as breast milk plus water, other fluids and foods) is associated with 11-fold increased risk of infant HIV infection when compared with exclusive breastfeeding.

7.2 Issues in reaching a decision about infant feeding

- When children born to women living with HIV can be ensured uninterrupted access to nutritionally adequate breast milk substitutes that are safely prepared and fed to them, they are at less risk of illness and death if they are not breastfed.
- However, when these conditions are not fulfilled, in particular in an environment where infectious diseases and malnutrition are the primary causes of death during infancy, artificial feeding substantially increases children's risk of illness and death.
- Lack of breastfeeding has been shown to increase the risk of malnutrition and life-threatening infectious diseases other than HIV, especially in the first year of life and exclusive breastfeeding appears to offer protection.
- For an individual mother, balancing risks and benefits is a complex, but necessary task. In addition to providing counseling on infant feeding options to HIV-positive mothers, there should be an effort to ensure positive perceptions of and attitudes towards breastfeeding within the general population
- Both parents have a responsibility for the health and welfare of their child, and alternative infant feeding methods have health and financial implications for the entire family.
- Confidentiality of HIV status, should be respected at all times within the family setting.
- Families need to understand the issues and must reach informed decisions about infant feeding alternatives. The mother will need her partner's and family's support whether she decides to exclusively breastfeed or not.
- Ultimately, the decision about feeding is the mother's.

7.3 Recommended infant-feeding for mothers who are HIV negative and mothers with unknown HIV status

1. Exclusive breast feeding for the first six months of life
2. Continue breast feeding for up to 2 years or longer
3. After the infant reaches 6 months of age, introduce complementary foods that provide sufficient calories and micronutrients and are safe

7.4 Recommended infant-feeding for mothers who are HIV-infected

The exclusive breast feeding is recommende for infants of HIV-infected woman for the first six months unless replacement feeding is Acceptable, Feasible, Affordable, Sustainable, and Safe (AFASS) for them and their infants before that time.

7.5 Options during the First Six Months for HIV-exposed infants

- Exclusive Breastfeeding from birth until AFASS criteria are met or the baby reaches 6 months (see Table 7.1 for transitioning to replacement feeding at 6 months)
- Breastmilk substitutes where AFASS criteria are met (Replacement feeds)
  - Commercial Infant Formula
  - Home-modified animal milk
- Wet-nursing by an HIV negative woman
- Expressed heat-treated breastmilk

7.6 Options during the Second Six Months for HIV-exposed infants (6 to 12 months of age)

- Breastmilk substitutes AND appropriate complementary feeding
- Breastfeeding until other options are safe and feasible AND complementary feeding
- Wet-nursing by an HIV negative woman AND complementary feeding
- Expressed heat-treated breastmilk AND complementary feeding
- Animal foods and/or specially formulated, fortified foods (Non-milk option): Not ideal

7.7 HIV-infected Children

- If a child is diagnosed as **HIV-infected**, the mother should be encouraged to continue breastfeeding the child beyond six months of age along with the addition of complementary foods.

Note: If a mother develops full blown AIDS, she should consider stopping breastfeeding immediately for her own health.

7.8 Exclusive Breastfeeding

- Women who choose to breastfeed should be advised to breastfeed exclusively
  - Babies should not receive any other milk, drinks or any solids not even water.
  - Baby must attach well to prevent breast problems which can increase the risk of HIV transmission. Mothers should be taught about proper positioning of the baby for breastfeeding.
  - Mothers with breast conditions should stop breastfeeding from the infected breast and seek prompt treatment (Cracked nipples, mastitis, abscesses, candida)
  - Mothers should seek medical care immediately if ill
  - Mothers should check baby's mouth for sores regularly and seek treatment early

7.9 Breastfeeding after 6 months

- **Decision about continued breastfeeding after 6 months**
  - The risk of illness and death as a result of artificial feeds decrease as the infant gets older. However, early BF cessation may pose a greater risk than BF as the infant will miss the protective benefits and may be exposed to pathogens in improperly prepared breastmilk substitutes.
  - At about 6 months infants are better able to tolerate undiluted animal milk and semi-solid foods, so replacement feed is easier, safer and cheaper than at an earlier age.
  - The appropriate time to stop BF must always be assessed on an individual basis.
  - **Under conditions common in resource-limited settings, many experts recommend a transition from exclusive breastfeeding to replacement feeding at about 6 months of age.**

7.10 Replacement Feeding (Breast milk substitutes)

- Replacement feeding is the process of feeding a child who is not receiving any breast milk, with a diet that provides all the nutrients the child needs.
- Suitable replacement feeds include commercial infant formula and animal milk that has been modified by adding water, sugar and a multivitamin supplement formulated especially for infants. The milk may be of cows, goats or buffalo. Formula and liquid "milk" can also be made from soyabeans
- Weaning (replacement feeding) should be abrupt and as rapid as possible to minimized the period of mixed feeding

TABLE 7.1: Switching from Breastfeeding to Replacement Feeding

- Express breastmilk.
- Accustom the infant to cup feeding by introducing expressed breastmilk by cup. One strategy is to offer expressed breastmilk by cup between regular breastfeeds. This will help the baby get used to cup feeding.
- Eliminate one feeding at the breast at a time once the infant accepts cup feeding and replace with expressed breastmilk given by cup.
- Express breastmilk and discard it if the breasts become engorged during this process. Use cold compresses to reduce the inflammation.
- Feed only the breastmilk substitute when transition is complete.
- Resist the desire to breastfeed at nighttime or when the child wants comfort.
- Practicing exclusive breastfeeding gives some protection against future pregnancies. Provide adequate contraception in addition and especially as women stop breastfeeding.

7.11 Complementary feeding for children over 6 months of age

- Non-breastfed infants and young children from 6 months of age should ideally continue to receive a suitable breast-milk substitute as well as complementary foods made from properly prepared and nutrient-enriched family foods.
- The provision of other foods and liquids in addition to milk is called complementary feeding, as the foods are additional or complementary to the milk rather than adequate on their own as the diet.
- When milk is part of the diet, complementary foods are needed 2-3 times a day at 6-8 months of age, and 3-4 times a day from 9 up to 24 months of age, with additional nutritious snacks offered once or twice a day. .
- Other milk products, such as boiled animal's milk or yoghurt, should be included as a source of protein and calcium; other animal products such as eggs, meat, liver, and fish should be given as a source of iron and zinc; and fruit and vegetables should be given to provide vitamins, especially vitamins A and C.
- Where no suitable breast-milk substitute is available after 6 months, complementary feeding should be given more frequently.
- However, it is advisable to continue with some other form of milk up to at least 2 years of age. It is very difficult to feed a child less than 2 years old adequately on complementary foods alone without some form of milk or other animal food product.
- Adding complementary foods too soon or in too great an amount can replace the milk and reduce intake. If the added foods are starchy and low in protein and micronutrients, this can result in a diet that is not adequate for an infant.

Suitable Complementary Foods for a child from 6 to 24 months

A good diet consists of a mixture of most of the following:

- a staple food such as a cereal (jwalo litto), with
- animal food such as, meat, fish, eggs
- milk
- pulses, such as beans, peas or lentils
- vegetables and fruit
- fats and oils such as vegetable oil, butter or ghee.

Iron and zinc requirements are particularly difficult to meet unless there is fish or meat regularly in the diet. Micronutrient supplements may be needed if these foods are not eaten in sufficient quantity.

To help a young child obtain enough energy and nutrients when much of the diet consists of bulky staple foods, families can:

- Feed the child frequently – 5 times a day;
- Add other nutrient rich foods, such as animal products, vegetables, fruit, oil and sugar, to enrich the porridge or staple foods.
- Include milk in the child's diet. Milk can also be a useful snack.

7.12 Modification of Mother's Milk

The other options, include expressed and heat treated breast-milk and wet nursing.

7.13. Consideration for Nutrition in HIV-Infected Children

- Malnutrition is a common condition in HIV-infected children and is major contributor to mortality in both HIV-uninfected and HIV-infected children.
- It is recommended to increase the energy intake of HIV-infected infants and children by 10% of the RDA for their age and sex if they are asymptomatic and by 20-30% of the RDA if they are symptomatic or recovering from acute infections.
- In children who rapidly gain weight because of adequate nutrition and ART, dosages of ARVs should be frequently reviewed.
- The recurrence of severe malnutrition that is not caused by a lack of food in children receiving ART may indicate treatment failure and the need to switch therapy.

7.13.1 Vitamin A (According to the National Protocol)

Every 6 months.

- 100,000 units for 6 months to 1 year of age.
- 200,000 units for 2 - 5 years of age.

7.13.2 De-worming (According to the National Protocol)

Every 6 months from 1 - 5 year of age

- Albendazole 200mg for < 2 yr old
- Albendazole 400mg for 2 - 5 years of age

chapter 8

Management of Opportunistic Infections in Children with HIV and AIDS

Introduction

Opportunistic infections (OI's) are common manifestations of the immunodeficiency associated with HIV. These include opportunistic protozoal, fungal and viral infections as well as repeated episodes of common childhood infections. Natural history of OI's among children differs from that in HIV-infected adults as they more often reflect primary infection with a pathogen. It is essential to be aware of the clinical features of specific OI's.

In general, progression of HIV and onset of OI's occurs as plasma viral load increases and CD4 count decreases. Effective prophylactic regimens against several OI's have resulted in a decline in their frequency, as well as an improvement in survival rates. Additionally, effective ARV therapy reduces the risk of development of OI's. It is essential to correctly diagnose and treat OIs, since many can be life threatening. The most common and frequent OI's are considered here as follows:

8.1 Diarrhea
8.2 Recurrent Bacterial Infections
8.3 Tuberculosis
8.4 Pneumocystis jiroveci Pneumonia (PCP)
8.5 Viral Infections
- Herpes Simplex Viruses 1 & 2 (HSV) Infections
- Varicella Zoster Virus (VZV)
- Herpes Zoster
- Cytomegalovirus(CMV)

8.6 Fungal Infections
- Candida Infections
- Cryptococcal Infections

8.7 Mycobacterium Avium Complex Disease (non-TB mycobacterium)
8.8 Toxoplasma Gondii Infection

8.1 Diarrhea

Important Features

- Chronic, recurrent or persistent is common in HIV infected children.
- Large watery stools and abdominal pain
- May include fever, dehydration, decreased appetite, feeding problems and malaise
- Cholangitis and cholecystitis seen with some parasitic causes of diarhhoea.
- May persist and lead to malnutrition, wasting and cachexia.
- Can be life threatening

Table 8.1: Common Causes of Diarrhoea in HIV-Infected Children

CATEGORY	SPECIFICS
Protozoa	Isospora belli, Cryptosporidium parvum, Microsporidia, Entamoeba histolytica, Giardia lamblia
Bacteria	Salmonella, Campylobacter, Shigella, Clostridium difficile and Mycobacterium Avium Complex
Viruses	CMV, adenovirus, HIV, HSV and Rota virus
Fungi	Histoplasma
Medications	Side effects of certain ARV's and other medications

Diagnosis and Treatment

The laboratory diagnosis of HIV-related diarrhea may not be available in all parts of Nepal. The following tables list distinctive clinical features, ideal diagnostics and recommended treatment for the most common conditions.

Table 8.2: Clinical Features, Diagnosis and Treatment of Certain Protozoal Infections

CLINICAL FEATURES AND DIAGNOSIS	TREATMENT
Cryptosporidium Parvum **Clinical Features:** ■ Frequent, non-bloody, watery, voluminous profuse and persistent diarrhea with cramps, fatigue, fever, vomiting and weight loss ■ Rarely, cholecystitis and cholangitis **Diagnosis:** ■ Microscopic examination of the stool with modified Kinyoun acid-fast stain *Note: Immunoflorescent assay and ELISA are expensive and less available options*	■ Supportive therapy with rehydration, electrolyte correction and nutritional support. ■ Recommended treatment is ART ■ No other effective therapy available. *Note: Azithromycin and Paromomycin have had some success in clinical trial settings.*
Isospora Belli **Clinical Features:** ■ Enteritis, watery non-inflammatory diarrhea with wasting ■ No fever **Diagnosis:** ■ AFB stool smears	■ TMP-SMX 20 mg TMP/kg/d in 4 div doses for 10 days followed by TMP-SMX 10 mg/kg/d in 2 div doses for 3 weeks ■ For Cotrim allergy, Pyrimethamine alone or with Folinic acid ■ Secondary Prophylaxis: TMP-SMX (5mgTMP/kg) 3 times a week
Cyclospora Species **Clinical Features:** ■ Enteritis, watery diarrhea **Diagnosis:** ■ AFB stool smears	■ TMP-SMX (10mg TMP/kg/d) in 2 div doses for 10 days ■ Secondary Prophylaxis: TMP-SMX (5mgTMP/kg) 3 times a week
Microsporidia **Clinical Features:** ■ Moderate to severe nonbloody watery diarrhea ■ Abdominal cramps, vomiting, weight loss ■ Acute or chronic **Diagnosis:** ■ Modified trichrome stain of concentrated stool	■ Supportive therapy with rehydration, electrolyte correction and nutritional support. ■ Recommended treatment is ART ■ No other effective therapy available. ■ Albendazole 400 mg twice daily has been reported to decrease symptoms in adults
Entamoeba Histolytica **Clinical Features:** ■ Diarrhea/dysentery ■ Extra-intestinal (Amebic Liver Abscess) ■ Asymptomatic cyst carrier **Diagnosis:** ■ Stool: trophozoites or cysts ■ Serological tests (ie IHA): Positive with tissue invasion ■ Endoscopy and biopsy if stool examination is negative *Note: Serological tests, PCR, endscopy and biopsy are expensive and less available options.*	■ Metronidazole 30-50mg/kg/d in 3 div doses for 10 days ■ For invasive or organ infection use: Metronidazole 50mg/kg/d div in 3 doses for 10 days followed by Paromomycin 30mg/kg/d div in 3 doses for 7 days
Giardia Lamblia **Clinical Features:** ■ Bloated abdomen, gassy feeling **Diagnosis:** ■ Stool: trophozoites or cysts *Note: Duodenal aspirate, string test, jejunal biopsy, serological tests and stool Giardia Ag are more expensive and less available options.*	■ Metronidazole 15 mg/kg/d in 3 div doses for 5 days *Note: Other treatment options include Tinidazole and Paromomycin.*

Table 8.3: Clinical Features, Diagnosis and Treatment of Viral GI Infections

CLINICAL FEATURES AND DIAGNOSIS	TREATMENT
Adenoviruses **Clinical Features:** ▪ Acute diarrhea **Diagnosis:** ▪ Routine stool studies are negative Note: Further work-up not generally done, but characteristic findings on sigmoidoscopy with mucosal biopsy	▪ Supportive therapy with rehydration, electrolyte correction and nutritional support.
Rotavirus **Clinical Features:** ▪ Acute watery diarrhea *Note: ELISA of stool is possible if available and affordable*	▪ Supportive therapy with rehydration, electrolyte correction and nutritional support

Table 8.4: Clinical Features, Diagnosis and Treatment of Bacterial GI Infections

Campylobacter **Clinical Features:** ▪ Watery or bloody diarrhea ▪ May have fever **Diagnosis:** ▪ Stool smear may show WBCs ▪ Stool culture or blood culture.	▪ Erythromycin 30-50mg/kg/d div 3-4 doses for 7 days. ▪ Supportive therapy with rehydration, electrolyte correction and nutritional support. *Note: Azithromycin and Ciprofloxacin are alternatives*
Note: Serology and Ig tests are possible depending on cost and availability **Shigella** **Clinical Features:** ▪ Watery or bloody diarrhea ▪ May have fever **Diagnosis:** ▪ Stool smear with WBCs ▪ Stool culture or blood culture.	▪ Supportive therapy with rehydration, electrolyte correction and nutritional support. ▪ Treat with oral antibiotics based on local sensitivities pattern. ▪ Oral Nalidixic acid 55mg/kg/d in 4 div doses for 5 days is used as first line drug ▪ Ciprofloxacin recommended in older or seriously ill children (15 30 mg/kg in 2 div doses for 3 days)
Salmonella **Clinical Features:** ▪ Watery diarrhea ▪ Can have blood in stool ▪ May have fever **Diagnosis:** ▪ Stool smear may have WBCs ▪ Stool culture or blood culture.	▪ Supportive therapy with rehydration, electrolyte correction and nutritional support. ▪ Duration of anti-microbial therapy: 10-14 days ▪ Ceftriaxone: 100mg/kg/d IV ▪ Ciprofloxacin: 15-30 mg/kg po or iv in 2 div doses for 3 days *Alternatives include Azithromycin, Cefotaxime, Ampicillin (only if susceptible)*
Clostridium Difficile **Clinical Features:** ▪ History of antibiotic use (most common Ampicillin, Cephalosporin and Clindamycin) ▪ Watery diarrhea, cramps, fever **Diagnosis:** ▪ Stool smear may have WBCs ▪ C. dificile toxin in the stool by ELISA	▪ Stop the current antimicrobial agent, if possible ▪ Supportive therapy with rehydration, electrolyte correction and nutritional support. ▪ Indications for antimicrobial therapy: severe illness, persistent symptoms or inability to discontinue antibiotics ▪ Metronidazole: 20-50mg/kg/d po div 3 doses ▪ Vancomycin: 25-50 mg/kg/d div q6hr for 14 days

8.2 Recurrent Bacterial Infections

Important Features

- Definition: Two or more bacteriologically documented, systemic bacterial infections in two years including septicemia, bacteremia, meningitis, pneumonia, or osteomyelitis.
- Iatrogenic factors often involved (eg. indwelling catheters, antibiotics and cytotoxic agents).

- Clinical manifestation depends upon the site of infection (see table below).
- Manifestations are similar in HIV-infected and HIV-uninfected children
- Always search for the causative agent to establish diagnosis

Chemoprophylaxis

Cotrimoxazole prophylaxis needed for children with recurrent bacterial infections using the same protocol as those requiring it based on Clinical Staging, Immunologic status or previous PCP event. See protocol and dosing in Chapter V.

Table 8.5: Recurrent Bacterial Infections Organisms, Clinical Manifestations and Diagnostic Evaluations

SITE OF INFECTION	COMMON ORGANISMS	CLINICAL MANIFESTATIONS	DIAGNOSTIC EVALUATION
Bacteremia	S. pneumonia, H.influenza, Salmonella species	Fever or hypothermia, poor feeding, signs of multi-organ dysfunction	Blood culture
Pneumonia	S. pneumonia, H. influenza, P. aeruginosa, S. aureus Differential diagnosis also includes: RSV, TB, influenza, PCP, parainfluenza, and other gram negative bacteria	Fever Cough Chest pain Tachypnea Crepitations	Chest X-ray Sputum culture
Meningitis	S. pneumonia, H. influenza, N. meningitis	Fever, headache, vomiting, altered sensorium, nuchal rigidity	CSF examination and culture
Osteomyelitis	Staphylococci	Fever, pain, redness and swelling at local site	Bone scan, Radiograph
Sinusitis	S. pneumonia, H. influenza	Persistent nasal discharge, fever and cough	Radiograph
Central venous catheter Infection	Staph.aureus & epidermidis, K. pneumoniae, Actinobacter and Pseudomonas species are less common	Redness and tenderness at local site of septicaemia	Culture from access harbinger site and from peripheral blood
Skin, ear and upper respiratory infections	S. pneumonia, H. influenza, Group A beta haemolytic streptococci	URTI: Fever, cough Skin: Pyoderma Ear: Earache, discharge	Culture from site of infection

Treatment

- The choice of antibiotic is based upon the site of infection, the isolated organism and its susceptibility pattern.
- Empiric therapy should be broad-spectrum

Table 8.6: Choice of Initial Empiric Antibiotic Therapy

SITE OF INFECTION	INITIAL EMPIRIC THERAPY
Bacteremia	Cefotaxime 200mg/kg/d IV div q6 hr doses OR Ceftriaxone 100mg/kg/d IV/IM q 24 hrs Note: Alternative is Cefuroxime, can add Vancomycin, if available in addition to Cephalosporin
Pneumonia	Outpatient: Amoxicillin 50 mg/kg/d div 3 daily doses Inpatient : Cefotaxime 200mg/kg/d div q8hrs IV OR Ceftriaxone 50-75mg/kg/d IV/IM once daily Don't forget, if possibility of PCP, add high dose Cotrimoxazole For severe infections, add anti-pseudomonal agent. If over 5 years old, consider adding Erythromycin 50mg/kg/d div 4 daily doses.
Meningitis	Ceftriaxone 100mg/kg/d IV div q 12 hrs OR Cefotaxime 200mg/kg/d IV div q6hr doses Note: Can add Vancomycin, if available, in addition to Cephalosporin

8.3 Tuberculosis

Important Features

- Tuberculosis (TB) is one of the most common HIV-related OI's.
- HIV increases the risk of activation of TB in latently infected children (10-30 times risk)
- HIV increases the susceptibility to both the primary infection (more common in children) as well as to reactivation of TB (more in adults) due to depressed immunity.
- Extra pulmonary, disseminated TB and drug-resistant tuberculosis is seen more frequently with HIV.
- Up to 25% of TB in children is extrapulmonary. The most common sites are the lymph nodes (LN), pleura, pericardium, meninges and miliary TB. Children with advanced HIV disease are at high risk for extrapulmonary TB.
- The principles for the treatment of TB in HIV-infected children are the same as in HIV-uninfected children.
- A trial of treatment with anti-TB drugs is not recommended as a method of confirming a presumptive diagnosis of TB in children.

Clinical Features

- Fever, cough, weight loss, night sweats and malaise are common.
- Extra-pulmonary disease may involve other tissues and organs such as the central nervous system, lymph nodes and mastoid.
- Findings can include miliary TB, hepatosplenomegaly, lymphadenopathy, TB meningitis and genito-urinary TB.

Diagnosis

- Diagnosis can be difficult due to unusual features, extra-pulmonary disease and the presence of other pulmonary conditions that can mimic the symptoms of TB.
- Need careful medical history with emphasis on history of TB contact.
- Mantoux may be negative with HIV. (≥5mm induration is positive)
- CXR may show lobar or multi-lobar infiltrates, diffuse interstitial disease and hilar adenopathy (also can be very nonspecific and even normal)
- Gold standard is isolation of acid-fast bacilli, but can be difficult to demonstrate.
- Samples can be obtained from sputum, gastric lavage, broncho-alveolar lavage, lymph node biopsy or other biopsy tissue.
- Obtaining sufficient sputum from infants and young children is difficult.
- Diagnosis often based on clinical features and history of TB contact.
- Crofton-Horne-Miller Scoring system can be followed.

Table 8.7: Recommended treatment regimens for each diagnostic category (NTP Guidelines, Nepal)

TB DIAGNOSTIC CATEGORY	TB PATIENTS	TB TREATMENT REGIMENS	
		INITIAL PHASE[a]	CONTINUATION PHASE[a]
I	New smear-positive New smear-negative pulmonary TB with extensive parenchymal disease, severe concomitant HIV disease or severe forms of extrapulmonary TB	2HRZE[b]	4HR below 8 years 6HE 8 years and above
II	Previously treated sputum smear-positive pulmonary TB: - relapse - treatment after default - treatment failure[c]	2 HRZES/1HRZE	5HRE
III	New smear-negative pulmonary TB (other than in Category I). Less severe forms of extrapulmonary TB.	2HRZ	4HR below 8 years 6HE 8 years and above
IV	Chronic and MDR-TB (still sputum-positive after supervised re-treatment)[d]	DOTS-Plus Standardized Regimen	

a. Direct observation of drug intake is required during the initial phase of treatment in smear-positive cases, and always in treatment including rifampicin.
b. Streptomycin may be used instead of ethambutol. In TB meningitis, ethambutol should be replaced by streptomycin.
c. Whenever possible, drug sensitivity testing is recommended before prescribing Category II treatment in failure cases. It is recommended that patients with proven MDR-TB use Category IV regimens.
d. Contacts of patients with culture-proven MDR-TB should be considered for early culture and sensitivity testing

NTP Guidelines recommend a 7 month continuation phase with daily isoniazid and rifampicin (7HR) for Category 1 patients with meningitis, miliary TB and spinal TB with neurological signs.

Use of TB drugs in children

- The treatment regimens and drug dosages in mg/kg of body weight are the same for children as for adults.
- Children usually tolerate TB drugs very well and serious side-effects are unusual.
- Do not give thioacetazone to HIV-infected children.
- Ethambutol is safe even in children too young to report early visual side-effects provided that the recommended dose is not exceeded.
- Since TB drugs are often not available in syrup form, give children portions of tablets according to weight.
- Health service staff must identify a guardian responsible for the child's treatment.

Adjuvant steroid treatment

Adjuvant steroid treatment is given in addition to anti-TB drug treatment.

- Steroids may further depress immunity and increase risk of opportunistic infections in HIV-positive patients. However, for TB/HIV patients the benefits of the use of steroids outweighs the risk for the following indications:
  - TB meningitis (decreased consciousness, neurological defects, or spinal block)
  - TB pericarditis (with effusion or constriction)
  - TB pleural effusion (when large with severe symptoms)
  - Hypoadrenalism (TB of adrenal glands)
  - TB laryngitis (with life-threatening airway obstruction)
  - Severe hypersensitivity reactions to anti-TB drugs
  - Renal tract TB (to prevent ureteric scarring)
  - Massive TB lymphadenitis with pressure effects

Recommended treatment doses of prednisolone:

- TB meningitis 1–2 mg/kg daily weeks 1–4, then decrease over a period of 8 weeks
- TB pericarditis 1–2 mg/kg daily for weeks 1–4 , then 0.5–1 mg/kg daily for weeks 5–8, then decrease over a period of 8 weeks
- TB pleural effusion 0.5–1 mg/kg daily for 1–2 week

HIV and TB Co-infection and ART

- Timing of ART in relation to TB Treatment: See Chapter 6
- Which medications to use: If child is already on ART or ART initiation cannot be delayed until TB treatment is completed, drug changes and substitutions may be needed as described in Chapter 6 to avoid significant drug interactions.
- Immune Reconstitution Syndrome (IRS): Paradoxical worsening clinically within the first few months of ART therapy for those with concomitant TB infection. Occurs with undiagnosed/untreated TB as well as those already on TB treatment.

8.4 Pneumocystis jiroveci pneumonia (PCP)

(Previously known as Pneumocystis cariini Pneumonia)

Important Features

- PCP is the most common OI associated with HIV in children
- It predominantly occurs between 3-6 months of age
- Can occur in infants less than 12 months of age despite good CD4 counts.
- PCP is characterized by rapidly progressive hypoxemia.

Clinical Features

- Child may have cough, fever, tachypnea and dyspnea.
- Onset can be abrupt or insidious with nonspecific symptoms (ie. poor feeding)
- Physical examination reveals tachycardia, signs of respiratory distress including accelerating tachynpea and chest retractions with either crepitations or sometimes no ausculatory findings
- Hypoxemia and respiratory failure can occur
- CXR may show hyperinflation with peribronchial thickening, bilateral alveolar or interstitial infiltrates, bilateral air space disease (air bronchograms, cavities, pleural effusion and spontaneous pneumothorax.

Diagnosis

- Confirmed by Wright-Giemsa staining of induced sputum or samples obtained by broncho-alveolar lavage which shows trophozoites and intracystic sporozoites.

Treatment

- PCP is a medical emergency and therapy should not be delayed. Respiratory support is given with supplemental oxygen.

Table 8.8 Drugs Used in the Treatment of Pneumocystis Jiroveci Pneumonia

DRUG	DOSING SCHEDULE	REMARKS
TMP-SMX	20 mg of TMP/kg/d I.V. in 4 div doses for 21 days (dose infuse over 1 hour) If IV therapy is not available high dose oral cotrimoxazole may be used	The drug of choice, switch to oral administration as soon as clinical improvement occurs for milder cases
Prednisone	1 mg/kg bid (days 1-5) 0.5 mg/kg bid (days 6-10) 0.5 mg/kg od (days 11-21)	Indicated for moderate or severe cases with hypoxemia

Note: IV Pentamidine is indicated for children with intolerance to TMP-SMX or poor improvement on TMP-SMX. Dapsone-TMP, Clindamycin-Primaquine and Atovaquone have all been used as alternatives in adults (no pediatric experience). Cost and availability may be limiting factors

Prevention

All children with previous episode of PCP as well as many children meeting criteria based on age, exposure status, clinical status (WHO Stage 2, 3 or 4) and/or CD4 count will require TMP-SMX (Cotrimoxazole) prophylaxis. See Chapter 5 for indications and dosing.

8.5. Viral Infection

Table 8.9: Clinical Features, Diagnosis and Treatment of Certain Viral Infections

CLINICAL FEATURES AND DIAGNOSIS	TREATMENT
HSV 1 and 2 **Clinical Features:** ■ HSV 1 generally transmitted by orolabial contact ■ HSV 2 generally transmitted by genital or anorectal contact ■ Both present as recurrent self-limited cluster of ulcers, in those with CD4 >100 ■ In immunosuppressed, other sites may be involved. Lesions may be large, painful and persistent. Episodes more frequent and severe ■ Severe stomatitis, superinfection, rectal fissures and fistulas can occur ■ Systemic HSV: esophageal ulceration, pneumonitis, hepatitis, meningoencephalitis,ventricultis, shock, sepsis-like syndrome and transverse myelitis. (with advanced AIDS) **Diagnosis:** ■ Typical clinical appearance *Note: Antibody titres, viral culture, IFA and PCR are expensive and less available options.*	■ Neonates: Acyclovir 60mg/kg/d in 3 div doses IV for 14 - 21 days. ■ Severe HSV including encephalitis (> 1 month of age): Acyclovir 30 mg/kg/d in 3 div doses IV for 21 days. ■ Primary gingivostomatitis or genital HSV Acyclovir 80 mg/kg/po in 3-4 div doses for 7 - 14 days ■ Consider prophylactic Acyclovir for those with severe oral recurrences (3-6 episodes per year) *Note: Famciclovir and Valacyclovir may be used in adolescents if available and affordable. Foscarnet is an alternative, but cost and availability are its limitations.*
Varicella Zoster Virus (Chicken Pox) **Clinical Features:** ■ Fever with generalized pruiritic vesicular rash ■ Advanced immunosupression: severe manifestations and recurrent, persistent or chronic infections are common. ■ Persistent infection: new lesions appear for more than a month after onset ■ Chronic infection: Lesions evolve into verrucous lesions or become necrotic. ■ Severe: High fever, numerous skin lesions and systemic involvement like pneumonia, hepatitis and encephalitis **Diagnosis**: ■ Clinical diagnosis *Note: In some areas laboratory tests are available such as antigen testing of lesions, viral culture, antibody levels and PCR, but cost may be prohibitive*	■ Acyclovir 30 mg/kg/d IV in 3 div doses for 7 days and until no new lesions appear (if severe) ■ Acyclovir 80mg/kg/d po in 4 div doses for milder disease *Note: Alternative is Foscarnet which is not widely available or affordable. Famciclovir and Valacylovir approved for use in adults.* *Note: Prophylaxis of HIV infected children without previous history of VZV with VZIG is possible in certain settings.*
Herpes Zoster (reactivation of VZV) **Clinical Features:** ■ Painful vesicular lesion with dermatomal distribution ■ May have multidermatomal involvement ■ Disseminated Zoster > 20 lesions outside of the primary dermatome ■ Bilateral involvement ■ Rare: retinitis pneumonitis, coagulopathy, hepatitis, marked constitutional symptoms and encephalitis ■ Post-herpetic neuralgia is common **Diagnosis:** ■ Clinical with classic presentation *Note: Viral isolation and viral antigen detection is possible, but rarely done and expensive.*	■ Severe Disease: Acyclovir 30mg/kg/d in 3 div doses IV q 8 hrs (esp. if high risk: Low CD4, neurologic complications, ophthalmic involvement, disseminated zoster) ■ Acyclovir 80mg/kg/d po in 4 divided doses for less severe disease *Note: Alternatives include Famciclovir and Foscarnet*

CLINICAL FEATURES AND DIAGNOSIS	TREATMENT
Cytomegalovirus (CMV): **Clinical Features:** ■ Transmission via saliva, sexual fluid or urine and from infected mother to baby. ■ Congenital CMV- small for dates, jaundice, petichiae, hepatosplenomegaly, CNS abnormalities and developmental delay ■ CMV disease develops with advanced immunosupression. ■ CMV Retinitis: - CD4 <50 are at high risk. - Blurred vision, floaters and flashes - Initially unilateral and painless, progresses to bilateral - Eventually retinal detachment and visual loss - Yellowish white infiltrates with retinal haemorrhages at the periphery ■ Gastrointestinal CMV Oesophagitis: substernal pain, dysphagia and anorexia Colitis: anorexia, abdominal pain, diarrhoea, fever and weight loss. CMV hepatitis and gastritis: rare in children ■ Pneumonitis Cough, breathlessness and hypoxaemia ■ Encephalitis Sub-acute dementia complex Difficult to distinguish from HIV-encephalopathy **Diagnosis:** ■ Retinitis: Fundoscopic appearance. ■ Gastrointestinal: Endoscopy/ Sigmoidoscopy with biopsy ■ Pneumonitis: CXR- diffuse interstitial infiltrates. Broncho Alveolar Lavage ■ Serologic test: Doesn't differentiate between current and resolved infection. Seroconversion may be significant ■ Urine culture for congenital, perinatal or early postnatal infections in infants *Note: Severely immunosuppressed children should undergo regular opthalmalogic examination*	■ Ganciclovir 10mg/kg/d in 2 div doses IV over 1-2 hrs for 14-21 days. ■ Life-long maintenance therapy required after acute treatment: Ganciclovir 5mg/kg/d IV 5 days per week Note: Ganciclovir may or may not be available due *to high costs.* *Note: Alternative drug is Foscarnet with even more limited availability and higher costs.*

8.6 Fungal Infections

9.6.1 Cryptococcal infections

Important Features

- Most common manifestation is Cryptococcal meningitis.
- Much less common in children than adults.
- Mostly seen in 6-12 yr old age group
- Disseminated disease can involve other organs such as the brain, lung, skin and eyes

Table 8.10: Clinical Features, Diagnosis and Treatment of Cryptococcal Infections

CLINICAL FEATURES AND DIAGNOSIS	TREATMENT
Clinical Features: ■ Meningoencephalitis: evolves over days to weeks with fever, headache and altered mental status ■ Skin lesions if disseminated: umbilicated papules, nodules, ulcers or plaques ■ Pulmonary: rare, fever, cough, adenopathy, infiltrates **Diagnosis:** ■ India ink staining of CSF ■ For suspected pneumonitis: CXR showing bronchopneumonia, nodular changes or lobar consolidation *Note: The following are useful tests, but may not be widely available or affordable:* -CSF Cryptococcal antigen (CRAG) -Fungal culture -Serum Cryptococcal antigen (CRAG), if LP is impossible or pulmonary infection suspected. CT scan (showing cryptococcal granulomas)	**Initial:** ■ Amphotericin B 0.7-1.5 mg/kg/d IV in one daily dose for 14 days with or without (depends on availability): Flucytosine100 mg/kg/d in 4 div doses for 14 days **Continuation (all need):** ■ Fluconazole 6-12 mg/kg/d IV or po in 2 div doses for 8 wks. Maximum dose: 200mg Life long secondary prophylaxis (all need):Fluconazole 6-12 mg/kg/d po in one daily dose. Maximum dose: 200mg *Note: Alternative for 8 weeks continuation phase is Itraconazole where cost and availability allow. Itraconazole and IV Amphotericin B can also be used for life-long prophylaxis.*

8.6.2 Candida Infections

Important Features

- Severe oral candidiasis often the first indication of HIV-infection
- Extensive oral thrush and diaper dermitis are common
- Disseminated disease can involving other organs such as the brain, lung, skin and eyes

Table 8.11: Clinical Features, Diagnosis and Treatment of Candidal Infections

CLINICAL FEATURES AND DIAGNOSIS	TREATMENT
Clinical Features: **Oral thrush** ■ Creamy white curdlike patches with underlying erythema. ■ Erythemtous, hyperplastic or angular chelitis ■ Decreased oral intake, odynophagia, dysphagia	**Oral Candidiasis:** ■ Nystatin susp 4-6mL po 4 times daily for 14 days ■ Clotrimazole mouth paint 4 times daily for 14 days Note: Alternatives include Fluconazole, Ketoconazole and Itraconazole
Oesophagial candiadiasis ■ Retrosternal pain, dysphagia, odynophagia, usually with oral thrush	**Oesophagial Candidiasis:** ■ Fluconazole 3-6 mg/kg/dpo once daily (maximum: 200mg) for 21 days ■ Ketoconazole 10 mg/kg/d div 2 doses (not as effective as Fluconazole, but much cheaper) *Note: Alternatives include Itraconzole and Amphotericin B*
Disseminated candidiasis ■ Sepsis and shock.	**Disseminated Candidiasis:** ■ Amphotericin B 0.5 – 1.5mg/kg/day i.v. for 14-21 days
Diagnosis: ■ Usually clinical ■ KOH stain of scraping: pseudohyphae ■ Endoscopy and biopsy, if available *Note: Fungal blood cultures can be helpful, but are not widely available.*	**Prophylaxis:** ■ For recurrent candidiasis, daily prophylaxis with Fluconazole is recommended. **Warning, azole drugs can have interactions with ARV medications. See Annex 2*

8.7 Mycobacterium Avium Complex Disease (non-TB mycobacterium)

Important Features

- Risk with low CD4 count (< 50 cells/ ml)
- Disseminated infection with MAC is rare
- Lungs, Liver, Spleen, gastrointestinal tract, bone marrow and lymph nodes are the common sites of involvement.
- Low incidence in this region.

Table 8.12: Clinical Features, Diagnosis and Treatment of Atypical Mycobacterial Infections

CLINICAL FEATURES AND DIAGNOSIS	TREATMENT
Clinical Features: ■ Indolent and slowly progressive ■ High grade fever, weight loss, abdominal pain and anaemia ■ Lymphadenitis ■ Night sweats, diarrhoea, malaise, ■ Hepatomegaly and intra-abdominal absceses ■ Meningoencephalitis ■ Osteomyelitis and soft tissue abscesses **Diagnosis:** ■ Anaemia and Neutropenia ■ CXR: non-specific changes like diffuse and focal infiltrates, cavitary lesions and hilar adenopathy ■ Blood cultures with radiometric assay (may require multiple cultures to isolate) ■ Histology showing AFB in macrophages *Note: Cultures are important, but not widely available in this setting. PCR also possible*	Regimen should include: ■ Azithromycin 10-12mg/kg/d po once daily (maximum: 500mg) PLUS ■ Ethambutol 15-20mg/kg/d po once daily (maximum 1gm) with or without a third drug: ■ Ciprofloxacin 20-30mg/kg IV or po once daily (maximum 1.5 gm) Note: Other possible drugs to substitute Include: Clarithromycin (in place of Azithro), Rifabutin (as an alternative third drug) and Amikacin (as an alternative third drug) Warning: Consultation with Pediatric HIV specialist is encouraged when deciding on treatment regimen for MAC *Note: Although used in some parts of the world, primary prophylaxis of MAC is generally not promoted in the Asian setting.*

8.8 Toxoplasma Gondii Infection

Important Features

- May manifest as congenital toxoplasmosis
- Transmission of toxoplasma to fetuses is most common with primary maternal toxo infection, but has been seen with chronic infection among HIV positive mothers.
- Very rarely presents with acquired CNS disease in childhood

TABLE 8.13: Clinical Features, Diagnosis and Treatment of Toxoplasmosis

CLINICAL FEATURES AND DIAGNOSIS	TREATMENT
Clinical Features: Congenital toxoplasmosis: ▪ Low birth weight ▪ Microcephaly ▪ Hydrocephalus ▪ Hepatosplenomegaly ▪ Choriorentinitis ▪ Can be fulminant and rapidly fatal CNS toxoplasmosis: ▪ Headache ▪ Fever ▪ Change in mental status, psychosis ▪ Seizures ▪ Focal neurological deficits such as hemiparesis, ataxia and cranial nerve palsies **Diagnosis:** Congenital toxoplasmosis: ▪ Serum IgM or IgA CNS Toxoplasmosis: ▪ Clinical presentation ▪ Presence of IgG antibodies ▪ CT scan: Multiple ring-enhancing lesions *Note: MRI and brain biopsy are less available diagnostic options*	**Congenital toxoplasmosis:** Treatment needed for all infected infants even without symptoms and all whose mothers had symptomatic toxoplasmosis in pregnancy. Pyrimethamine 2 mg/kg/d for 2 days, then 1 mg/kg/d for 2-6 months then 1 mg/kg 3 times/week PLUS Sulfadiazine loading dose 100 mg/kg/d in 2 div doses PLUS Leucovorin (folinic acid) 5-20 mg/d given 3 times per week Total duration should be 12 months **Acquired Toxoplasmosis:** Pyrimethamine 2 mg/kg/d for 2 days, then 1 mg/kg/d (max 25 mg/d) PLUS Sulfadiazine loading dose 75 mg/kg/d Followed by 50 mg/kg/d PLUS Leucovorin (folinic acid) 5-20 mg/day 3 times a week Continue for at least 4-6 weeks beyond resolution of signs and symptoms. Curative therapy should be followed by lifelong prophylaxis. *Note: Above regimens are recommended treatments, but may be unaffordable or unavailable locally. TMP-SMX (5mg/kg TMP) IV or po bid for 30 days may be substituted for above regimen (not studied in children). Reference: Sanford Guide to HIV/AIDS Therapy 2004* *Note: Add Prednisolone 1 mg/kg/d for chorioretinitis or elevated CSF protein*

chapter 9

Immunization of Children Exposed / Infected with HIV

9.1 Introduction

The majority of children with maternally transmitted HIV infection acquire the infection during or shortly after birth. Early in life they are immunologically normal and only later without specific treatment do they develop progressive immunodeficiency. The safety and efficacy of vaccines administered to these children depend on the immunological status of the child at the time of vaccination.

"Children with symptoms suggestive of HIV may have a poorer response to immunization than children without symptoms. Early immunization is important because children with HIV infection are at higher risk of developing severe forms of preventable diseases." UNAIDS

9.2 Safety and efficacy of vaccination in HIV-infected children:

- Following the immunization of HIV-infected infants most vaccines have shown satisfactory immunogenicity.
- Few adverse events have been observed with vaccination of HIV-infected children.
- WHO guidelines support the routine use of Oral Polio and Measles live vaccines in HIV-infected children.

9.3 Immunization Schedule

The current WHO guidelines for immunizing children known to have HIV infection and for infants born to HIV-infected women differ only slightly from Nepal's National Immunization Schedule. Immunization should be done as early in life as possible, as per national recommendations, to optimize the immune response and for early protection of the HIV-infected child from common as well as opportunistic infections.

Nepal National Immunization Schedule for HIV exposed or infected infants

AGE OF INFANT	VACCINE
Birth	BCG
6 Weeks	DPT-1 OPV-1 HB-1
10 Weeks	DPT-2 OPV-2 HB-2
14 Weeks	DPT-3 OPV-3 HB-3
6 Months	Extra dose of Measles
9 Months	Measles

BCG- Bacille Calmette Guerin, OPV-Oral Polio Vaccine, HB-Hepatitis B

1. BCG:

WHO recommends(2007) that children who are known to be HIV-infected, even if asymptomatic, should not be immunized with BCG vaccine. Recent evidence shows that children who were HIV-infected when vaccinated with BCG at birth and who later developed AIDS, were at increased risk of developing disseminated BCG disease. Among these children, the benefits of potentially preventing severe TB are outweighed by the risks associated with the use of BCG vaccine. However, because of the difficulties in identifying infants infected with HIV at birth, BCG vaccination may need to be given at birth to all infants regardless of HIV exposure, in areas with high endemicity of tuberculosis and populations with high prevalence.

2. DTP:

Children who have had recurrent convulsions or active central nervous system disease or who had shock or convulsions within 3 days of receiving a DPT vaccination should not receive subsequent DPT vaccinations. For those children, substitute the DT formulation. All subsequent DT immunization may be given

3. OPV:

If the child has diarrhea and is scheduled to receive OPV, the dose should be given as scheduled. However, the dose should not be counted in the schedule, and an additional dose of OPV should be given after the diarrhea has resolved.

4. HB:

There are multiple Hepatitis B vaccinations schedules depending on local epidemiology. Provide 3 doses of the vaccine at least four weeks apart (minimum four week interval). Doses may be given as noted above or first dose can be given at birth, followed by a second and third dose at the time of the first and third DPT vaccination. Alternatively, a four dose schedule may be used where the dose at birth is followed by three additional doses, following the schedules commonly used for DPT.

5. MEASLES:

Because of the increased risk of early and severe measles infection, HIV-exposed infants who are not severely immunocompromised should receive a dose of standard measles vaccine (or where measles-mumps-rubella (MMR) combined vaccine is given, combined MMR vaccine is recommended whenever one or more of the individual components are indicated) at 6 months of age with a second dose as soon after the age of 9 months as possible. Children who are severely immunocompromised (based on age-specific CD4 lymphocyte) due to HIV infection should not receive measles vaccine until immunological improvement is observed.

9.4 Optional Vaccines

1. YELLOW FEVER:

The live attenuated vaccine should not be administered to individuals with **symptomatic** HIV infection**.** However **asymptomatic** children in endemic areas should receive the vaccine at 9 months of age

2. HIB:

The first dose of Haemophilus influenza type b vaccine can be given at six weeks of age or older. Give three doses at 4-8 week interval. Some countries recommend a booster dose at 12-18 months of age. Hib should be delayed if the child is severely immunocompromised.

3. VARICELLA VACCINE:

The first dose should be given only to asymptomatic, non-immunocompromised children. The recommended schedule is one dose at or after 12 months. Administer second dose at 4-6 years; may be administered 3 months or more after the first dose. Consider giving varicella vaccine within 3 days to asymptomatic, non-immunocompromised children following household contact with a varicella case as it reduces infection rate and severity of cases.

4. MENINGOCOCCAL MENINGITIS VACCINE:

Safe, though immunogenicity may be low. Not recommended by WHO. Different countries dosing schedule varies widely. Recommended at 2 years of age with a booster every 3 years.

5. PNEUMOCOCCAL CONJUGATE VACCINE:

The first dose of PCV can be given at 6 weeks of age or older, and then at intervals of at least 4 weeks. The vaccine may be administered along with other vaccines provided that a separate syringe and injection site are used.

5. HEPATITIS A VACCINE

Safe and effective. Recommended at 12 and 18 mo of age.

- All children who have been exposed to HIV should be fully immunized according to age. Because most children who are HIV-infected do not have severe immune suppression during the first year of life, immunization should occur as early as possible after the recommended age to optimize the immune response.
- **BCG and live attenuated vaccines (including influenza, Japanese encephalitis, measles, mumps, rubella, typhoid, varicella and yellow fever)** should not be given to children with signs or symptoms of HIV infection.

9.5. Immunoglobulins

- Infants born to HBsAg-positive mothers should receive Hep B vaccine and 0.5 ml hepatitis B immunoglobulin (HBIG) ideally within 12 hours of birth (no later than age 1 week), at separate sites.

chapter 10

Counselling of HIV Infected Children and Their Parents

Child:	0 to 18 years of age (CRC/UNICEF)
Adolescents:	10 to 19 years of age (WHO/UNFPA)
Young people:	15 to 24 years of age (WHO/UNFPA)
Orphan:	0-18 whose mother (maternal orphans) or father (paternal orphans) or both (double orphans) are dead UNICEF/UNAIDS/WHO)

10.1 HIV and AIDS and the rights of the child

Regarding the counselling services for HIV infected children and their parents, it is important to review the rights of the child in the context of HIV/AIDS. The access to voluntary, confidential HIV counselling and testing services is fundamental to the rights and health of children and critical to their ability to reduce the risk of contracting or transmitting HIV, to access HIV care, treatment and support and to plan for their future. Consistent with obligations under Article 24 of the Convention on the Rights of the Child (CRC), states are to ensure that no child is deprived of his or her right of access to the necessary health services.

10.2 Policy Background

All policy guidelines on testing HIV antibodies support the need for confidential, voluntary counselling and testing and find mandatory testing to be a violation of human rights. All HIV tests should be voluntary with guaranteed confidentiality and adequate pre- and post-test counselling.

The *UNAIDS/WHO Policy Statement on HIV Testing, June 2004* states clearly that UNAIDS/WHO support the 3 C's: **confidential**; be accompanied by **counselling**; and only be conducted with informed **consent**, meaning that it is both informed and voluntary. Testing for HIV antibodies is more than a mere biological test as it involves ethical, human and legal dimensions. UNAIDS and WHO do not support mandatory testing of individuals on public health grounds.

In July 2003, National HIV/AIDS VCT guidelines for Nepal was developed by the National Centre for AIDS & STD Control (NCASC) of the Ministry of Health and Population(MOHP) with its implementing partners. The guidelines contain specific reference to consent and confidentiality: clients need to provide informed consent. Written consent is required for HIV testing in all age groups whether an adult, 'mature' minor or child. The guidelines provide that this involves and includes education on HIV, disclosure of advantages and disadvantages of HIV testing, listening to the client and asking and answering questions before proceeding.

10.3 Targeted VCT interventions in Children

Conditions for Voluntary Counselling and Testing for Children

It is strongly recommended that the following minimum conditions be in place before Voluntary Counselling and Testing is offered to children:

- Age-appropriate pre- and post-test counselling

- Availability of child-friendly, quality care services including the provision of medicines for opportunistic infections
- Availability of continued support including sustained counselling
- Availability of NGO or social welfare services to guarantee the care and support of children through 18 years of age who do not have any family network
- Awareness raising on HIV and AIDS and advocacy in the communities where the children come from if they are still with their parents
- There should be informed consent for counseling and testing. For informed consent of minors(below 18 years) refer to the latest VCT guidelines

10.4 Pediatric Disclosure: Talking to Children about HIV

Disclosure about all things related to HIV and AIDS is a process that requires repeated, continuous, and attentive conversation with children. Once disclosure to a child occurs, dialogue about the topic will need to continue. It will change and evolve as children progress through different developmental stages, and as treatments and circumstances change and transform. Children who are well informed about all aspects of HIV and AIDS will ultimately contribute to the strength of families and communities who are facing the epidemic. Youth who have experienced open and honest information will mature into adults who are equipped both to manage and prevent HIV and AIDS.

The parents may be stressed, worried, anxious, tense, sleepless or easily irritated until they find out whether their infant is infected or not. Voluntary counselling and testing (VCT) services can play an important role in helping parents to decide about whether to inform a child about their own or a family member's HIV status and when to do it. Some considerations are:

- Maturity and health of the child has to be considered
- Very young children will not understand the stigma and discrimination that can happen because of HIV and AIDS
- Truth can often be less threatening to a child than the fear of the unknown. Sometimes, if the child is not informed, he/she may have suspicions because of overheard conversations or noticing differences at home. Children can often make up their own complicated and incorrect explanations. Avoiding talking to a child about illness in the family may make it easier for the parent to cope, but it can make the child feel anxious, guilty and upset. If the child cannot talk about his/her fears, it can lead to many problems.

When informing a child:

- Language and concepts used should be appropriate to their age
- First ask them what they think and understand about HIV/AIDS
- Words, pictures and drawings should be used to explain about HIV
- Be direct and use language they can understand
- Ask them if they have any questions they would like to ask
- Ask the child to draw a picture about it. This may help to understand what they are thinking and their reaction. It is good to talk about their feelings with the family so that the child can feel supported and can understand what is happening. A lot can be learnt about how a child is feeling by listening to them, their parents and looking at the pictures they draw.

10.4.1 How to tell a child

While each family will have different needs and questions, it may be helpful to begin the conversation by addressing the four domains listed below. By gradually reviewing – and expanding upon – each set of questions, families will be more likely to engage in a comprehensive process of considering disclosure. Providers will also have more opportunities to share relevant stories and guidance, and caregivers who decide to disclose will have opportunities to make careful plans and to practice how to begin.

The child (or children):

- Is the child symptomatic? Taking medication?
- How old is the child? How verbal? Is s/he functioning as an adult?
- Is the child living with a sick parent or sick family members?
- Is the child asking questions about HIV?
- Does the child appear distressed, anxious, or worried?
- Is the child sexually active and at risk of contracting or spreading HIV?

The parent / adult caregiver(s):

- Has the parent/caregiver been tested for HIV?
- Is the parent/caregiver infected? Symptomatic? Taking medication?
- If the adult is ill, is s/he in need of help from children in the household?
- Is the infected adult an important attachment figure for the child?

The family / household:

- Are any adults in the household HIV-infected? Who is aware?
- Are any other children in the household HIV-infected? Who is aware?
- How many family members are taking HIV-related medication?
- Is the family unit cohesive, or characterized by separations and/or conflicts?

The community:

- Is testing and treatment generally available in the community?
- Are there people in the community who are open about their own HIV status? Does the child know anyone in the community who is open about his/her HIV status?
- How strong is the stigma surrounding HIV in the community? Are there risks to the family (e.g. isolation, discrimination) if inadvertent disclosure occurs?
- Are there resources within the community for children – e.g. a youth group, and/or trusted adults that they can talk to?

10.4.2 Assessing Readiness for Disclosure

Parents and caregivers who have decided to discuss HIV with their children will often ask providers if their child is ready for disclosure. While there is no perfect way to determine the answer, adults can easily look for clues that suggest a child is seeking more information. One valuable way to assess a child's readiness for disclosure is through individual counseling sessions with the child. Another is in the context of group counseling settings, where a number of children in similar circumstances are encouraged to meet together with the guidance of one or more counselors. Clearly, these counseling sessions are only indicated if the parent or caregiver consents to this kind of help.

The effort to keep HIV secret and to continually hide the truth from a child can be exhausting and ultimately difficult to sustain; it can drain energy and time from more important tasks. Secrecy can also impede a child's ability to come to terms with his/her illness and may impede older children's ability to keep themselves safe in sexual relationships.

The following are some examples of language that parents and providers may find helpful as they adjust their comments to a child's questions and developmental level.

To a 4 or 5-year-old:

"The blood in your body has a germ (or virus) in it that can make you sick—that's why you need to take medicine."

"It is important to take your medicine every day so that your body will stay strong."

"A virus is something that gets inside your body, into your blood, and can make you sick. Like a cold. A cold is a virus. HIV is also a virus and it is in your blood(….and in Mommy's/Daddy's).

To a school-aged child:
"You were born with the HIV virus because it passed from Mummy's blood to yours when you were in her tummy."

"Having HIV does not mean that anything is wrong with who you are. It is a virus in your blood. There are all different kinds of viruses that people can have."

"HIV is the name of the virus in your blood. AIDS is the name of the illness that happens if HIV is not treated. You take medicine to treat the HIV virus so that you will not get sick."

"Having HIV is something private and something that you can decide about telling others. You don't have to tell other people if you don't want to. On the other hand, it is OK to tell other people who may need to know (e.g., teacher, nurse, etc. if parent/caregiver approves). HIV is nothing to be ashamed of."

To an adolescent:
"You have HIV. HIV is a virus. A virus is something that gets inside your body, into your blood, and can make you sick. It does not necessarily mean that you are going to get very sick. You have the power to control the virus by taking your medication every day. "

"Knowing about HIV and having it in your blood, gives you a special responsibility not pass the virus to other people. You can prevent getting the virus again, or giving it to others by (explain, based on teen's current risk situation and sexual maturity).

"Having HIV does not mean that you cannot live a full life with loving, sexual relationships. It does mean that you need to plan carefully about your future with others so that you make good decisions about your safety and the welfare of others."

"Lots of teens with HIV around the world have found that having the virus gives them a special kind of strength— strength to educate others about HIV, to prevent the spread of the virus; and to change people's misinformation and prejudices. You may decide that you want to use your HIV status to make a positive difference in other people's lives."

In all HIV disclosure conversations, no matter what age a child is, it is helpful to let a child/teen know that s/he can always ask more questions, and that adults will do the best they can to supply answers.

10.5 Adherence in Children

- Adherence can be particularly difficult for children and their caretakers. It requires both the commitment of a responsible adult and the involvement of an ill child. The child's developmental stage will influence the extent to which s/he can or will cooperate with medication administration, as will the parent-child relationship.
- Pediatric formulations are not always suited for administration to infants and young children; they may taste bad or be difficult to swallow. Pediatric antiretroviral regimens are frequently complex, requiring caretakers to measure liquid formulations, crush pills, open capsules, or dissolve tablets in water; doses may increase as the child gains weight. Furthermore, children are often tended by more than one caretaker, complicating both administration and assessment of adherence, and provoking disclosure issues.

These factors should not discourage programs from including children – after all, the lifesaving benefits of pediatric antiretroviral treatment dramatically outweigh the challenges. But they do mean that special attention to and expertise in pediatric adherence is an essential component of

care. We recommend a four-part approach to pediatric adherence, focusing on education, preparation, ongoing assessment, and support. This chapter will focus on adherence to treatment; adherence to care is also of utmost importance.

10.5.1 Education

- Pediatric care is a partnership between clinicians, caregivers and children. This collaboration is particularly important in HIV and AIDS care, and is critical to the success of pediatric antiretroviral treatment. An informed and committed adult, supported by an experienced multidisciplinary care team, is a mandatory part of the equation.

- Antiretroviral treatment is different from any other medications the child (or family) has taken. It is important to explore expectations, and to explain exactly what is required for treatment success. Caretakers should know that the goal is to take every dose, every day, for life. Medications must be taken on schedule, in the right combination, and at the correct dose. Coordinating treatment with meals, school, and other activities is a challenge, and caretakers should be aware of how difficult it can be.

- Using simple terms, visual aids, and relevant analogies, program staff should clearly explain why such high levels of adherence are required. Caretakers should understand that missing doses of medications can lead to treatment failure, and that taking medications irregularly or intermittently may confer all of the risks and none of the benefits of antiretroviral treatment.

10.5.2 Preparation

Taking the time to prepare patients and families can make the difference between treatment success and treatment failure, and should be a routine part of prescribing antiretroviral therapy. For ease of administration, consider Fixed Drug Combination (FDC) tablets in the treatment regimen especially in infants.The caretakers should be able to confidently answer the questions below before medication is prescribed. The team should help caretakers practice medication administration, anticipate problems and solutions, and understand what to do in case of difficulty. Peer support can be invaluable; parents may learn as many practical tips from other parents as they do from the care team.

- **Who will administer the medications?**

While the primary caretaker is likely to be the person working with the multidisciplinary team, other adults may also be involved with the child's care. Ideally, everyone who cares for the child would know how to administer the treatments. Stigma and secrecy complicate adherence for children, as they do for adults, and ART preparation will need to be personalized to the circumstances of each household.

- **What medications will be given?**

While children and caregivers do not necessarily need to know the formal or technical names of each medication, they must be able to confidently identify each one, and know how it is to be stored, measured, and administered. Pediatric formulations can make this particularly difficult – for example, many of the ARV syrups are the same color. Clearly labeling, marking, or color-coding the medications can be enormously helpful, and a close partnership with the dispensing pharmacist is important.

- **When will medications be given?**

ARVs should be given at the same time every day. Some ARVs do need to be taken on an empty stomach and others with food. Caretakers should know when to give medications – a watch is not required, but some practical system of timekeeping (e.g. sunrise, sunset) will be important.

■ **How will medications be given?**

The details of ART administration are particularly complex for children, and this aspect of preparation should be reviewed in detail and practiced carefully. Caretakers must know how to measure the doses – do tablets need to be cut or crushed? Should syrups be measured with a specific measure or with a syringe? Should medicines be taken with or without food? Does the taste of a particular ARV need to be masked? Can the medicines be taken at the same time? What should be done if a child spits out or vomits the medication?

10.5.3 Assessment

■ Adherence assessment is an integral part of an adherence support program. There is no perfect way to measure adherence in the clinical setting, although the importance of good communication between family and provider, and the utility of multidisciplinary teams cannot be overstated. At a minimum, families should be asked about adherence at every visit and pharmacy records should be reviewed on a regular basis. Asking patients to report on missed doses during the last week prior to the visit can be a useful way to assess adherence.

■ Asking specific, open ended questions about concerns with administration or tolerance of medication is often a good way to learn of adherence problems. Pill counts, home visits, and parallel histories from different family members can also be helpful, although these will not be appropriate in all settings. As children grow, they should be included in the discussion of adherence. Many children learn to participate in their own care, and take on increasing responsibilities as they age. Older children should be asked about missed doses and about problems taking the medications.

10.5.4 Ongoing Support

Adherence support should not be reserved for only those with problems taking medications, but should be offered to all patients throughout the course of treatment. Lifelong adherence to complex regimens is a difficult task and it is far better to prevent problems by identifying and supporting effective strategies, than to try and remedy them once they have occurred.

Psychosocial support for adherence can take the form of counseling to explore disclosure issues, peer groups to provide emotional support, or adherence partners who make a commitment to help with the child's ART. Practical support includes adherence aids (pillboxes, blister packs, calendars, labeled syringes etc.), the preparatory steps above, and a creative and personalized approach to problem-solving.

By anticipating that adherence may falter over time, providers can develop a systematic approach to prevention and correction. If problems are identified, the cycle starts again, with education, preparation, assessment, and support.

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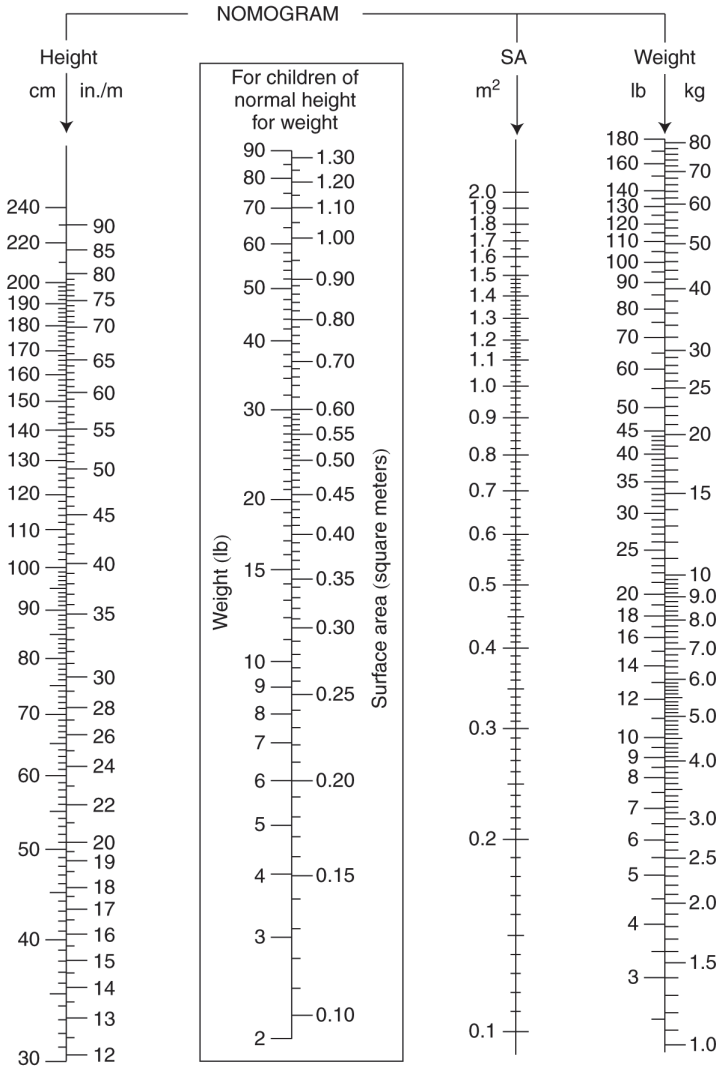
ANNEX 1:
Pediatric Antiretroviral Drug Doges

Tables of simplified paediatric ARV dose ranges (WHO 2006)

ARV doses need adjustment with change in body weight during follow-up as the child responds to ART with catch-up in growth and weight. These tables provide suggested simplified dose schedules based upon the existing formulations available in most countries. They provide the closest dosing possible using the specified formulation, and indicate where it is not possible to get a reasonable dosing range with a formulation or where the drug is usually not recommended for use in this age. Doses are provided in weight bands and have assumed the basic conversion of body mass to weight as outlined in the table.

AGE OR WEIGHT OF CHILD	DRUG DOSAGE BY SURFACE AREA (M^2) OF THE CHILD
Neonatal (< 1 month)	0.2–0.25 m^2
Young infant (1–<3 months)	0.25–0.35 m^2
Child 5–9 kg	0.3–0.45 m^2
Child 10–14 kg	0.45–0.6 m^2
Child 15–19 kg	0.6–0.8 m^2
Child 20–24 kg	0.8–0.9 m^2
Child 25–29 kg	0.9–1.1 m^2
Child 30–39 kg	1.1–1.3 m^2

Example: if the recommended dose is given as 400mg/m^2 twice per day, then for a child in the weight range 15–19 kg the recommended dose will be: (0.6–0.8) x 400 = 244–316 mg twice per day



Note: Nomogram modified from data of E. Boyd by C.D. West; from Behrman, R.E., Kliegman, R.M., & Jenson, H.B. (eds.). (2000). Nelson textbook of pediatrics (16th ed.). Philadelphia: W.B. Saunders.

Antiretroviral Drugs Pediatric Dose Chart - 2008

Weight	Zidovudine (ZDV or AZT)			Lamivudine (3TC)	
	240mg/m² / dose **Twice daily**			4mg/kg /dose **Twice daily**	
KG	**LIQUID** 10mg/ml	**CAPSULE** 100mg	**TABLET** 300mg	**LIQUID** 10mg/ml	**TABLET** 150 mg
5-6	7 ml	-	-	3 ml	-
7-9	9 ml	-	-	4 ml	-
10-11	10 ml	-	-	5 ml	-
12-14	12 ml	-	-	6 ml	-
15-19	-	2 morning, 1 evening	1/2	7 ml	1/2
20-24	-	2	1/2	-	1 morning ½ evening
25-29	-	2	1 morning ½ evening	-	1
30-35	-	3	1	-	1
35-40	-	3	1	-	1
≥ 40	-	3	1	-	1

Zidovudine tablets can be crushed and capsules may be opened and dispersed in water or onto a small amount of food and immediately ingested. Oral solution is stable at room temperature but light sensitive. Do not use with Stavudine due to antagonistic effect. Use with caution in children with anemia.

Lamivudine tablets can be divided into two equal halves and crushed and dispersed in water or onto a small amount of food and immediately ingested. Oral solution is stable at room temperature. Use within one month of opening.

Weight	Nevirapine (NVP)		Stavudine (d4T)			
	Induction dose **Once daily** for 14 days Maintenance dose 160-200 mg/m^2/dose **Twice Daily**		1mg/Kg/dose **Twice daily**			
KG	**LIQUID** 10mg/ml	**TABLET** 200 mg	**LIQUID** 1mg/ml	**CAPSULE** 15 mg	**CAPSULE** 20 mg	**CAPSULE** 30 mg
5-6	6 ml	-	6ml	-	-	-
7-9	8 ml	-	9 ml	-	1/2	-
10-11	10 ml	1/2	11 ml	-	1/2	-
12-14	11 ml	1/2	-	1	-	1/2
15-19	14 ml	1 morning ½ evening	-	1	1	1/2
20-24	-	1 morning ½ evening	-	-	1	-
25-29	-	1	-	2	-	1
30-35	-	1	-	2	-	1
35-40	-	1	-	-	-	1
≥ 40	-	1	-	-	-	1

Nevirapine tablets can be divided into two equal halves and crushed and dispersed in water or onto a small amount of food and immediately ingested. Oral solution is stable at room temperature. Shake well before use. Rash can occur during the first 14 days of dosing. If severe rash occurs (especially if accompanied by fever, blisters or mucosal ulcerations), discountinue drug. Avoid coadministration with Rifampicin if possible.

Stavudine capsules may be opened and dispersed in water or onto a small amount of food and immediately ingested. The oral solution needs to be refigerated and shaken well before use. Do not use with Zidovudine due to antagonistic effect.

Weight	Efavirenz (EFV)		Abacavir (ABC)	
	Dose: 15 mg/Kg >3 yrs or 10 Kg **Once daily**		8mg/Kg/dose **Twice daily**	
KG	**CAPSULE** 200 mg	**CAPSULE** 600 mg	**LIQUID** 20mg/ml	**TABLET** 300 mg
5-6	-	-	2.5 ml	-
7-9	-	-	4 ml	-
10-11	1	-	5 ml	-
12-14	1	-	6 ml	1/2
15-19	1	1/2	7 ml	1/2
20-24	1½	1/2	-	1 morning ½ evening
25-29	2	-	-	1
30-35	2	-	-	1
35-40	2	-	-	1
≥ 40	-	1	-	1

Efavirenz is not approved for children <3 years and below 10 kg weight. It can be given with or without food, but high fat meals should be avoided for best absorption. Preferably given at bed time to reduce CNS side effects, especially during first two weeks. Capsules can be opened and added to small amount of sweet food or drink to disguise peppery taste.

Abacavir is available as a tablet or a yellow oral solution. The solution and tablets can be stored at room temperature. Tablets can be divided into two equal halves and crushed and dispersed in water or onto a small amount of food and immediatley ingested. It can cause severe hypersensitivity reactions and should never be used if it occurs.

Weight	Didanosine(ddI)			Lopinavir/ritonavir (LPV/r)	
	90 - 120 mg/m^2/dose **Twice daily**			**Dose of LPV** 5-7 Kg: 16mg/Kg/dose 8-9 Kg: 14mg/Kg/dose 10-13 Kg: 12mg/Kg/dose 14-39 Kg: 10mg/Kg/dose **Twice daily**	
KG	**LIQUID** 10mg/ml	**TABLET** 25 mg	**TABLET** 250 mg	**LIQUID** LPV/r 80mg/20mg/ml	**TABLET** LPV/r 200/50mg
5-6	5 ml	2	-	1.5 ml	-
7-9	6 ml	2	-	2 ml	-
10-11	7 ml	3 morning 2 evening	-	2 ml	-
12-14	8 ml	3	-	2 ml	1
15-19	9 ml	4	-	2.5 ml	1
20-24	-	5 BD	1 OD	3 ml	1
25-29	-	5 BD	1 OD	3.5 ml	2 morning 1 evening
30-35	-	5 BD	1 OD	4 ml	2
35-40	-	5 BD	1 OD	5 ml	2
≥ 40	-	-	1 OD	-	2

Didanosine should be given on an empty stomach one hour before or two hours after a meal. The suspension needs to be refigerated and shakel well before admisistering.
At least two tablets of appropriate strength must be used at any one time of adequeate buffering (e.g. If the dose is 50 mg, administer two 25 mg tablets instead of one 50 mg tablet). The tablets should be chewed, crushed or dispersed in water before they are taken. Capsules are designed for once daily dosing.

Lopinavir/ritonavir oral solution should be taken with food. Oral solution should be refrigerated. Oral solution is bitter to taste. No food restriction with tablets. Tablets cannot be split.

Fixed drug combination ARV drugs

Weight	Zidovudine and Lamivudine	Stavudine and Lamivudine	Zidovudine / Lamivudine / Nevirapine
KG	ZDV / 3TC (300mg/150mg) **Twice daily**	d4T / 3TC (30mg/150mg) **Twice daily**	ZDV/ 3TC / NVP (300mg/150mg/200mg) **Twice daily**
5-8	-	-	-
9-10	-	-	-
11-14	-	1/2	-
15-19	1/2	1 morning ½ evening	½ BD Plus ½ extra NVP in evening
20-24	1 morning, ½ evening	1 morning ½ evening	1 morning ½ evening
25-29	1 morning ½ evening	1	1 morning, ½ evening Plus ½ extra NVP in evening
30-39	1	1	1
≥ 40	1	1	1

Weight	Stavudine / Lamivudine / Nevirapine		
KG	Pediatric d4T-30/3TC/NVP 30mg/150mg/200mg **Twice daily**	Pediatric (Junior) d4T/3TC/NVP (12mg/60mg/100mg) **Twice daily**	Pediatric (Baby) d4T/3TC/NVP (6mg/30mg/50mg) **Twice daily**
5-8	-	1/2	1
9-10	-	-	1½
11-14	1/2	1	2
15-19	1 morning ½ evening	1½	3
20-24	1 morning ½ evening	2	-
25-29	1	-	-
30-39	1	-	-
≥ 40	1	-	-

ANNEX 2
ARV Drug Interactions

TABLE 1: First Line ARV Drug Interactions

IF PATIENT IS TAKING:	DO NOT CO-ADMINISTER WITH THESE DRUGS(CONSIDER ALTERNATIVE TREATMENT)	OTHER CAUTIONS
NVP	Rifampicin Ketoconazole	For adolescents: Do not rely on oestrogen -based oral contraceptives . Switch to another form of contraception or use additional protection
3TC	No major drug interactions	
d4T	Do not give with AZT (ZDV)	Higher risk of d4T neuropathy when also taking INH
AZT (ZDV)	Do not give with d4T or ganciclovir	Higher risk of anaemia when also taking acyclovir or sulfa drugs
EFV	Diazepam (OK for convulsions in emergency) Other benzodiazepines other than Lorazepam Phenobarbitol Phenytoin Protease inhibitor ARVs	Do not take with high-fat meals.

Chronic HIV care with ARV therapy: Integrated management of adolescent and adult illness: Interim guidelines for first level facility health workers. Geneva, WHO, December 2003.

TABLE 2: Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors

	NEVIRAPINE (NVP)	EFAVIRENZ (EFV)	INDINAVIR (IDV)	LOPINAVIR (LPV/R)	NELFINAVIR (NFV)	SAQUINAVIR (SQV)
Nevirapine		No effect on NVP. EFV AUC decreased 22% Recommendation: Standard dosing Efavirenz	NVP increased twofold. IDV decreased 28% Recommendation: Change IDV dose to 1000 mg three times daily No change NVP	No effect on NVP. LPV trough decreased 55% Recommendation: Consider LPV/r 533 mg/133 mg twice daily No change NVP	No effect on NVP NFV levels increased 10% Recommendation: Standard dosing Nelfinavir (NFV)	No effect on NVP SQV decreased 25% Recommendation: Standard dosing Saquinavir (SQV)
Efavirenz			No effect on EFV. IDV decreased 31% Recommendation: Change IDV dose to 1000 mg three times daily No change EFV	No effect on EFV LPV AUC decreased 40% Recommendation: Consider LPV/r 533 mg/133 mg twice daily No change EFV	No effect on EFV NFV increased 20% Recommendation: Standard dosing	EFV decreased 12% . SQV decreased 62% Recommendation: Do not coadminister (SQV/r boosting may be possible)
Indinavir				No effect on LPV IDV AUC and trough increased Recommendation: Change IDV dose to 600 mg twice daily No change LPV	NFV increased 80 percent. IDV increased 50% Recommendation: Limited data for IDV 1200 mg twice daily with NFV 1250 mg twice daily	SQV increased fourfold to sevenfold No effect on IDV Recommendation: Insufficient data to provide recommendation

	NELFINAVIR (NVP)	EFAVIRENZ (EFV)	INDINAVIR (IDV)	LOPINAVIR (LPV/R)	NELFINAVIR (NFV)	SAQUINAVIR (SQV)
Lopinavir					No data	SQV AUC/trough increased Recommendation: SQV 800 mg twice daily No change LPV/r
Nelfinavir						SQV increased twofold to fivefold NFV increased 20% Recommendation: Fortovase 1200 mg twice daily No change NFV
Antifungal Ketocon-azole	NVP increased 15-30 % Ketoconazole decreased 63% Recommen-dation: Do not coadminister	No data	IDV increased 68% Recommendation: Change IDV to 600 mg three times daily	LPV decreased 13% Ketoconazole increased threefold Recommendation: None	No dose adjustment	SQV increased threefold Recommendation: Standard dosing
Antimycob acterials Rifampin	NVP decreased 37% Recommendation: Use with caution only if no alternatives available	EFV decreased 25-33% Recommendation: Consider standard dosing	IDV decreased 89% Recommendation: Do not coadminister	LPV AUC decreased 75% Recommendation: Do not coadminister	NFV decreased 82% Recommendation: Do not coadminister	SQV decreased 84 % when given without RTV Recommendation: If using SQV/RTV rifampin can be used at 600 mg/day or two or three times weekly. High incidence LFT abnormalities.
Clarithro-mycin	NVP increased 26%. Clarithromycin decreased 30% Recommen-dation: Standard dosing	EFV unchanged Clarithromycin decreased 39%. Recommendation: Do not coadminister	Clarithromycin increased 53% Recommendation: Standard dosing	No data	No data	Clarithromycin increased 45%. SQV increased 177 % Recommendation: Standard dosing

	NELFINAVIR (NVP)	EFAVIRENZ (EFV)	INDINAVIR (IDV)	LOPINAVIR (LPV/R)	NELFINAVIR (NFV)	SAQUINAVIR (SQV)
Oral contr-aceptives	Estradiol decreased 20 % Recommenda-tion: Use alternative or additional methods	Estradiol increased 37%; no data on other components Recommendation: Use alternative or additional methods	When used with RTV: estradiol decreased Recommendation: Use alternative or additional methods	Estradiol decreased 42% Recommendation: Use alternative or additional methods	Estradiol decreased 47%; norethindrone decreased 18% Recommendation: Use alternative or additional methods	When used with RTV: estradiol decreased Recommendation: Use alternative or additional methods
Methadone	Methadone decreased significantly Recommen-dation: Opioid withdrawal reported; may require increase in methadone dose	Methadone decreased significantly Recommendation: Opioid withdrawal reported; may require increase in methadone dose	No change, but there may be a decrease if given with low dose RTV Recommendation: When IDV is given with low dose RTV: opioid withdrawal possible; may require increase in methadone dose	Methadone AUC decreased 53% Recommendation: Opioid withdrawal possible; may require increase in methadone dose	May decrease methadone levels Recommendation: Opioid withdrawal possible; may require increase in methadone dose	No data but may decrease if given with low dose RTV Recommendation: When given with low dose RTV: opioid withdrawal possible; may require increase in methadone dose
Anticon-vulsant: Pheno-barbital	Unknown	Unknown		Anticonvulsant unknown, but may decrease LPV levels substantially Recommendation: Monitor anticon-vulsant levels	Anticonvulsant Unknown, but may decrease NFV levels substantially Recommendation: Monitor anticon-vulsant levels	Anticonvulsant Unknown, but may decrease SQV levels substantially Recommendation: Monitor anticon-vulsant levels
Lipid-lowering agents: Simvastatin Lovastatin Atorastatin	No data	No data	Potential for large increase in statin levels (except pravastatin) Recommendation: Do not coadminister except pravastatin; no dose adjustment	Potential for large increase in statin levels Recommendation: Do not coadminister	Potential for large increase in statin levels Recommendation: Do not coadminister	Potential for large increase in statin levels Recommendation: Do not coadminister

Source: Scaling Up Antiretroviral Therapy in Resource Limited Settings: Guidelines for a Public Health Approach. Geneva: WHO, 2002, pp. 112-113

ANNEX 3

Presumptive and definitive criteria for recognizing HIV-related clinical events in infants and children with established HIV infection

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Cliincal Stage 1		
Asymptomatic	No HIV-related symptoms reported and no clinical signs on examination	Clinical diagnosis
Persistent generalized lymphadenopathy (PGL)	Persistent enlarged lymph nodes > lcm at two or more non-contiguous sites(excluding inguinal), without known cause	Clinical diagnosis
Cliincal Stage 2		
Unexplained a persistent hepatosplenomegaly	Enlarged liver and spleen without obvious cause	Clinical diagnosis
Papular pruritic eruptions	Papular pruritic vesicular lesions	Clinical diagnosis
Fungal nail infections	Fungal paronychia (painful, red and swollen nail bed) or onycholysis (painless separation of the nail from the nail bed). Proximal white subungual onchomycosis is uncommon without immunodeficiency.	Clinical diagnosis
Angular cheilitis	Splits or cracks at the angle of the mouth not attributable to iron or vitamin deficiency, and usually responding to antifungal treatment.	Clinical diagnosis
Lineal gingival erythema (LGE)	Erythematous band that follows the contour of the free gingival line; may be associated with spontaneous bleeding.	Clinical diagnosis
Extensive wart virus infection	Characteristic warty skin lesions; small fleshy grainy bumps, often rough, flat on sole of feet (plantar warts); facial, more than 5% of body area or disfiguring.	Clinical diagnosis
Extensive molluscum contagiosum infection	Characteristic skin lesions: small fleshcoloured or pink, dome-shaped or umbilicated growths may be inflamed or red; facial, more than 5% of body area or disfiguring. Giant molluscum may indicate more advanced immunodeficiency.	Clinical diagnosis
Recurrent oral ulceration	Current event plus at least one previous episode in past six months. Aphthous ulceration, typically with a halo of inflammation and yellow-grey pseudomembrane.	Clinical diagnosis

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Unexplained persistent parotid enlargement	Asymptomatic bilateral swelling that may spontaneously resolve and recur, in absence of other known cause, usually painless.	Clinical diagnosis
Herpes zoster	Painful rash with fluid-filled blisters, dermatomal distribution, can be haemorrhagic on erythematous background, and can become large and confluent. Does not cross the midline	Clinical diagnosis
Recurrent or chronic upper respiratory tract infection (URTI)	Current event with at least one episode in past 6 months. Symptom complex; fever with unilateral face pain and nasal discharge (sinusitis) or painful swollen eardrum (otitis media), sore throat with productive cough (bronchitis), sore throat (pharyngitis) and barking croup-like cough (LTB). Persistent or recurrent ear discharge.	Clinical diagnosis
Clinical Stage 3		
Unexplained moderate malnutrition	Low weight-for-age, up to -2 standard deviations (SDs) from the mean, not explained by poor or inadequate feeding and / or other infections, and not adequately responding to standard management.	Documented loss of or low body weight, upto –2 SD from the mean, failure to gain weight on standard management and no other cause identified during investigation.
Unexplained persistent diarrhoea	Unexplained persistent (14 days or more)diarrhoea (loose or watery stool, three or more times daily), not responding to standard treatment.	Stools observed and documented as unformed. Culture and microscopy reveal no pathogens.
Unexplained persistent fever (>37.6ºC intermittent or constant, for longer than one month)	Reports of fever or night sweats for longer than one month, either intermittent or constant, with reported lack of response to antibiotics or antimalarials. No other obvious foci of disease reported or found on examination. Malaria must be excluded in malarious areas.	Documented fever of >37.6ºC with negative blood culture, negative malaria slide and normal or unchanged CXR, and no other obvious foci of disease.

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Persistent oral candidiasis (after first 6-8 weeks of life)	Persistent or recurring creamy white to yellow soft small plaques which can be scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender (erythematous form)	Microscopy or culture
Oral hairy leukoplakia	Fine small linear patches on lateral borders of tongue, generally bilaterally, which do not scrape off	Clinical diagnosis
Acute necrotizing ulcerative gingivitis or stomatitis, or acute necrotizing ulcerative periodontitis	Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odour, and rapid loss of bone and/or soft tissue.	Clinical diagnosis
Lymph node TB	Non-acute, painless "cold" enlargement of peripheral lymph nodes, localized to one region. Response to standard anti-TB treatment in one month.	Histology or fine needle aspirate positive for Ziehl–Neelsen (ZN) stain Culture.
Pulmonary TB	Nonspecific symptoms, such as chroniccough, fever, night sweats, anorexia andweight loss. In the older children, productive cough and haemoptysis. History of contact with adult with smear-positive PTB. No response to standard broad spectrum-antibiotic treatment.	One or more sputum smear positive for acid-fast bacilli and/or radiographic abnormalities consistent with active TB and/or sputum culture positive for M. tuberculosis.
Severe recurrent bacterial pneumonia	Cough with fast breathing, chest in drawing, nasal flaring, wheezing, and grunting. Crackles or consolidation on auscultation. Responds to course of antibiotics. Current episode plus one or more in previous 6 months.	Isolation of bacteria from appropriate clinical specimens (induced sputum, BAL, lung aspirate).
Symptomatic lymphocytic interstitial pneumonitis (LIP)	No presumptive clinical diagnosis.	CXR: bilateral reticulonodular interstitial pulmonary infiltrates present for more than two months with no response to antibiotic treatment and no other pathogen found. Oxygen saturation persistently <90%. May present with cor pulmonale and may have increased exercise-induced fatigue. Characteristic histology.

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Chronic HIV-associated lung disease (including bronchiectasis)	History of cough productive of copious amounts of purulent sputum (bronchiectasis only), with or without clubbing, halitosis, and crepitations and/or wheezes on auscultation	CXR may show honeycomb appearance (small cysts) and/or persistent areas of opacification and/or widespread lung destruction, with fibrosis and loss of volume
Unexplained anaemia (<8 g/dl), neutropenia (<0.5 x 10^9/L) or chronic thrombocytopenia (<50 x 10^9/L)	No presumptive clinical diagnosis	Laboratory testing not explained by other non-HIV conditions, not responding to standard therapy with haematinics, antimalarials or anthelmintics as outlined in WHO IMCI guidelines
Clinical Stage 4		
Unexplained severe wasting, stunting or severe malnutrition not adequately responding to standard therapy	Persistent weight loss wasting, stunting or malnutrition not explained by poor or inadequate feeding, other infections and not adequately responding in two weeks to standard therapy. Visible severe wasting of muscles, with or without oedema of both feet, and/or weight-for-height of – 3SD, as defined by WHO IMCI guidelines.	Documented weight for height or weight for age of more than – 3SD from the mean with or without oedema.
Pneumocystis pneumonia (PCP)	Dry cough, progressive difficulty in breathing,cyanosis, tachypnoea and fever; chest indrawing or stridor. (Severe or very severe pneumonia as in IMCI.) Usually of rapid onset especially in infants under six months of age. Response to high-dose co-trimoxazole with/without prednisolone. CXR typical bilateral perihilar diffuse infiltrates.	Cytology or immunofluorescent microscopy of induced sputum or bronchoalveolar lavage (BAL), or histology of lung tissue.
Recurrent bacterial infection, e.g. empyema, pyomyositis, bone or joint infection, meningitis but excluding pneumonia	Fever accompanied by specific symptoms or signs that localize infection. Responds to antibiotics. Current episode plus one or more in previous 6 months.	Culture of appropriate clinical specimen
Chronic herpes simplex infection (orolabial or cutaneous of more than 1 month's duration or visceral at any site)	Severe and progressive painful orolabial, genital, or anorectal lesions caused by HSV infection present for more than one month.	Culture and/or histology

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)	Difficulty in swallowing, or pain on swallowing (food and fluids). In young children, suspect particularly if oral candida observed and food refusal occurs and/or difficulties or crying when feeding.	Macroscopic appearance at endoscopy, microscopy of specimen from tissue or macroscopic appearance at bronchoscopy or histology.
Extrapulmonary TB	Systemic illness usually with prolonged fever, night sweats, weight loss. Clinical features depend on organs involved, such as sterile pyuria, pericarditis, ascitis, pleural effusion, meningitis, arthritis or orchitis, pericardial or abdominal.	Positive microscopy showing acid-fast bacilli or culture of M. tuberculosis from blood or other relevant specimen except sputum or BAL. Biopy and histology.
Kaposi sarcoma	Typical appearance in skin or oropharynx of persistent, initially flat, patches with a pink or blood-bruise colour, skin lesions that usually develop into nodules.	Macroscopic appearance of by histology.
CMV retinitis or CMV infection affecting another organ, with onset at age over 1 month	Retinitis only CMV retinitis may be diagnosed by experienced clinicians: typical eye lesions on serial fundoscopic examination; discrete patches of retinal whitening with distinct borders, spreading centrifugally, often following blood vessels, associated with retinal vasculitis, haemorrhage and necrosis.	Histology or cytomegalovirus demonstrated in CSF by polymerase chain reaction(PCR).
CNS toxoplasmosis onset after age 1 month	Fever, headache, focal neurological system signs and convulsions. Usually responds within 10 days to specific therapy.	Computed tomography (CT) scan (or other neuroimaging) showing multiple intracranial lesions with mass effect or enhancing with contrast.
Extrapulmonary cryptococcosis (including meningitis)	Meningitis: usually subacute, fever with increasing severe headache, meningism,confusion, behavioural changes that respond to cryptococcal therapy.	CSF microscopy (India ink or Gram stain), serum or CSF cryptococcal antigen test or culture.

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
HIV encephalopathy	At least one of the following, progressing over at least two months in the absence of another illness: - failure to attain, or loss of, developmental milestones, loss of intellectual ability; or - progressive impaired brain growth demonstrated by stagnation of head circumference; or - acquired symmetrical motor deficit accompanied by two or more of the following: paresis, pathological reflexes, ataxia, gait disturbances	Neuroimaging demonstrating atrophy and basal ganglia calcification and exclusion of other causes
Disseminated mycosis (coccidioidomycosis, histoplasmosis, penicilliosis)	No presumptive clinical diagnosis	Histology: usually granuloma formation Isolation: antigen detection from affected tissue; culture or microscopy from clinical specimen or blood culture
Disseminated microbacteriosis other than tuberculous.	No presumptive clinical diagnosis	Nonspecific clinical symptoms including progressive weight loss, fever, anaemia, night sweats, fatigue or diarrhoea; plus culture of atypical mycobacteria species from stool, blood, body fluid or other body tissue, excluding lung
Chronic cryptosporidiosis (with diahorrea)	No presumptive clinical diagnosis	Cysts identified on modified ZN stain
Chronic isosporiasis	No presumptive clinical diagnosis	Identification of Isospora
Cerebral or B cell non-Hodgkin lymphoma	No presumptive clinical diagnosis	Diagnosed by CNS neuroimaging, histology of relevant specimen
Progressive multifocal leukoencephalopathy (PML)	No presumptive clinical diagnosis	Progressive neurological disorder together with hypodense white matter lesions on neuroimaging or positive polyomavirus JC polymerase chain reaction on CSF
Symptomatic HIV-associated nephropathy	No presumptive clinical diagnosis	Renal biopsy
Symptomatic HIV-associated cardiomyopathy	No presumptive clinical diagnosis	Cardiomegaly and evidence of poor left ventricular function confirmed by echocardiography

ANNEX 4

Severity Grading of Selected Clinical and Laboratory Toxicities most commanly seen with recommende Antiretroviral drugs for children

PARAMETER	MILD	MODERATE	SEVERE	SEVERE AND POTENTIALLY LIFE-THREATENING
GENERAL GUIDANCE ON ESTIMATING SEVERITY GRADE				
Characterization of symptoms and general guidance on management	Symptoms causing no or minimal interference with usual social and functional activities:[a] No therapy needed, monitor	Symptoms causing greater than minimal interference with usual social and functional activities: may require minimal intervention and monitoring	Symptoms causing inability to perform usual social and functional activities: requires medical care and possible hospitalization	Symptoms causing inability to perform basic self-care functions:[b] requires medical or operative intervention to prevent permanent impairment, persistent disability or death
HAEMATOLOGY[c] ***STANDARD INTERNATIONAL UNITS ARE LISTED IN ITALICS***				
Absolute neutrophil count	750 – <1000/mm^3 *0.75 x 10^9 – <1 x 10^9/l*	500 – 749/mm^3 *0.5 x 10^9 – 0.749 x 10^9/l*	250 – 500/mm^3 *0.25 x 10^9 – 0.5 x 10^9/l*	<250/mm^3 *<0.250 x 10^9/l*
Haemoglobin (child >60 days of age)	8.5 – 10.0 g/dl *1.32 – 1.55 mmol/l*	7.5 – <8.5 g/dl *1.16 – <1.32 mmol/l*	6.5 – <7.5 g/dl *1.01 – <1.16 mmol/l*	<6.5 g/dl *<1.01 mmol/l* Or severe clinical symptoms attributable to anaemia (e.g. cardiac failure), refractory to supportive therapy
Platelets	100 000 – <125 000/mm^3 *100 x 10^9 – 125 x 10^9/l*	50 000 – <100 000/mm^3 *50 x 10^9 – <100 x 10^9/l*	25 000 – <50 000/mm^3 *25 x 10^9 – <50 x 10^9/l*	<25 000/mm^3 *<25 x 10^9/l or bleeding*
GASTROINTESTINAL[c]				
LABORATORY				
ALT (SGPT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	>10.0 x ULN
AST (SGOT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	>10.0 x ULN
Bilirubin (>2 weeks of age)	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	>5.0 x ULN
Lipase	1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	>5.0 x ULN
Pancreatic amylase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	>5.0 x ULN

PARAMETER	MILD	MODERATE	SEVERE	SEVERE AND POTENTIALLY LIFE-THREATENING
CLINICAL				
Diarrhoea ≥1 year of age	Transient or intermittent episodes of unformed stools OR increase of ≤3 stools over baseline per day	Persistent episodes of unformed to watery stools OR increase of 4–6 stools over baseline per day	Grossly bloody diarrhoea OR increase of ≥7 stools per day OR intravenous fluid replacement indicated	Life-threatening consequences (e.g. hypotensive shock)
<1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR hypotensive shock
Nausea	Transient (<24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for >48 hours OR aggressive rehydration indicated (e.g. intravenous fluids)	Persistent nausea with no or minimal oral intake resulting in dehydration with aggressive rehydration indicated
Pancreatitis	Not applicable	Symptomatic AND hospitalization not indicated (other than emergency treatment)	Symptomatic AND hospitalization indicated	Life-threatening consequences (e.g. circulatory failure, haemorrhage, sepsis)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR aggressive rehydration indicated (e.g. intravenous fluids)	Life-threatening consequences (e.g. hypotensive shock)
ALLERGIC/DERMATOLOGICAL				
Acute systemic allergic reaction	Localized urticaria (weals) lasting a few hours	Localized urticaria with medical intervention indicated OR mild angiooedema	Generalized urticaria OR angio-oedema with medical intervention indicated OR symptomatic mild bronchospasm	Acute anaphylaxis OR lifethreatening bronchospasm or laryngeal oedema

PARAMETER	MILD	MODERATE	SEVERE	SEVERE AND POTENTIALLY LIFE-THREATENING
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens Johnson syndrome OR ulceration of mucous membrane involving two or more distinct mucosal sites OR toxic epidermal necrolysis (TEN)
NEUROLOGICAL				
Alteration in personality, behaviour or mood[b]	Alteration causing no or minimal interference with usual social and functional activities[b]	Alteration causing greater than minimal interference with usual social and functional activities[b]	Alteration causing inability to perform usual social and functional activities[b] AND intervention indicated	Behaviour potentially harmful to self or others OR life-threatening consequences
Altered mental status	Changes causing no or minimal interference with usual social and functional activities[b]	Mild lethargy or somnolence causing greater than minimal interference with usual social and functional activities[b]	Onset of confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social and functional activities[b]	Onset of delirium, obtundation or coma
Neuromuscular weakness (including myopathy and neuropathy)	Asymptomatic with decreased strength on examination OR minimal muscle weakness causing no or minimal interference with usual social and functional activities[b]	Muscle weakness causing greater than minimal interference with usual social and functional activities[b]	Muscle weakness causing inability to perform usual social and functional activities[b]	Disabling muscle weakness causing inability to perform basic self-care functions OR respiratory muscle weakness impairing ventilation
Neurosensory alteration (including painful neuropathy)	Asymptomatic with sensory alteration on examination OR minimal paraesthesia causing no or minimal interference with usual social and functional activities	Sensory alteration or paraesthesia causing greater than minimal interference with usual social and functional activities	Sensory alteration or paraesthesia causing inability to perform usual social and functional activities	Disabling sensory alteration or paraesthesia causing inability to perform basic self-care functions.[c]

PARAMETER	MILD	MODERATE	SEVERE	SEVERE AND POTENTIALLY LIFE-THREATENING
OTHER LABORATORY PARAMETERS *STANDARD INTERNATIONAL UNITS ARE LISTED IN ITALICS*				
Cholesterol (fasting, paediatric <18 years old)	170 – <200 mg/dl *4.40 – 5.15 mmol/l*	200 – 300 mg/dl *5.16 – 7.77 mmol/l*	>300 mg/dl *>7.77 mmol/l*	Not applicable
Glucose, serum, high: non-fasting	116 – <161 mg/dl *6.44 – <8.89 mmol/l*	161 – <251 mg/dl *8.89 – <13.89 mmol/l*	251 – 500 mg/dl *13.89 – 27.75mmol/l*	>500 mg/dl *>27.75 mmol/l*
Glucose, serum, high: fasting	110 – <126 mg/dl *6.11 – <6.95 mmol/l*	126 – <251 mg/dl *6.95 – <13.89 mmol/l*	251 – 500 mg/dl *13.89 – 27.75 mmol/l*	>500 mg/dl *>27.75 mmol/l*
Lactate	<2.0 x ULN without acidosis	≥2.0 x ULN without acidosis	Increased lactate with pH <7.3 without life-threatening consequences or related condition present	Increased lactate with pH <7.3 with life-threatening consequences (e.g. neurological findings, coma) or related condition present
Triglycerides (fasting)	Not applicable	500 – <751 mg/dl *5.65 – <8.49 mmol/l*	751 – 1200 mg/dl *8.49 – 13.56 mmol/l*	>1200 mg/dl *>13.56 mmol/l*

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

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

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

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

ANNEX 5

List of PMTCT Centres in Nepal

SN	PMTCT Code	PMTCT Centres	District
1	PMTCT C01	MATERNITY HOSPITAL, THAPATHALI	KATHMANDU
2	PMTCT C02	BHERI ZONAL HOSPITAL, NEPALGUNG	BANKE
3	PMTCT C03	BPKIHS, DHARAN	SUNSARI
4	PMTCT C04	TUTH, MAHARAJGUNJ	KATHMANDU
5	PMTCT C05	NARAYANI SUBREGIONAL HOSPITAL, BIRGUNJ	PARSA
6	PMTCT C06	WESTERN REGIONAL HOSPITAL, POKHARA	KASKI
7	PMTCT C07	MAHAKALI ZONAL HOSPITAL, MAHENDRANAGAR	KANCHANPUR
8	PMTCT C08	ACHHAM DISTRICT HOSPITAL, ACHHAM	ACHHAM
9	PMTCT C09	KOSHI ZONAL HOSPITAL, BIRATNAGAR	MORANG
10	PMTCT C010	BHARATPUR HOSPITAL, CHITWAN	CHITAWAN
11	PMTCT C11	MECHI ZONAL HOSPITAL, JHAPA	JHAPA
12	PMTCT C012	JANAKPUR ZONAL HOSPITAL	JANAKPUR
13	PMTCT C013	BAGLUNG DISTRICT HOSPITAL, BAGLUNG	BAGLUNG
14	PMTCT C014	PALPA MISSION HOSPITAL	PALPA
15	PMTCT C015	MID-WEST REGIONAL HOSPITAL, SURKHET	SURKHET

List of ART Centres in Nepal

SN	ART Code	ART Centres	District
1	ART C01	TEKU HOSPITAL,TEKU	KATHMANDU
2	ART C02	BHERI ZONAL HOSPITAL, NEPALGUNJ	BANKE
3	ART C03	SPARSHA NEPAL, SANEPA	KATHMANDU
4	ART C04	TUTH, MAHARAJGUNJ	KATHMANDU
5	ART C05	BPKIHS, DHARAN	SUNSARI
6	ART C06	WESTERN REGIONAL HOSPITAL, POKHARA	KASKI
7	ART C07	NARAYANI SUB-REGIONAL HOSPITAL, BIRGUNJ	PARSA
8	ART C08	MAHAKALI ZONAL HOSPITAL, MAHENDRANAGAR	KANCHANPUR
9	ART C09	SETI ZONAL HOSPITAL, DHANGADI	KAILALI
10	ART C10	DOTI DISTRICT HOSPITAL, SILGUDHI	DOTI
11	ART C11	LUMBINI ZONAL HOSPITAL, BUTWAL	RUPANDEHI
12	ART C12	ACHHAM DISTRICT HOSPITAL, ACHHAM	ACHHAM
13	ART C13	BAGLUNG DISTRICT HOSPITAL, BAGLUNG	BAGLUNG
14	ART C14	KOSHI ZONAL HOSPITAL, BIRATNAGAR	MORANG
15	ART C15	BHARATPUR HOSPITAL, CHITWAN	CHITAWAN
16	ART C16	MECHI ZONAL HOSPITAL, JHAPA	JHAPA
17	ART C17	PEDIATRIC ART CENTER - KANTI BAL HOSPITAL	KATHMANDU
18	ART C18	JANKPUR ZONAL HOSPITAL	JANAKPUR
19	ART C19	PALPA MISSION HOSPITAL, PALPA	PALPA
20	ART C20	MID-WEST REGIONAL HOSPITAL, SURKHET	SURKHET
21	ART C21	MAHENDRA HOSPITAL	DANG
22	ART C22	MAITI NEPAL, KATHMANDU	KATHMANDU
23	ART C23	SAGARMATHA ZONAL HOSPITAL, RAJBIRAJ	SAPTARI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