

**Prevention of
Parent-to-Child
Transmission of HIV**



**Management of HIV Infection
in Children in Pakistan**

Paedatric Guidelines



National AIDS Control Programme
Ministry of Health
Government of Pakistan



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PREFACE

In the light of increasing new HIV infections in women and the inherent risk of mother to child transmission of HIV from HIV infected mothers to their infants it is time to establish pediatric HIV treatment and care centers and national guidelines for management of HIV infection in children in Pakistan. This publication on “Clinical Management of HIV Infection in Children in Pakistan” was developed after extensive review of international guidelines on Pediatric HIV clinical management and adapted to the local context of commonly presenting infections, healthcare system limitations, and other “ground realities”. For building consensus and expert opinion a national consultative workshop was held in Islamabad in February 2006. In addition detailed meetings were held with practicing pediatricians, obstetricians, infectious disease experts, public health experts, policy planners, UN agencies, and PLWHA representatives for their insight and input into the adaptation process.

These Clinical Guidelines are designed to help develop a system of practical clinical algorithms for delivering optimal and effective pediatric HIV care including antiretroviral therapy, adherence counseling, management and prevention of opportunistic infections, diagnosis of HIV infection in infants/children, understanding immunological and virological markers, and overall integration of HIV care within pediatric care settings.

This document was developed keeping in mind the health care system of Pakistan, its strengths and limitations, and offers clinical guidance on management of HIV infected children. These guidelines should serve as a reference point for pediatricians in deciding when to suspect HIV infection, address diagnostic issues, which regimens to use, how to deal with side effects, alternative regimens, risks of and strategies to mitigate development of drug resistance.

Recommendations made in these guidelines are the current “evidence based best practices” for resource limited settings and should be strictly adhered to by health care providers to maximize the benefits, reduce risk of resistance and failure of ART, and achieve high quality integrated pediatric care in Pakistan. Finally, these guidelines are based on strong scientific evidence and will need to be regularly revised as new information from ongoing clinical trials becomes available.

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ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
AFB	Acid-fast bacillus
AIDS	Acquired immuno deficiency syndrome
ALT	Alanine transaminase
ARV	Antiretroviral
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
BCG	Bacillus Calmette Gurrein Vaccine
CBC	Complete blood count
CD4	CD4+ T Lymphocyte
CNS	Central nervous system
CTX	Cotrimoxazole
d4T	Stavudine
ddI	Didanosine
DNA	Deoxyribonucleic acid
DPT	Diphtheria, Pertussis, Tetanus Vaccine
EFV	Efavirenz
EPI	Expanded Programme on Immunizations
FDC	Fixed dose combination
GI	Gastro-intestinal
HAART	Highly-active antiretroviral therapy
Hb	Hemoglobin
Hib	<i>Haemophilus influenzae</i> type b
HIV	Human immunodeficiency virus
IMCI	Integrated Management of Childhood Illness (WHO-UNICEF initiative)
IRS	Immune reconstitution syndrome
LIP	Lymphoid Interstitial Pneumonia
LPV	Lopinavir
LPV/r	Lopinavir/ritonavir
MAC	Mycobacterium Avium Complex
MAI	<i>Mycobacterium Avium Intracellulerae</i>
MMR	Measles, Mumps, Rubella
MTCT	Mother-to-child transmission of HIV
NACP	National AIDS Control Programme, Pakistan
NFV	Nelfinavir
NGO	Non-governmental Organization
NRTI	Nucleoside reverse transcriptase inhibitor
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
OI	Opportunistic infection
PCP	<i>Pneumocystis jiroveci</i> pneumonia (previously <i>Pneumocystis carinii</i>)
PCR	Polymerase chain reaction

PMTCT	Prevention of Mother-to-Child Transmission of HIV
PTCT	Parent-to-Child Transmission of HIV
PPTCT	Prevention of Parent-to-Child Transmission of HIV
RDA	Recommended Daily Allowance
RTV	Ritonavir
SQV	Saquinavir
STI	Sexually transmitted infection
TB	Tuberculosis
TLC	Total lymphocyte count
UN	United Nations
UNAIDS	United Nations Joint Co-Sponsored Program on HIV/AIDS
UNICEF	United Nations Children's Fund
VCT	Voluntary Counseling and Testing
WBC	White blood cell
WHO	World Health Organization
ZDV	Zidovudine

INTRODUCTION

The global HIV pandemic involves a significant proportion of children, with an estimated 2.3 million children living with HIV/AIDS in the world today (2005 UN estimates). The vast majority of these children are living in Asia and southern Africa. Most pediatric HIV infections are acquired through mother-to-child transmission (MTCT), occurring during pregnancy, child-birth, or breast-feeding.

An increasing number of women and children infected with HIV are being reported in Pakistan. Although there are currently only 40 documented cases of perinatally acquired HIV infection among children in Pakistan (NACP 2005), several factors suggest that this number is a significant under-estimate. These include lack of awareness about HIV/AIDS among the general population and health care professionals, stigma associated with HIV/AIDS, lack of diagnostic testing facilities, and difficulties of making a diagnosis in children, especially in a country where childhood malnutrition rates are as high as 30%.

To date, the majority of HIV-infected children reported in Pakistan have been born to mothers whose husbands' acquired HIV while working abroad (identified on visa-related screening). In the absence of specific information regarding parental HIV status, testing for HIV in children who present for serious illness is rare in health care settings in Pakistan. However, as national screening programs for voluntary counseling and testing (VCT) for HIV develop in Pakistan, and clinicians gain more awareness about HIV, it is expected that more HIV-infected individuals, including women and children will be identified.

These guidelines address the clinical care of HIV-exposed and infected children. It is recognized that the most effective and efficient way to keep the number of HIV-infected children in Pakistan at a minimum is to focus efforts on preventing spread of HIV among vulnerable groups as well as the general population. Through the efforts of the national and provincial AIDS control programs and the international health agencies, services for HIV prevention, counseling, and testing among vulnerable groups, as well as treatment including antiretroviral therapy and patient support programs are being developed in Pakistan. An integral part of this effort is developing services for prevention of mother-to-child transmission of HIV (PMTCT), as well as antiretroviral therapy (ART) for HIV-infected women and children who have indications for treatment.

The Prevention of Parent-to-Child Transmission (PPTCT) of HIV: Strategic Framework for Pakistan (NACP 2006) emphasizes the comprehensive four-pronged strategy for prevention of PTCT in Pakistan (Table 1). Being a generally low-prevalence country, the major focus is on efforts targeted towards preventing HIV infection in the general population as well as high-risk groups such as intravenous drug users, migrant workers, and commercial sex workers.

Table 1: Strategic framework for prevention of mother to child transmission of HIV

Four Pillars of Prevention of Parent to Child Transmission of HIV			
<i>Prong 1</i>	<i>Prong 2</i>	<i>Prong 3</i>	<i>Prong 4</i>
Increasing HIV prevention and general awareness in women and men	Preventing unwanted pregnancies in HIV positive women	Preventing HIV transmission from HIV infected mother to her infant	Linking HIV positive women and their children into a continuum of care and support services

The initial approach recommended for medical interventions to prevent HIV among the infants of HIV-infected mothers (Prong 3) is based upon appropriate identification of HIV positive pregnant women, development of suitable infrastructure and availability of supplies and HIV health care-related human resources at selected tertiary care hospitals in the country, and development of referral links of these hospitals with obstetric care providers, VCT service providers, and other outreach programs and services. As mentioned, it is expected that as these programs are established and scaled up, more HIV-exposed and infected children will be identified.

The NACP, Pakistan has developed separate guidelines for PMTCT (Prevention of Mother to Child Transmission of HIV - Clinical Guidelines for Pakistan, 2006). A summary of the Clinical Protocols is given in Section XV, and dose regimens are listed in Annex 12).

Care and support of children with HIV infection is a complex challenge for many reasons, even more so in resource-limited environments. Often, parents are sick and dying or children may already be orphans. Children have a faster progression from HIV infection to full-blown AIDS and death, compared to adults. Routine childhood infections occur at an increased frequency and severity, and opportunistic infections may get confused with other serious illnesses. Effective antiretroviral (ARV) drugs are often not available in pediatric formulations, and the available formulations are costly. Drug compliance and long-term toxicities are significant issues. Diagnosis of HIV infection in young children is also difficult because antibody-based tests do not discriminate between mother-related HIV exposure or HIV infection, and expensive virological tests are needed to confirm infant HIV status which are not yet available in Pakistan. Finally, there are significant health systems strengthening and human resource capacity development needs for providing optimal and compassionate care and support for HIV-infected children and their families.

Despite the complex management issues, the use of ART has substantially changed the face of pediatric HIV infection in countries where it has been successfully implemented. HIV-infected children placed on ART now survive to adolescence and adulthood, with HIV care issues becoming similar to many chronic diseases. Although global efforts are increasing access to ART in developing countries, the challenge is daunting, and re-emphasizes the importance of preventing children from getting HIV infection in the first place.

OBJECTIVES AND SCOPE

These guidelines cover recommendations related to the fourth prong of the PMTCT strategic framework for Pakistan – i.e. clinical care of infants and children known or suspected to be HIV-infected. The guidelines have been adapted from recent WHO recommendations for resource-constrained countries which utilize evidence-based information and expert consensus where evidence is lacking. They were developed in consultation with national experts and representatives from UNICEF, UNAIDS, and WHO.

These guidelines are aimed at pediatricians, programme managers of AIDS control programmes, and other health care and public health professionals involved in the care of children with known or suspected HIV, in the public sector and the private sector in Pakistan.

The objectives of these guidelines are to

- Provide an overview of information related to MTCT of HIV and its prevention
- Provide an overview of HIV infection in children
- Provide recommendations on diagnosis of HIV in infants and children who have known HIV exposure, and sick children with unknown HIV exposure but clinically suspected to have HIV infection
- Provide recommendations on management of HIV exposed and infected children, including routine clinical care, infant feeding advice, assessment of immunological status, when to initiate anti-retroviral therapy, and prevention of opportunistic infections
- Discuss various ARV regimens for children, including potential toxicity and resistance issues
- Serve as a reference for health care professionals providing care and counseling to HIV exposed and infected infants and children, and their families.

Clinical management of HIV infection in children is complex and the need for appropriate capacity development and training of healthcare providers in Pakistan is recognized. It is also expected that these guidelines will need to be reviewed and updated at regular intervals as new and relevant scientific information regarding pediatric HIV becomes available.

BACKGROUND INFORMATION ON MOTHER-TO-CHILD TRANSMISSION OF HIV

Since the beginning of the pandemic, an estimated 5.9 million children have been infected with HIV worldwide, over 200,000 of them in Asia. Approximately 0.7 million children were newly infected with HIV in 2005, the vast majority in sub-Saharan Africa. HIV among children causes serious illness and suffering and threatens to reverse progress in improving child survival in countries hardest hit by the pandemic. Most HIV-infected children acquire the infection from their mother, either during pregnancy, labor and delivery, or during breast-feeding (Table 2). In the absence of any intervention, the risk of MTCT of HIV is 15-30% in non-breast-feeding populations, and 30-45% among populations with prolonged breast-feeding (Table 2). Prolonged breast-feeding approximately doubles the risk of MTCT.

Table 2: Rates of MTCT transmission of HIV without any interventions

Scenario	Rate of Transmission
During pregnancy	5-10%
During labor and delivery	10-20%
During breast-feeding	5-20%
Overall, without breast-feeding	15-30%
Overall, with breast-feeding for 6 months	25-35%
Overall, with breast-feeding for 18-24 months	30-45%

HIV infection in the mother has serious adverse effects on the fetus. HIV infected pregnant women have increased rates of spontaneous abortion, low birth weight babies, stillbirths, preterm labor, premature rupture of membranes, other sexually transmitted diseases, pneumonia, and urinary tract infections.

MTCT is usually the result of a chain of events that most often involves an HIV-infected man infecting his wife, who then infects her baby, and even subsequent babies if the infection is not picked up in time. In Pakistan, the usual scenario encountered are migrant workers who are deported on account of a positive HIV test obtained on health screening for visas. These deportees who are usually illiterate then come home and infect their wives. The problem comes to light when the deportee develops symptoms related to AIDS.

Most transmission during pregnancy occurs in the third trimester. The placenta is thought to play a protective role, but transmission can occur if the placenta is infected or if the mother has a very high viral load associated with recent infection or advanced immunodeficiency.

Infants are at greatest acute risk of infection during labor and delivery. Infants may acquire HIV by aspirating or imbibing maternal blood or secretions that contain HIV, or through

mixing of maternal and fetal blood as the placenta separates. Factors associated with an increased risk of MTCT during labor and delivery include: duration of membrane rupture, acute chorioamnionitis, and invasive delivery techniques (artificial rupture of membranes, fetal electrode sampling, use of forceps or suction apparatus etc.). Prolonged duration of rupture of membranes (beyond 4 hours) has been shown to be an important risk factor. In an American study, duration of rupture of membranes of over 4 hours nearly doubled the risk of infection, regardless of the eventual mode of delivery.

Although the risk of HIV transmission to the infant through breast milk persists for the duration of breast-feeding, it appears to be higher in infants given mixed feeding rather than exclusive breast-feeding. The exact mechanisms are not well-understood but may relate to increased gut permeability providing an entry point for the virus among infants fed other diets, or because non-exclusive breast feeding may reflect breast pathology such as mastitis or cracked and bleeding nipples.

HIV infected children tend to show quicker progression to florid AIDS compared to adults, with approximately 20% dying by 12 months of age. Often optimal child care is significantly hampered by the presence of sick and dying parents or the lack of parents to take care of a sick child. This makes optimizing PPTCT interventions all the more important.

OVERVIEW OF HIV INFECTION IN CHILDREN

HIV damages the human immune system by causing destruction of CD4+ lymphocytes, which makes HIV-infected individuals susceptible to a whole host of opportunistic pathogens, as well as inability to mount robust immune responses to usual childhood pathogens. Generally, this process takes place over several years, during which the child remains asymptomatic, but in a sub-set of children, disease progresses very rapidly after birth, causing death in the first 2 years of life. These children are thought to be infected early in the in utero period. This rapid progression correlates with higher viral burden and faster depletion of infected CD4 lymphocytes. They have a rapid disease course, often develop *Pneumocystis pneumonia* in the first few months of life, and if untreated die by 6-9 months of age.

The clinical features of HIV infection in children are highly variable. As discussed, some HIV positive children develop severe HIV-related signs and symptoms in the first year of life. However, the majority of perinatally-infected newborns present with a much slower progression of disease. These children typically have a negative viral culture or PCR in the first week of life, and are considered to be infected intra-partum. The viral load increases by 2-3 months of age, then slowly declines over the next 24 months as the immune system tries to contain the virus as evidenced by intense hypergamma-globulinemia (raised IgG levels). Over time, as the virus destroys the CD4 cells, viral load starts to increase again, usually after the 4th or 5th year of life, and infected children become symptomatic.

1. CLINICAL FEATURES OF HIV INFECTION IN CHILDREN

The high rates of malnutrition and childhood infections such as severe pneumonia, diarrhea, and tuberculosis in developing countries can confuse the clinical picture of HIV infection in children. However, there are many clinical signs or conditions that are quite specific to HIV infection which should be strongly suspected if these conditions are present. A brief summary is presented below, with details in the tables on clinical staging of HIV infection (Chapter V). Descriptions of specific clinical entities are presented in Annex 1.

1.1. Signs or conditions very specific to HIV-infected children

- Pneumocystic pneumonia (PCP)
- Esophageal candidiasis
- Lymphoid interstitial pneumonia (LIP)
- Kaposi's sarcoma

1.2. Signs that may indicate possible HIV infection

- Recurrent infection: three or more severe episodes of a bacterial infection (such as pneumonia, meningitis, sepsis, cellulitis) in the past 12 months
- Oral thrush: after the neonatal period, the presence of oral thrush in the absence of

antibiotic treatment, or lasting over 30 days despite treatment, or recurring, or extending beyond the tongue

- Chronic parotitis: the presence of unilateral or bilateral parotid swelling for more than 14 days
- Generalized lymphadenopathy: the presence of enlarged lymph nodes in two or more non-inguinal regions without any apparent underlying cause
- Hepatomegaly with no apparent cause
- Persistent and/or recurrent fever
- Neurological dysfunction: progressive neurological impairment, microcephaly, developmental delay, hypertonia, encephalopathy
- Herpes zoster
- HIV dermatitis: typical skin rashes include erythematous papular rashes, extensive fungal infections of the skin, scalp, and nails, and extensive molluscum contagiosum
- Chronic suppurative lung disease

1.3. Signs common in HIV-infected children, but also common in ill, non-HIV-infected children

- Chronic otitis media
- Persistent diarrhea
- Moderate or severe malnutrition

DIAGNOSIS OF HIV INFECTION IN CHILDREN

This section summarizes WHO recommendations for diagnosing HIV infection in children and are also applicable for Pakistan. The definitive diagnosis of HIV infection in children at any age requires diagnostic testing that confirms the presence of human immunodeficiency virus. Antibody testing identifies HIV antibody. However, as maternal HIV antibody transferred passively during pregnancy can persist for as long as 18 months in a child born to an HIV-infected mother, interpretation of positive HIV antibody test results is difficult in children under 18 months of age. In order to definitely diagnose HIV infection in children less than 18 months of age, assays that detect the virus or its components (i.e., virological tests) are therefore required. Virological tests that can be used in children include:

- assays to detect plasma HIV DNA
- assays to detect plasma HIV RNA
- assays to detect Immune Complex Dissociated (ICD) p24 antigen

DNA-based assays are the most reliable for diagnosis and recommended by the NACP for diagnosis in infants. However, virological tests are expensive and not yet easily available in Pakistan. Amongst these, Real time PCR is the most promising. Real time PCR is cheaper and easier to standardize than conventional PCR, providing several advantages in the early diagnosis of HIV infection in children and the monitoring of ART effectiveness. These facilities will need to be available in Pakistan to support initiation of PMTCT services and monitoring effectiveness of ARV drugs in children and adults.

While HIV antibody testing cannot be used to definitely diagnose HIV infection in infants under 18 months of age, it can be used to exclude HIV infection as early as 9 to 12 months of age in infants who are not breastfeeding or who have ceased breastfeeding 6 weeks or more prior to the antibody test, as most uninfected HIV-exposed infants will lose maternal antibody by age 12 months.

In children 18 months of age or older, HIV antibody tests, including rapid antibody tests (either rapid HIV tests or HIV enzyme immuno essays [EIAs] or a combination of both), can be reliably used to definitively diagnose HIV infection in the same manner as they are used in adults.

If HIV infection is diagnosed in a young child or infant usually the mother herself is also HIV infected and other siblings may also be infected; appropriate counseling and support therefore needs to be provided when testing for HIV in children.

1. DIAGNOSIS IN CHILDREN LESS THAN 18 MONTHS OF AGE

Definitive laboratory diagnosis of HIV infection in children less than 18 months of age can

only be made by conducting virological testing. Positive tests performed using one of the virological tests recommended above establish the diagnosis of HIV for purposes of clinical management. For virological testing whole blood has to be collected from young infants and has to be sent immediately to the laboratory.

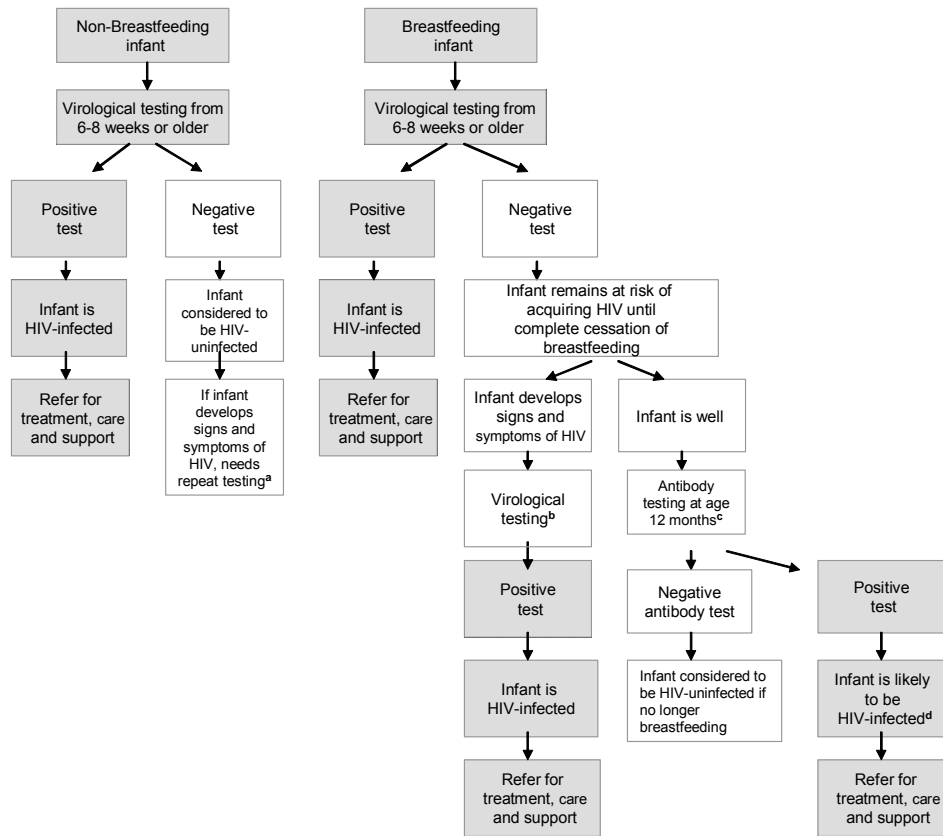
The first virological testing should be conducted at or around the first postnatal visit for the child (usually at 6-8 weeks following birth) (Figure 1). The reliability of the laboratory (determined by standard quality assessment) is fundamental to ensure accurate test results. In children diagnosed with HIV infection based on one positive virological test, HIV antibody testing should ideally be performed after 18 months of age to confirm HIV infection (Figure 1).

1.1. Diagnosing HIV infection in breastfeeding infants

If an infant or child is breastfeeding, he or she remains at risk of acquiring HIV infection throughout the breastfeeding period, and therefore a negative virological test in an infant who is continuing to breastfeed does not rule out HIV infection. Virological assays to detect HIV infection should be performed at least 6 weeks or longer after complete cessation of breastfeeding. If the child is between 9-18 months of age at the time of discontinuation of breastfeeding, HIV antibody testing can be performed first. Only children who have HIV antibody present (i.e., those infants and children who have either persisting maternal antibodies or who acquired HIV during breastfeeding) are likely to be HIV-infected and therefore need further virological testing for definitive diagnosis of infection.

Figure 1. Establishing HIV infection in infants and children in resource-limited settings to enable HIV care and ART (not to be used for exclusion of HIV infection)

A. Establishing HIV infection in infants and children less than 18 months of age with confirmed HIV exposure



Notes:

- In infants and children less than 18 months of age considered to be HIV-uninfected who develop signs or symptoms suggestive of HIV, virological testing should be performed.
- Where virological testing is not available, antibody testing can be performed. By the age of 12 months most uninfected children will have lost maternal antibody and positive antibody testing at this time usually indicates HIV infection in the child (96% specificity). In infants younger than 12 months where antibody testing is still positive, a presumptive clinical diagnosis for severe HIV disease may need to be made as it is not possible to reliably establish HIV infection with antibody testing before the age of 12 months (i.e., specificity at age 9-12 months is 74%-96%). In this situation, confirmation of the presumptive clinical diagnosis of HIV infection by virological testing should be sought as soon as possible.
- Antibody testing can be performed at age 12 months (see above).
- Where the infant is being considered to be HIV-infected based upon a positive antibody test performed at 12 months of age or older, the result should be confirmed by virological testing (in children less than 18 months of age) or by antibody testing (once older than 18 months of age).

B. Establishing HIV infection with antibody testing in children \geq 18 months old

In those children older than 18 months of age, antibody testing should be used to confirm HIV infection. A child that is confirmed HIV antibody positive (i.e. reactive tests from two or more different HIV tests) is HIV infected, and referral for treatment, care and support is required. A negative antibody test implies that the child is not HIV infected. However, if the child is still breastfeeding, she/he is still exposed to HIV infection, and HIV antibody testing should then be repeated at least 6 - 12 weeks after the complete cessation of breastfeeding.

1.2 HIV-exposed symptomatic infants and children

Any child younger than 12 months of age known to be HIV-exposed and developing signs and symptoms of HIV infection should be referred for virological testing to an HIV specialist. Positive virological results at any stage indicate HIV infection.

If virological testing is not available, see later sections (page 16) on presumptive diagnosis of HIV infection and clinical criteria for initiating ART (pages 29-32).

1.3 HIV-exposed asymptomatic infants and children

By the age of 12 months, most uninfected HIV-exposed children will have lost maternal antibody and HIV antibody positive testing in a child at this age can be considered indicative of probable HIV infection in the child (i.e., 94.5% seroreversion at age 12 months; 96% specificity), and should be confirmed by a second antibody test after age 18 months.

1.4 Diagnosing HIV infection where mother or infant has received ARV drugs for PMTCT

When HIV DNA assays are used for diagnosis, use of ARV drugs in the mother or infant for PMTCT should not affect the test results. HIV DNA remains detectable in the peripheral blood mononuclear cells of HIV-infected children who have received ART and have undetectable viral replication as measured by HIV RNA assays, and so testing (i.e., DNA PCR) can be conducted in infants born to mothers who received ART. However, it is not yet reliably established if the sensitivity of HIV RNA antigen assays is affected by maternal and infant ARV prophylaxis of MTCT. When RNA assays are being used for early diagnosis, experts recommend that the assay should be delayed until at least 4 weeks after prophylaxis has been completed.

1.5 Diagnosing infection when the mother is on ART

DNA detection will be unaffected by maternal ART. It is not known whether maternal ART during breastfeeding affects HIV RNA detection in the infant in light of the relatively high ART levels found in the infants of breast feeding mothers. In addition, the sensitivity and reliability of HIV RNA assays used in infants who are breastfeeding from a mother on ART is not known.

2. CHILDREN 18 MONTHS OF AGE AND OLDER

Definitive HIV diagnosis in children 18 months of age and older (with known or unknown HIV exposure) can be made with antibody tests, following standard testing algorithms used for adults (Figure 1). Confirmation of the positive antibody test result should be done by duplicate testing using a different HIV antibody test. The use of rapid antibody tests for diagnosis has the advantage that test results become available at the time of clinic visit. Table 2 summarizes the recommended methodologies for establishing the presence of HIV infection in different situations.

Table 2. Summary of recommendations on methods for establishing the presence of HIV infection in infants and children

Method of diagnosis	Recommendations for use
Virological methods (DNA or RNA PCR)	To diagnose infection in infants under age 18 months; initial testing is recommended from 8 weeks of age
HIV antibody testing	To diagnose HIV infection in mother or identify HIV exposure of infant
	To diagnose HIV infection in children 18 months of age or older
	To identify HIV positive children under 18 months of age in whom HIV infection is likely ^a

Notes:

- a. Children less than 18 months of age who have positive HIV antibody tests include children who are truly HIV-infected, as well as those who still have maternal antibody but are uninfected. By the age of 12 months most uninfected children will have lost maternal antibody and positive antibody testing at this time usually indicates probable HIV infection in the child (96% specificity).

3. PRESUMPTIVE CLINICAL DIAGNOSIS OF HIV INFECTION

No single clinical diagnostic algorithm has proved to be highly sensitive or specific for diagnosis of HIV infection. 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 under age 18 months where access to virological testing is not yet available (see Chapter V, Fig. 2). Presumptive clinical diagnosis in children 18 months of age or older is not indicated because standard HIV antibody testing is diagnostic of HIV infection at this age. Some clinical conditions are very unusual without HIV infection (i.e., pneumocystis pneumonia, oesophageal candidiasis, lymphoid interstitial pneumonitis, Kaposi’s sarcoma and cryptococcal meningitis), and the diagnosis of these conditions thus strongly suggests HIV infection and indicates the need to perform an HIV antibody test.

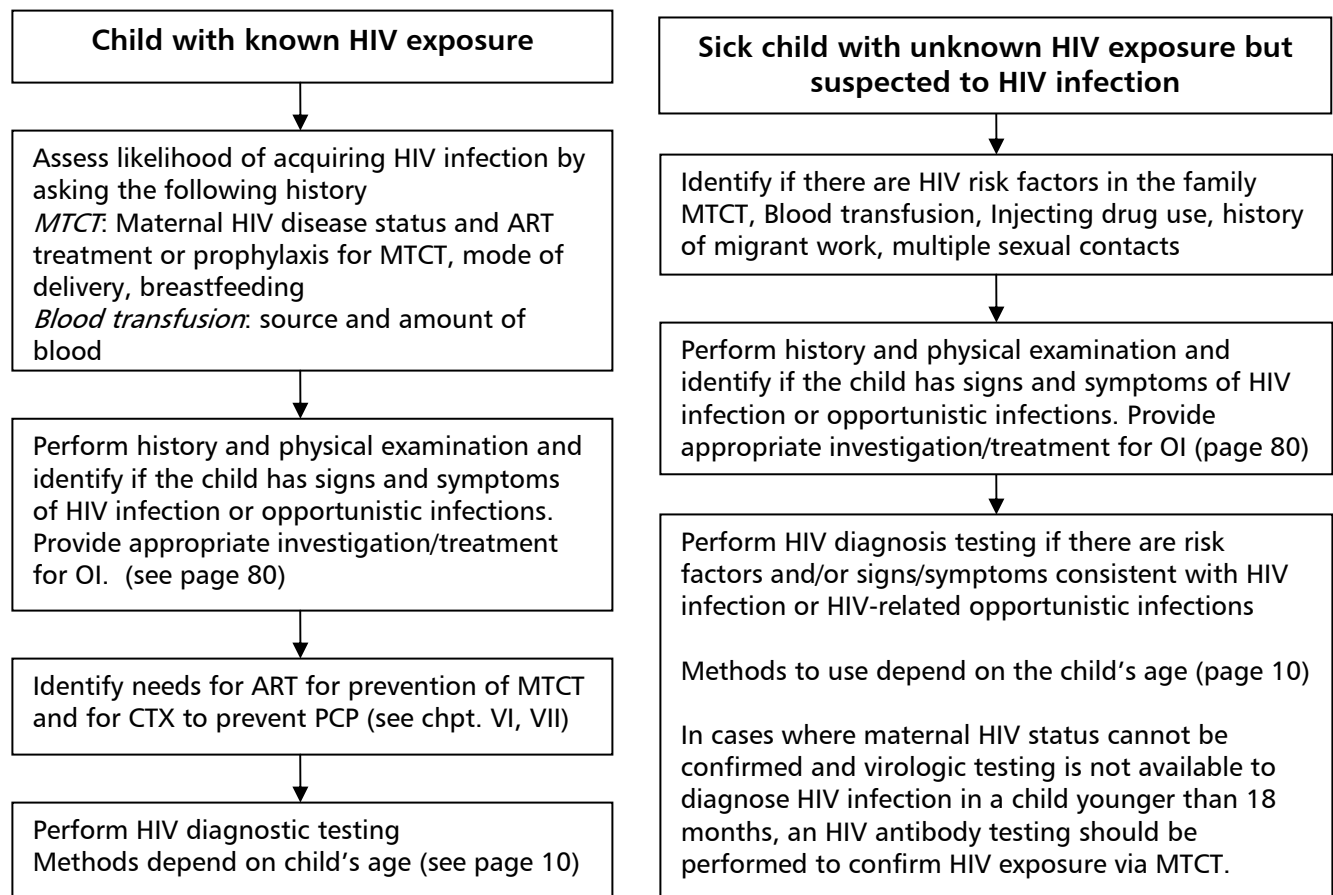
4. HIV TESTING AND COUNSELING

Parents or guardians should be counseled about the suspicion of HIV before testing is performed on their children. If there is no emergency, counseling is best done by individuals trained in HIV care. All testing should be voluntary and free of coercion. Patient confidentiality and respect should be maintained at all times.

CLINICAL ASSESSMENT OF HIV-INFECTED AND HIV-EXPOSED CHILDREN

The algorithm in Figure 2 can be used by pediatricians and other clinical care providers for the initial evaluation and management of children with known exposure to HIV, or a sick child with symptoms suggestive of HIV infection but unknown history of exposure. Consultation with an infectious disease specialist is recommended, wherever feasible.

Figure 2: Initial assessment of a child with known HIV exposure or a sick child with unknown HIV exposure but suspected to have HIV infection



Notes:

- HIV expert consultation should be sought wherever feasible
- When HIV is suspected, compassionate counseling before HIV testing should be arranged
- Maternal advanced HIV disease and low CD4 are risk factors for HIV transmission
- Successful treatment with ART in mothers lower the chance of transmission
- PMTCT using ZDV monotherapy alone, ZDV + NVP single dose, NVP single dose alone are associated with transmission rates of approximately 5-10%, 3-5%, 10-20% respectively.
- A child remains at risk for HIV acquisition as long as he/she is breastfed.

1. CLINICAL STAGING OF HIV INFECTION IN CHILDREN

Clinical staging criteria (Table 3) have been developed by WHO to help in the assessment of severity of HIV infection and guide clinical decision-making. Clinical staging is for use where HIV infection has been confirmed (i.e. serological or virological evidence of HIV infection). It is informative for assessment at baseline or entry into HIV care and can also be used to guide decisions on when to start cotrimoxazole prophylaxis for PCP in HIV-infected children over age 1 year (note: all HIV-exposed children and HIV-infected children under age 1 year should receive cotrimoxazole prophylaxis) and other HIV-related interventions including when to start, switch or stop ART in HIV-infected children, particularly in situations where CD4 is not available.

The WHO Paediatric Clinical Classification of HIV related disease has recently been revised and is now harmonized with the adult classification system (Table 3).

Table 3. WHO classification of HIV-associated clinical disease^a

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

Notes: a. Annex I provides further details on staging events and criteria for recognizing them.

Table 4 provides further details on staging events and Annex 1 describes criteria for recognizing them.

TABLE 4. PROPOSED REVISED WHO CLINICAL STAGING OF HIV/AIDS FOR INFANTS AND CHILDREN WITH ESTABLISHED HIV INFECTION^{a, b}

Primary HIV infection
Asymptomatic Acute retroviral syndrome
Clinical Stage 1
Asymptomatic Persistent generalized lymphadenopathy
Clinical Stage 2
Unexplained persistent hepatosplenomegaly Papular pruritic eruptions Extensive wart virus infection Extensive molluscum contagiosum Recurrent oral ulcerations Unexplained persistent parotid enlargement Lineal gingival erythema Herpes zoster Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis) Fungal nail infections

Clinical Stage 3

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 (outside first 6- 8 weeks of life)
Oral hairy leukoplakia
Acute necrotizing ulcerative gingivitis/periodontitis
Lymph node TB
Pulmonary tuberculosis
Severe recurrent presumed bacterial pneumonia
Symptomatic lymphoid interstitial pneumonitis
Chronic HIV-associated lung disease including bronchiectasis
Unexplained anaemia (<8g/dl), neutropenia (<500/mm³) or chronic thrombocytopenia (<50 000/mm³)
HIV-associated cardiomyopathy or HIV-associated nephropathy

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, penicilliosis)
Chronic Cryptosporidiosis
Chronic Isosporiasis
Disseminated non-tuberculous mycobacteria infection
Acquired HIV-associated rectal fistula
Cerebral or B cell non-Hodgkin lymphoma
Progressive multifocal leukoencephalopathy

Notes:

- a. Diagnosis of HIV infection according to recommendations in Chapter IV
- b. All clinical events or conditions referred to are described in Annex I

ROUTINE HEALTH CARE AND MONITORING OF HIV- INFECTED AND HIV-EXPOSED CHILDREN

1. MANAGEMENT OF HIV EXPOSED CHILDREN LESS THAN 18 MONTHS OLD IN WHOM DIAGNOSIS HAS NOT YET BEEN CONFIRMED

As virological testing is not readily available in Pakistan, it is likely that HIV status will not be determined in most HIV-exposed children until 12-18 months of age. These children should remain under monitoring of a pediatrician and should continue to receive all routine child healthcare including immunizations (see page 22), cotrimoxazole for prophylaxis against PCP (see page 17), and advice and counseling on safe infant feeding (see page 16). Table 5 summarizes recommendations on management of HIV exposed children less than 18 months old in whom there is diagnostic uncertainty about HIV status.

Table 5. Recommendations on management of children less than 18 months old who are exposed to HIV but infection status has not been determined

- Assess growth and nutritional status, and intervention needs
- Provide immunizations (page 22)
- Provide safe feeding advice and counseling
- Provide cotrimoxazole prophylaxis for prevention of *Pneumocystis jiroveci* (PCP) pneumonia (page 17)
- Assess for signs and symptoms of HIV. If these are consistent with severe HIV disease, consider starting ART (Chapter V)
- Assess signs and symptoms of opportunistic infections, and provide diagnosis and treatment if suspected
- Assess family situation and provide guidance, support and treatment to family members with or at risk for HIV infection.
- Offer HIV antibody test starting from 9-12 months of age. HIV can be excluded if HIV antibody is negative provided that the child has not been breastfed for > 6 weeks). HIV antibody test that is positive at age < 18 months does not confirm HIV infection as maternal antibody could still be present, in such cases, repeat HIV antibody testing at age ≥ 18 months needs to be performed. A positive HIV antibody test at age ≥ 18 months confirms HIV diagnosis.

2. COUNSELING AND SUPPORT FOR SAFE INFANT FEEDING

Breast-feeding exposes the infant of an HIV-infected mother to significant risks of MTCT. Prolonged breast-feeding (> 18 months) approximately doubles the risk of HIV transmission to the infant, and this continued risk of transmission has reduced the overall effectiveness of efforts to prevent MTCT. On the other hand, multiple studies from developing countries have shown that not breast-feeding during the first few months of life increases the risk of mortality from infectious diseases several fold.

Promotion of exclusive breast-feeding is one of the most effective strategies for improving child survival and nutritional status of children in developing countries. Recognizing the risk of HIV to the infant from breast-feeding, as well as the risks associated with not breast-feeding, and the variation in individual circumstances of HIV infected women regarding affordability and acceptance of replacement feeding, WHO guidelines state "*when replacement feeding is acceptable, feasible, affordable, sustainable, and safe, avoidance of all breast-feeding by HIV-infected mothers is recommended. Otherwise, exclusive breastfeeding is recommended during the first months of life and then should be discontinued as soon as it is feasible*".

In Pakistan, healthcare providers should make a careful assessment of the mother's ability to provide safe replacement feeding (ability to purchase powdered infant formula on a regular basis, ability to sterilize bottles, and access to clean water) in a sustainable manner, acceptability of substitute feeding to the mother, and counsel the mother about the most appropriate choice for her situation.

For women in whom replacement feeding is not possible, or not desired by the mother, exclusive breastfeeding should be advised, as rates of MTCT are lower in babies given breast milk exclusively compared with mixed feedings. Breastfeeding should be discontinued at six months of age after which the baby should receive a nutritionally balanced diet of safe complementary foods.

The effect of prolonged use of ARV drugs by the mother for prophylaxis against MTCT due to breast-feeding is not yet known and multiple studies are underway to address this question. In situations where the mother is interested in a brief period of breast-feeding for personal and social reasons and can safely switch to replacement feeding after a few weeks, use of longer periods of ARV prophylaxis in the mother may be warranted after discussion of the options available with an infectious disease expert.

3. COTRIMOXAZOLE (CTX) PROPHYLAXIS FOR PREVENTION OF PNEUMOCYSTIC PNEUMONIA (PCP)

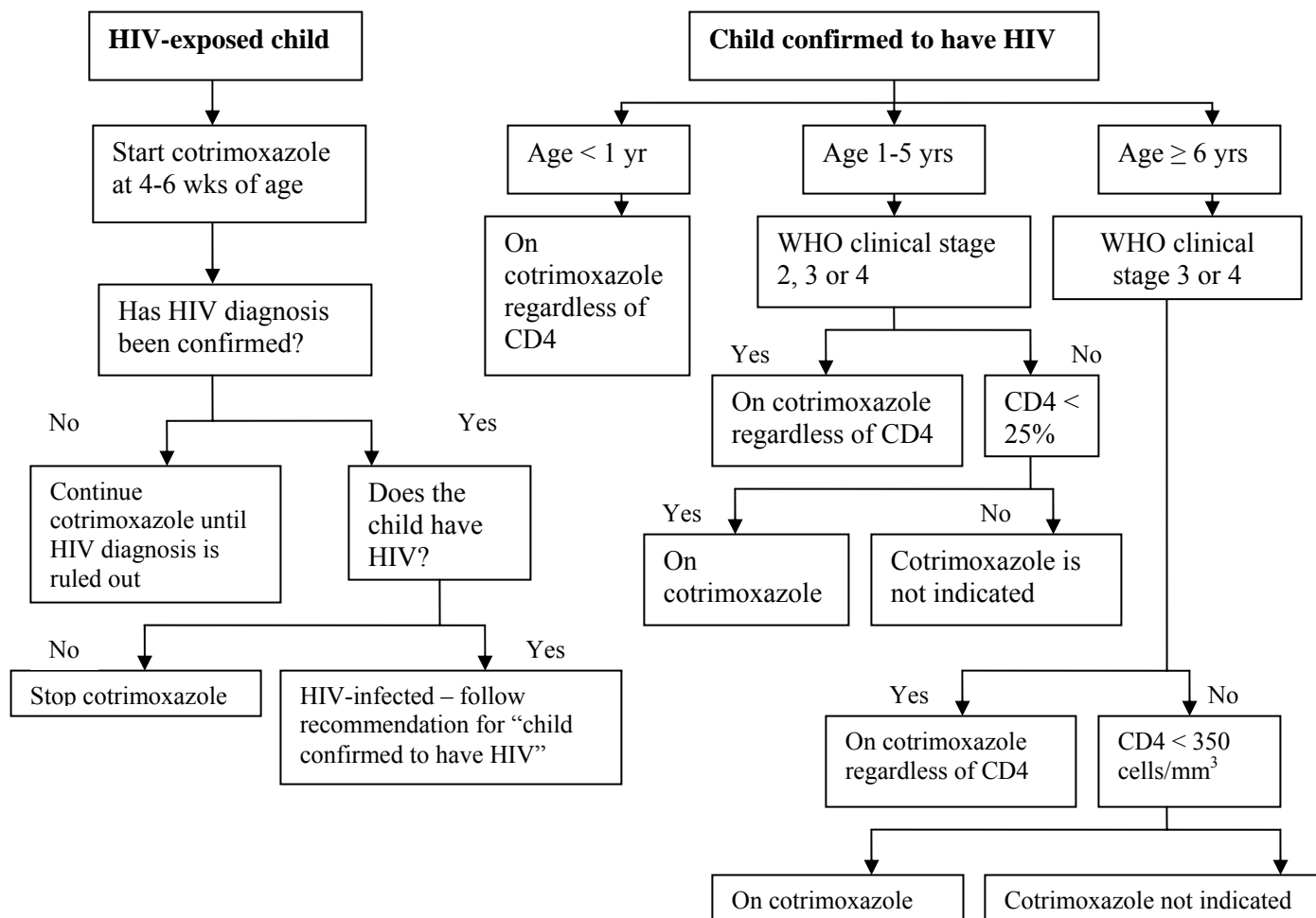
Pneumocystis jirovecii (previously called *Pneumocystis carinii*) is an opportunistic pathogen that can cause severe pneumonia which is often fatal in immunocompromised people with defective cell-mediated immunity. HIV-infected individuals are at increased risk of PCP at all ages, once their immune system has deteriorated. However, children < 12 months of age have the highest risk of PCP, with peak age of 3-6 months. This age is also problematic because often HIV diagnosis has not been suspected or confirmed by this time. Therefore,

infants often die of PCP before being recognized as having confirmed HIV infection. For this reason, CTX prophylaxis should be given to all HIV-exposed infants under age 18 months, starting at 6 weeks of age and continued until HIV infection can be excluded (Figure 3). If the child is breast-feeding, CTX prophylaxis should be continued until HIV can be excluded by diagnostic testing 6 weeks after complete cessation of breast-feeding.

If HIV infection is confirmed, CTX prophylaxis in children > 1 year can be guided by the clinical stage of the disease (Tables 3 and 4) and CD4 lymphocyte % (Figure 3). Unlike adults, absolute CD4 count is high in infants and decreases with age to reach adult values at approximately six years. Therefore, adult CD4 count thresholds are not applicable to younger children (see Chapter VII and Table 10). As CD4 % is a more reliable predictor of immune suppression and risk of PCP in children, it is used to evaluate need for PCP prophylaxis in children <- 6 years. After 5 years of age, CD4 count threshold values established for adults can be used (Figure 3).

CTX prophylaxis has also been shown to provide some protection against invasive bacterial diseases in African countries.

Figure 3. Cotrimoxazole prophylaxis for *Pneumocystis jiroveci* pneumonia (PCP)



Notes:

Cotrimoxazole dosing is shown in Annex 6C

Patient information: Patients need to be clear that while cotrimoxazole does not cure HIV, regular dosing is essential for protection of children from infections that are more common or more likely to occur in HIV infection. Cotrimoxazole does not replace the need for antiretroviral therapy

4. MANAGEMENT OF CHILDREN IN WHOM HIV INFECTION HAS BEEN CONFIRMED

Children with confirmed HIV infection should be referred to HIV specialists whenever feasible, for comprehensive assessment of clinical condition, immunological status, and evaluation for indications for initiating anti-retroviral therapy as well as ability to adhere to ART if prescribed (Table 6). However, routine health care and monitoring of HIV-infected children can be undertaken by general pediatricians, working in close coordination with infectious disease specialists as well as other members of the HIV care and support team (counselors, outreach workers). Components of such care include regular growth monitoring and nutritional assessment, neuro-developmental assessments, provision of safe feeding advice and nutritional support as needed, provision of age appropriate immunizations (see page 22 and Table 8), prophylaxis for prevention of opportunistic infections (see Annex 6), laboratory monitoring as indicated, assessment of adherence to therapy, management of common childhood infections such as acute respiratory infections, and diarrhea, as well as compassionate counseling and support, including referral to outreach services for families needing social support or food assistance (Table 7).

Table 6 summarizes recommendations for the initial assessment of a child with confirmed HIV infection. Guidelines for assessing immunological status and initiation of ART are discussed in Chapter VII.

Table 7 summarizes recommendations for routine care and monitoring of HIV-infected children who are not on ART. As discussed, it is expected that pediatricians working in consultation with infectious disease experts should be able to perform most of the components of routine clinical care for HIV-infected children, especially those who do not yet have indications for starting ART. The objectives of regular follow up of those infected and not on ART are:

- for early detection of cases requiring ART
- for management of HIV-related and other inter-current illnesses
- to ensure patient compliance with cotrimoxazole prophylaxis
- to monitor growth and development (including neurodevelopment) and provide other routine care such as immunizations
- to provide counseling, support, and referral as needed

Table 6: Assessment and management after HIV diagnosis is confirmed

- Assess growth and nutritional status, and intervention needs
- Assess immunization status and provide appropriate immunizations (page 22)
- Assess signs and symptoms for opportunistic infections (Chapter 14, and Annex 4). Assess TB exposure. If opportunistic infection is suspected, diagnosis and treatment takes priority over ART initiation
- Ensure that the child is on cotrimoxazole (page 18, and Annex 6A)
- Identify any concomitant medications use that may have drug interactions with ART
- Staging of HIV disease using immunological criteria (WHO stages from “not significant” to “severe immune suppression”, pages 26-28)
 - Perform CD4 (CD4% is preferred in children < 5 years and CD4 count is preferred in children ≥ 5 years)
 - In order to calculate CD4% and count, CBC needs to be performed as well.
- Use total lymphocyte count to stage severe immune suppression only if CD4 testing is not available (Table 11, page 28)
- Assess whether the child fits criteria for ART initiation (page 28)
- Assess family situation including but not limited to number of persons with or at risk for HIV infection and their current health/treatment status
 - Identify primary caregiver for the child and his/her ability and willingness to adhere to follow up and treatment especially ART
 - Assess family members’ understanding of HIV disease and treatment
 - Assess disclosure status of HIV diagnosis within the family (whether the child knows his/her diagnosis and whether anyone else know, and also if the child knows the parent(s)’ HIV status)
 - Assess family financial status including ability to pay for transportation to clinic, ability to afford adequate food/nutritional supplements for the child, ability to pay for any treatment needed and ability to refrigerate certain antiretrovirals.

Table 7. Monitoring of HIV infected children not on ART

Items	Baseline	Month 1	Month 2	Month 3	Month 6	Every 6 months
Clinical evaluation and HIV staging: (history and physical exam and neurodevelopmental assessment)	X	X ¹	X ¹	X ¹	X	X
Weight, height	X	X	X	X	X	X
Nutritional status and needs	X	X	X	X	X	X
Cotrimoxazole needs and adherence ²	X	X	X	X	X	X
Hb and WBC	X					X
ALT ³	X					
CD4% or count ⁴	X					X
TLC ⁵	X					X
OI prevention and treatment needs ⁶	X	X	X	X	X	X

- In addition to these suggested follow up appointments, caregivers should be advised to bring the child in if he/she is sick
- If the child has missed a visit, attempts should be made to call or visit the child's home.

¹ Children <12 months of age have a higher risk of HIV disease progression and should be followed more frequently than older children.

² See page 17 for cotrimoxazole preventive therapy

³ ALT at baseline is the minimum monitoring for possible liver impairment. Children with high ALT (> 5 times upper limit of normal) should have full liver function test performed as well as assessment for hepatitis B or hepatitis C or other hepatic disease. Other chemistry tests depend on symptoms

⁴ CD4% is used in children < 5 years of age. For children ≥ 5 years of age, CD4 count is mainly used.

⁵ Total lymphocyte count (TLC) can be used when CD4 is not available to classify severe immunodeficiency which is a criterion to start ART (page 28).

⁶ Identifying TB exposure is important (Annex 3).

5. RECOMMENDATIONS FOR IMMUNIZATIONS IN HIV-INFECTED AND HIV-EXPOSED CHILDREN

Children infected with HIV are very vulnerable to severe, overwhelming infections by usual childhood pathogens such as pneumococci and Haemophilus influenzae. HIV-infected immunocompromised children can die of overwhelming pneumococcal bacteremia and sepsis within a few hours of infection. Additionally measles and varicella infections tend to be very severe, with increased mortality.

Routine immunizations appear to be generally safe for children with HIV infection. Although immune responses may be sub-optimal in some HIV-infected children, because of the severe nature of infections and associated mortality, routine immunization of all children with HIV exposure or confirmed HIV infection is recommended with few

exceptions. The routine EPI schedule can be followed, but with an extra dose of measles vaccine to be given at age 6 months (Table 8). BCG vaccine is avoided in children with symptomatic HIV infection because of the risk of disseminated BCG infection.

Although pneumococcal conjugate vaccine, *Haemophilus influenzae* type b vaccine (Hib), and varicella vaccines are not part of the EPI schedule in Pakistan, they are available in the private market and strong consideration should be given to immunizing HIV-infected children with these vaccines because of the propensity of HIV-infected children to develop severe, life-threatening infections with these pathogens. It is expected that NACP will make provisions for access to these vaccines for HIV-infected children.

Table 8 summarizes recommendations for immunizing asymptomatic HIV-exposed and HIV-infected children and symptomatic HIV-infected children.

Table 8. Recommendations for immunization of HIV-exposed and HIV-infected children*

Vaccine	Asymptomatic HIV infection	Symptomatic HIV infection
BCG	Yes (birth)	No
DPT	Yes (6, 10, and 14 weeks)	Yes
Oral polio vaccine	Yes (0, 6, 10, and 14 weeks)	Yes
Measles	Yes (6 and 9 months)	Yes
Hepatitis B	Yes	Yes

*Note: HIV- infected children in industrialized countries also receive MMR vaccine at 15 months unless CD4 <15%, *Haemophilus influenzae* b vaccines, pneumococcal vaccines, and varicella vaccines. These life-saving vaccines should also be considered for HIV-infected children in Pakistan.

6. NUTRITIONAL ASSESSMENT AND SUPPORT

Malnutrition remains a major contributor to mortality in both, HIV-uninfected and infected children in developing countries. In HIV-infected children, wasting (i.e. low weight for height/length) has been associated with reduced duration of survival while weight loss increases the rate of infectious complications in children with AIDS.

These guidelines provide in the following a brief summary of key nutritional interventions relevant to the care of HIV-infected infants and children in Pakistan prior to or while on ART.

In view of the close interrelation of HIV infection, nutritional status and growth, NACP recommends that early nutritional intervention (i.e. nutritional assessment and support) should be an integral part of the care plan of HIV-infected children.

Nutritional assessment i.e., the systematic evaluation of current nutritional status, diet, and nutrition-related symptoms, is critical in early identification of malnutrition and poor

growth as well as for monitoring of HIV disease progression and treatment efficacy for children on ART. Nutritional assessment should be part of routine clinical monitoring of HIV-infected children whether or not receiving ART. As for all infants, HIV-infected infants should be measured monthly, ideally using standardized growth curves. Thereafter, children should be weighed at each review and full nutritional assessments be performed every three months unless the child requires particular attention due to growth problems or special nutritional requirements (Table 7)

HIV infected children have increased energy needs. In asymptomatic HIV-infected children, resting energy expenditure is increased by about 10% while in HIV-infected children who experience growth failure energy needs may be increased 50% and 100%. Increased utilization and excretion of nutrients in HIV infection can also lead to micronutrient deficiencies. Nutritional support should thus include early efforts to ensure adequate nutrient intake based on easily available nutritious and affordable foods and ensure intake of micronutrients equivalent to one Recommended Daily Allowance (RDA). It is recommended to increase the energy intake of HIV-infected infants and children by 10% of the RDA for their age and sex where asymptomatic and by 20-30% of RDA when symptomatic or recovering from acute infections. These are minimal requirements and more may be needed in children with nutritional deficiencies.

There is insufficient information at present to make firm recommendations on routine micronutrient supplementation of HIV-infected children. However there is good evidence for large-dose Vitamin A supplementation for reducing overall morbidity and diarrheal morbidity as well as all-cause mortality. Vitamin A supplements should be given according to Pakistan IMCI recommended high-dose prevention schedule for children at high risk¹ of Vitamin A deficiency. Zinc supplementation during diarrheal episodes also reduces morbidity in both HIV-infected and uninfected children and is recommended in Pakistan.

Counseling mothers about breastfeeding or safe substitute feeding and all children and their caretakers about food and water hygiene are further core elements of nutritional support.

Table 9 summarizes nutritional recommendations for HIV-infected children in Pakistan.

¹ Children at high risk of Vitamin A deficiency include – among others - children with severe infections or severe protein-energy malnutrition.

Table 9: Recommendations for nutritional support for HIV-infected children

- Regular growth monitoring
- Safe infant feeding advice (substitute feeds if acceptable, affordable, feasible, sustainable, and safe, otherwise exclusive breast-feeding, and early weaning)
- Dietary counseling for asymptomatic children to increase energy intake by 10% compared to HIV uninfected children
- Dietary counseling for symptomatic children to increase energy intake by 20-30% compared to HIV uninfected children
- Counseling on importance of balanced diet including affordable choices from all food groups (micronutrient requirement of 1 RDA for age)
- Counseling on high energy, affordable food options in children with growth failure
- Counseling on use of clean water, hygienic food
- Vitamin A supplementation every 6 months (double check frequency, insert dose)
- Zinc supplementation during diarrheal episodes (10 mg once daily for 10 days in children older than 6 months if weight is \leq 10 kg, and 20 mg if weight is $>$ 10 kg.
- Assessment and management for underlying HIV-associated illnesses
- Assessment for need to initiate ART
- Referral to outreach service providers for food assistance, if needed

In children experiencing growth failure (i.e., failure to gain weight or weight loss between regular measurements) or feeding difficulties, more intensive evaluation is indicated. Underlying illnesses should be carefully sought and managed according to Pakistan's National IMCI guidelines. Children should be evaluated for the need to start or switch ART (Chapter VII), families should be educated about appropriate food choices and referrals made to outreach service providers for food assistance, if needed. In addition, selection of specific, palatable high-energy foods in children with conditions that interfere with normal ingestion or digestion (such as sore throat or mouth, oral thrush, or diarrhea) may relieve symptoms and at the same time ensure sufficient energy intake.

7. WHEN TO REFER?

Many times the needed facilities or expertise will not be available at a health center/hospital where a child with suspected or confirmed HIV has come for treatment. If the child is not suffering from a life-threatening condition that requires urgent treatment, and referral can be arranged, referral to a pediatric infectious disease specialist or HIV treatment center is advised in the following circumstances.

- For HIV testing with pre- and post-test counseling
- For further investigations to confirm diagnosis
- For evaluation of immunological status and need to initiate ART
- For management of complicated HIV-related conditions and infections
- For evaluation of possible treatment failure
- For second line treatment if there has been little or no response to treatment
- For HIV medication related toxicities
- For HIV-related expert counseling

Additionally families should be referred to outreach NGOs providing home-based services, assistance with food and adherence to medications etc.

WHEN TO START ANTI-RETROVIRAL THERAPY IN INFANTS AND CHILDREN

The decision to start ART in an infant or child should be based on consideration of the following factors

- Clinical condition of the child and severity of disease (Clinical Staging: Tables 3 and 4)
- Immunological status of the child as measured by CD4 percentage or count (Table 10)
- Presence of co-morbidities such as TB or severe end-organ damage (e.g. in thalassaemia, cirrhosis) which may worsen anticipated toxicities
- Evaluation of the social environment of the child (ability of family to adhere to therapy and medical care, access to nutrition and support, availability of committed family member who agrees to long-term care of the child)

Clinical assessment of the child with HIV infection has been discussed above (Tables 3 and 4). The clinical stage of illness is correlated with risk of mortality and indicates the urgency with which to start ARV. Treatment with ARV improves clinical status and results in reversal of clinical stage in most children. However, whenever possible, decision to start ART in children with Clinical Stage 3 or 4 disease should also take into account CD4 measurements because they assist in monitoring response to therapy.

1. IMMUNOLOGICAL ASSESSMENT OF HIV INFECTED CHILDREN

Measurements of CD4 lymphocytes assess the severity of HIV-related immunodeficiency and guides decision on initiation of ART before a child gets clinically advanced disease. Results of CD4 measurement should be used in conjunction with clinical assessment. Healthy infants without HIV have much higher total lymphocyte count (TLC) and CD4 levels than those observed in uninfected adults, and slowly decline to adult values by the age of about 6 years; CD4 percentage (i.e., % CD4) values also vary with age, but less than CD4 counts. Therefore taking account of the age of the child is essential in interpreting CD4 counts and percentages (Table 10). The measurement of the %CD4 is more informative in children less than 5 years of age. Absolute CD4 counts (and less so %CD4) fluctuate within an individual and values can vary with intercurrent illness, physiological changes, or test variability. Serial measurements are therefore more informative than individual values and also reflect trends over time. As with clinical status, immunological recovery occurs with successful ART. Because of the variability of both CD4 (% and absolute count), if possible, two values below threshold of severe immunodeficiency should be obtained prior to initiation of ART based on immunological criteria alone, particularly before starting a child on ART with no or mild symptoms of HIV (i.e., Clinical Stage 1 and 2). Results of CD4 measurement are also useful to monitor responses to treatment.

Table 10. CD4 criteria of severe HIV immunodeficiency

Immunological marker ^a	Age-specific recommendation to initiate ART ^b			
	≤11 months	12 months-35 months	36 months-59 months	≥5 years
CD4 % ^c	<25%	<20%	<15%	<15%
CD4 count ^c	<1500 cells/mm ³	<750 cells/mm ³	<350 cells/mm ³	<200 cells/mm ³

Notes:

- a. Immunological markers supplement clinical assessment and should therefore be used in combination with clinical staging; ideally, CD4 is measured after stabilization of acute presenting conditions.
- b. ART should be initiated by these cut-off levels, regardless of clinical stage; a drop of CD4 below these levels significantly increases the risk of disease progression and mortality.
- c. % CD4 is preferred for children <5 years of age.

These established threshold values for indicating severe immunodeficiency are correlated with annual mortality risks. The annual mortality risk above the threshold values is 5% or less. However, it is important to note that in young infants (under 6 months of age), %CD4 or absolute CD4 count is less predictive of mortality, as there is a high risk of death even at high %CD4 (e.g., CD4 ≥25% or 1500 cells/mm³).

The thresholds described also indicate the levels at or below which ART in children is indicated. Asymptomatic HIV-infected children (i.e. those with Clinical Stage 1 and 2 disease) should be considered for ART when immunological values begin to drop to values close to the described threshold values (Table 10 and Table 12). A drop below threshold values should however be avoided.

Advanced HIV disease, or development of severe HIV-related conditions always requires ART irrespective of whether defined clinically or immunologically (see Tables 3 and 4). However, in children aged 12 months and older who have specific Clinical Stage 3 conditions (tuberculosis, lymphocytic interstitial pneumonia, thrombocytopenia and oral hairy leukoplakia), CD4 measurements are useful in determining whether therapy is needed immediately or can be deferred until the specific clinical condition is treated: a CD4 level >20% in children aged 12 – 35 months of age or >15% or >200 cells/mm³ in children 5 years of age and older may suggest that it is reasonable to delay the start of ART. For example, in children with pulmonary or lymph node tuberculosis, the result of CD4 measurement and clinical status can guide whether ART is urgently required or can be delayed (Chapter XII).

If CD4 measurements are not available, total lymphocyte count (TLC) may be used to evaluate need to initiate ART in infants or children (Table 11). As for CD4 levels, the predictive value of TLC for mortality in children < 6 months of age is poor, and deaths can occur even at high TLC values. The TLC thresholds can be used in guiding the need for therapy in children with WHO Paediatric Clinical Stage 2 disease up to 8 years of age (Tables 11 and 12). There are less data available to make recommendations on the use of TLC for decision-making in children older than 8 years of age.

Table 11. TLC criteria of severe HIV immunodeficiency requiring ART; use in infants and children with clinical stage 2 if CD4 measurement is not available

Immunological marker ^a	Age-specific recommendation to initiate ART ^b			
	≤11 months	12 months-35 months	36 months-59 months	5 - 8 years
TLC	<4000 cells/mm ³	<3000 cells/mm ³	<2500 cells/mm ³	<2000 cells/mm ³ ^(c)
Notes: a. Immunological markers supplement clinical assessment and should therefore be used in combination with the clinical staging. b. A drop of TLC below these levels significantly increases the risk of disease progression and mortality. c. There are less data available to make recommendations on the use of TLC for decision making in children older than 8 years of age.				

2. CRITERIA FOR INITIATING ANTIRETROVIRAL THERAPY IN HIV- INFECTED CHILDREN

Table 12 summarizes the recommendations for initiating ART in HIV infected infants and children according to clinical stage and availability of immunological markers. Because of the cost and complexity of viral load testing, NACP does not currently recommend their routine use in Pakistan for initiating or monitoring ART.

Table 12. Recommendations for initiating ART in HIV infected infants and children according to clinical stage and availability of immunological markers

WHO Paediatric Stage	Availability of CD4 cell measurements	Age-specific treatment recommendation	
		<12 months	≥12 months
1	CD4 No CD4 ^b	CD4-guided ^d Do not treat	LIP - lymphocytic interstitial pneumonia; OHL- Oral hairy leukoplakia; TB – tuberculosis
2	CD4 No CD4 ^b	CD4-guided ^d TLC-guided ^d	
3 ^a	CD4 No CD4 ^b	Treat all	Treat all, CD4 guided in those children with TB ^c , LIP, OHL, thrombocytopenia Treat all ^c

4 ^a	CD4 No CD4 ^b	Treat all
Notes: a. Stabilize any opportunistic infection prior to initiation of ARV therapy. b. Baseline CD4 is useful to monitor ART even if it is not required to initiate ART. c. In children with pulmonary or lymph node tuberculosis, the CD4 level and clinical status should be used to determine the need for and timing of initiation of ART in relation to tuberculosis treatment d. For CD4 or TLC values, refer to Tables 10 and 11, respectively.		

2.1 Criteria for starting ART in infants and children with presumptive diagnosis of severe HIV disease

If access to virological testing is not immediately available, WHO has developed clinical criteria for presumptive diagnosis of severe HIV disease in a child less than 18 months of age to allow appropriate management of the potentially HIV-infected child, including the need for ART, because such children are at a high risk of death. The diagnosis of HIV infection should be confirmed by virological testing as soon as possible.

Initiation of ART based on presumptive clinical diagnosis of severe HIV disease is not recommended for use by clinical care providers who are not appropriately trained in HIV care or administration of ART. Use of clinical criteria to make a presumptive diagnosis of HIV infection is not needed in children 18 months of age and older as antibody testing establishes HIV infection status.

Table 13. Clinical criteria for presumptive diagnosis of severe HIV disease in infants and children less than 18 months of age requiring ART in situations where virological testing is not available

<p>A presumptive diagnosis of severe HIV disease should be made if:</p> <ul style="list-style-type: none"> ▪ The infant is confirmed HIV antibody positive; <p><i>and</i></p> <ul style="list-style-type: none"> ▪ Diagnosis of any AIDS-indicator condition(s) can be made; <p><i>or</i></p> <ul style="list-style-type: none"> ▪ The infant is symptomatic with two or more of the following: <ul style="list-style-type: none"> ○ Oral thrush^a; ○ Severe pneumonia^a; ○ Severe sepsis^a. <p>Other factors that support the diagnosis of severe HIV disease in an HIV seropositive infant include:</p> <ul style="list-style-type: none"> ▪ Recent HIV-related maternal death; <i>or</i> advanced HIV disease in the mother; ▪ CD4 < 20%. <p>Confirmation of the diagnosis of HIV infection should be sought as soon as possible.</p>

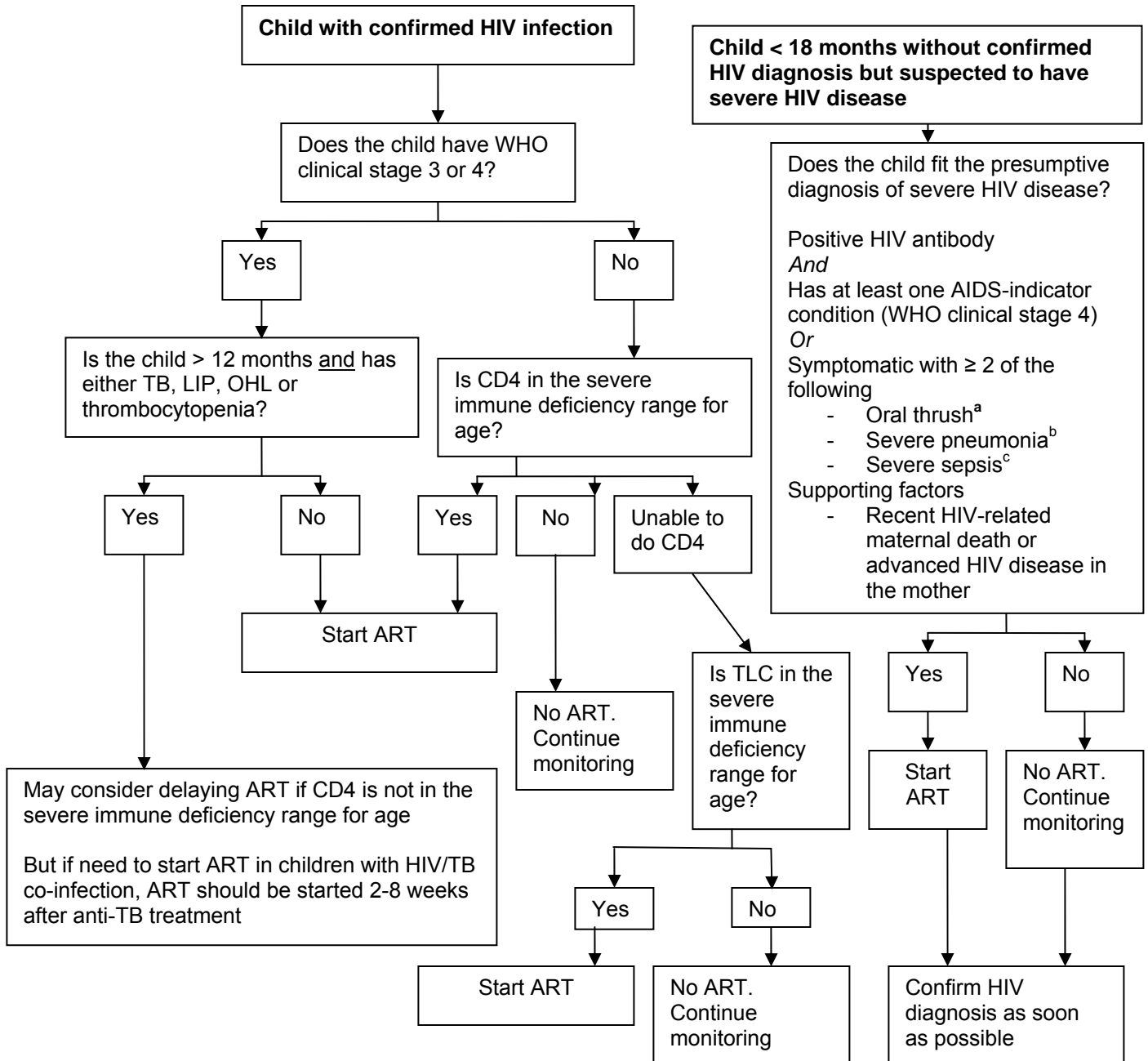
Notes:

a. As per IMCI definition:

- Oral thrush: Creamy white to yellow soft small plaques on red or normally coloured 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.
- Severe pneumonia: Cough or difficult breathing in a child with chest indrawing, stridor or any of the IMCI general danger signs; i.e., lethargic or unconscious, not able to drink or breastfeed, vomiting, and presence or history of convulsions during current illness; responding to antibiotics.
- Severe sepsis: Fever or low body temperature in a young infant with any severe sign such as fast breathing, chest indrawing, bulging fontanelle, lethargy, reduced movement, not feeding or sucking breast milk, convulsions etc.

Table 13 lists the criteria for presumptive clinical diagnosis of HIV in infants and children less than 18 months old and Figure 7 summarizes the overall WHO recommendations for starting ART in infants and children in an algorithm form.

Figure 7: Clinical and immunological criteria for starting ART in infants and children



Notes

- Risk of death is high if the child has WHO clinical stage 3 or 4.
- Children < 12 months of age and especially < 6 months of age have the highest risk of HIV disease progression and death even with normal CD4
- Tuberculosis (TB) particularly pulmonary and lymph node TB, lympho-interstitial pneumonitis (LIP), oral hairy leukoplakia (OHL) and thrombocytopenia (platelet count < 50,000/mm³) are WHO clinical stage 3 diseases that can occur in the presence of relatively good CD4 and are not associated with as high risk of death as the other stage 3 diseases; therefore, ART initiation may be deferred if CD4 is not in the severe immune suppression range.

- CD4 can fluctuate within an individual and values can vary with intercurrent illness, physiological changes or test variability. If possible, two values below the threshold should be obtained prior to initiation of ART based on CD4 criteria alone.
- Monitoring in children who are not yet eligible for ART initiation should include clinical evaluation and CD4 or TLC if CD4 is not available every 3-6 months with consideration for more frequent follow up in infants and younger children, and in children approaching clinical and CD4 or TLC threshold for initiating ART.

ANTI-RETROVIRAL THERAPY FOR CHILDREN IN PAKISTAN – OVERVIEW AND RECOMMENDATIONS

ARV drugs have revolutionized the care of people with HIV/AIDS. Although ARV drugs are not a cure for HIV, their use results in dramatic improvement in child survival and quality of life. The clinical and immunological criteria as well as social factors to be considered in initiating ART in children have been discussed above (Chapter VII). WHO has developed simplified treatment guidelines for use in resource-limited countries. However, once the decision to initiate treatment has been made, multiple challenges in the successful management of ART in children need to be addressed. These are:

- Resistance to single or dual agents is quick to emerge, and combinations of at least 3 drugs need to be used.
- Many drugs are not available in pediatric formulations
- Dosage of many drugs in children is not known
- Compliance is affected by taste/palatability of medications
- Complicated dosing regimens are not suitable for children
- Maternal ART during pregnancy or breast-feeding may affect viral resistance and choice of therapy in children
- Dosing in children is based on either body surface area or weight and children require frequent adjustment of dosages
- Long-term toxicity is a major consideration in therapy
- Because of parental illness, care-providers may frequently be not available/changing
- As children get older, they may not understand the need to continue therapy

1. ANTIRETROVIRAL DRUGS

Antiretroviral drugs fall into three main classes of drugs:

- Nucleoside analogue reverse transcriptase inhibitors (NRTIs)
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Protease inhibitors (PIs)

Table 14 lists ARV agents that are recommended for use in developing countries. Triple therapy is the standard of care. WHO guidelines are for the use of two NRTIs and one NNRTI as the initial first-line therapy in children, while protease inhibitors are reserved for second-line therapy. The Pakistan guidelines are based on current WHO recommendations and will be updated as new information becomes available.

Detailed information on dosing, preparations, storage and special instructions on administration of drugs listed below is provided in Annex 7.

Table 14. Antiretroviral agents recommended for use in HIV-infected children in developing countries

Nucleoside analogue reverse transcriptase inhibitors (NRTIs)	
• Zidovudine	ZDV (AZT)
• Lamivudine	3TC
• Stavudine	d4T
• Didanosine	ddI
• Abacavir	ABC
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	
• Nevirapine	NVP
• Efavirenz	EFV
Protease inhibitors (PIs)	
• Nelfinavir	NFV
• Liponavir/ritonavir	LPV/r
• Saquinavir	SQV

1.1 Nucleoside analogue reverse transcriptase inhibitors (NRTIs)

The NRTIs were the first class of antiretroviral drugs available for the treatment of HIV infection. Once they are converted intracellularly to active nucleoside metabolites they are potent inhibitors of the HIV reverse transcriptase enzyme which is responsible for the reverse transcription of viral RNA into DNA. The drugs from the NRTI class recommended for use in Pakistan are described below.

Lamivudine (3TC), a cytidine analogue, is a potent NRTI with an excellent record of efficacy, safety and tolerability in HIV-infected children, and is a core component of the dual NRTI backbone of therapy. It is usually given twice daily in children and has been incorporated into a number of fixed-dose combinations (FDC).

Stavudine (d4T) is a thymidine analogue NRTI that is initially better tolerated than ZDV and does not require haemoglobin or laboratory monitoring. However, among the NRTIs, it has been consistently most associated with lipodystrophy and lactic acidosis. In addition, elevated hepatic transaminases and pancreatitis have been observed. d4T can also cause peripheral neuropathy, though these complications are less common in children than in adults. d4T liquid formulations require a cold chain and capsule size starts at 15 mg only. It is worth emphasizing that d4T and ZDV should never be used together because of proven antagonism between them.

Zidovudine (ZDV) is a thymidine analogue in the NRTI class. Although ZDV is generally well tolerated in children, it has also been associated with metabolic complications of therapy but to a lesser extent than d4T. Initial drug-related side-

effects are more frequent with ZDV and the drug can cause severe anaemia and neutropaenia; haemoglobin monitoring before and during treatment with ZDV is thus useful. Large volumes of ZDV liquid formula are often poorly tolerated. d4T can be substituted for ZDV in the event of intolerance to the latter and vice versa, except in cases of suspected lactic acidosis in which instance neither drug should be restarted.

Abacavir (ABC), a guanosine analogue, has been included in the WHO revised paediatric guidelines as an alternative NRTI in first-line therapy, and is included in the NACP formulary too. Clinical trial results in antiretroviral-naïve persons demonstrating efficacy, availability of ABC in paediatric formulation, and the resulting potential to deliver family-based care of HIV-infected parents and children with ABC/3TC offset concerns about introducing an additional first line drug. ABC-containing dual NRTI regimens (ABC/3TC or ABC/ZDV) may be more effective than ZDV+3TC-containing regimens in children with HIV-1 who have not been previously treated. Trial results have also suggested a similar safety profile in children to that in adults, with very little hematologic toxicity. NRTI combinations containing ABC therefore provide a good NRTI backbone for use with NNRTI (or as part of a triple nucleoside regimen when NVP and EFV can't be used; e.g. infants with TB). Of all the NRTI drugs, ABC has the least effect on mitochondrial DNA, and would be the preferred substitute for d4T in a child who developed lactic acidosis while receiving a d4T-containing regimen. ABC could also be substituted for ZDV in the event of intolerance. However, ABC is associated with a potentially fatal hypersensitivity reaction in a small proportion of children (about 3%) who receive the drug. In infants and children suspected of having a hypersensitivity reaction, ABC should be stopped and not restarted. Children and/or their caregivers should be advised about the risk of this serious hypersensitivity reaction and the need to immediately consult their care provider if signs or symptoms of a hypersensitivity reaction occur.

1.2 Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

NNRTI-based regimens are now the most widely prescribed combinations for initial therapy. They are potent, but a single mutation can induce cross-class resistance. The NNRTIs efavirenz (EFV) and nevirapine (NVP) both have demonstrated clinical efficacy when administered in appropriate combination regimens in children. However, differences in toxicity profile, the potential for interaction with other treatments, lack of dosing information for EFV in young children, and cost, are factors that need to be taken into consideration when choosing an NNRTI.

Efavirenz (EFV) is metabolized via the cytochrome P450 pathway. It is not currently recommended for use in infants and children younger than 3 years of age or weighing less than 10 kg because there is no established dosing. EFV is primarily associated with toxicities related to the central nervous system (CNS), teratogenicity and rash. Rash is more frequent in children than adults, is generally mild, and usually does not require discontinuation of therapy. The CNS symptoms typically abate after 10 to 14 days in the majority of patients; observational studies reported the transient CNS disturbance in 26%-36% of children receiving EFV. EFV should be avoided in children with a history of severe psychiatric illness, when there is a potential for pregnancy (unless effective contraception can be assured) and during

the first trimester of pregnancy. In these situations, NVP may be the better choice (see below). EFV may be considered as the NNRTI of choice in children with TB/HIV coinfection (see Chapter 12).

Nevirapine (NVP) is highly lipophilic and widely distributed in the body. As with EFV, NVP is metabolized via cytochrome P 450. NVP, as is true for all NNRTI drugs, should only be given in combination with other retroviral drugs, except when used as single-dose prophylaxis as an interim measure to reduce the risk of perinatal HIV transmission. NVP has a higher incidence of rash than other ARVs. NVP related rash may be severe and life-threatening, including Stevens-Johnson syndrome, and as noted above, NVP is also associated with a rare but potentially life-threatening risk of hepatotoxicity. In these situations, NVP should be permanently discontinued and not restarted. This makes the drug less suitable for treating children who use other hepatotoxic medications, or drugs that can cause rash, or both, such as rifampicin for the treatment of tuberculosis. There are limited data on the use of NVP in children co-infected with HIV and Hepatitis B. NVP is currently the only NNRTI syrup available for infants. It also exists as part of three-drug FDC which could be used for older children when quality-assured formulations of proven bioequivalence are available.

NVP should be used with caution in adolescent girls with CD4 count between 250-350 cells/mm³ because of higher risk of hepatotoxicity; if used in such adolescent girls, careful monitoring is needed during the first 12 weeks of therapy, ideally including liver enzyme monitoring.

1.3 Protease Inhibitors (PIs)

Protease inhibitors are potent anti-retroviral agents that are used in many adult treatment regimens. However, several constraints such as availability of suitable pediatric formulations, dosing information, cold chain requirement, and expense have limited their use in children. Because of the diminished potential of almost any second-line nucleoside component, a low dose ritonavir (RTV)-enhanced PI (PI/r) component, i.e. lopinavir (LPV)/r, or saquinavir (SQV)/r, is generally preferable to nelfinavir (NFV) alone for second-line regimens. Advantages of PI-based regimens include proven clinical efficacy and well-described toxicities. SQV/r can be considered as an alternative in children weighing more than 25 kg (who therefore can receive the adult dose) and who are able to swallow capsules. Other limitations related to the use of RTV-boosted PIs include the requirement for the presence of a cold chain for most products and poor tolerability of RTV.

NACP recommends that the PI-class of drugs should be reserved for second-line therapy because the use of PIs in an initial treatment regimen compromises any subsequent second-line regimen.

2. RECOMMENDATIONS FOR FIRST-LINE REGIMENS

The *preferred option* when choosing a first-line regimen for infants and children is a reverse transcriptase inhibitor (RTI)-based regimen which consists of two nucleoside reverse transcriptase inhibitors (NRTIs) plus one non-nucleoside reverse transcriptase inhibitor

(NNRTI) (Table 15). NRTI/NNRTI-based regimens are efficacious, generally less expensive, generic formulations are more often available and a cold chain is not required. In addition, they preserve a potent new class (i.e., protease inhibitors [PI]) for second-line. Disadvantages include different half lives, the fact that a single mutation is associated with resistance to some drugs (e.g., lamivudine [3TC], NNRTIs), and for the NNRTI drugs a single mutation can induce resistance to all currently available drugs in the class.

EFV is not currently recommended for use in children less than 3 years of age or weighing less than 10 kg because of a lack of appropriate dosing information. Consequently, for children aged less than 3 years or weighing less than 10 kg, NVP is the recommended NNRTI. Additional concerns of NNRTIs as components of first-line regimens relate to their use in adolescents (hepatotoxicity of NVP in adolescent girls with CD4 absolute cell counts >250/mm³). Available data in infants and children indicate a very low incidence of hepatic toxicity with NVP without association with CD4 count.

Table 15. Summary of recommended preferred first-line ARV regimens for infants and children

Regimen of 2 NRTI plus 1 NNRTI ^a :
ZDV ^b + 3TC ^c + NVP ^d / EFV ^e
d4T ^b + 3TC ^c + NVP ^d / EFV ^e
ABC ^f + 3TC ^c + NVP ^d / EFV ^e
<p>Notes:</p> <ul style="list-style-type: none"> a. The use of ZDV, d4T, ABC with 3TC results in several possible dual nucleoside combinations including ZDV + 3TC; d4T + 3TC; ABC + 3TC. b. ZDV should not be given in combination with d4T. c. 3TC is a component of all the recommended first-line regimens d. NVP should be avoided in post pubertal adolescent girls (considered as adults for treatment purposes) with baseline CD4 absolute cell counts >250/mm³. e. EFV is not currently recommended for children <3 years of age or < 10kg, and should be avoided in post pubertal adolescent girls who are sexually active f. ABC is included in the list of recommended first line regimens, but because of expense and small risk of serious hypersensitivity reaction, should be reserved for children in whom ZDV (anemia) and d4T (lactic acidosis) need to be avoided

It is not known whether ARV choices should be modified for infants who have been exposed to ARVs used for PMTCT or whose mothers are on ARV during breast-feeding. Until more information becomes available, these guidelines also apply to babies exposed to ARVs through PMTCT interventions or through breast-feeding.

2.1 Considerations in the choice of first-line regimens (which first-line regimen to use?)

The availability of four NRTIs and 2 NNRTIs as possible choices in selecting first-line regimens makes several combinations of 2NRTI plus 1NRTI regimens possible. The following steps will help in the selection of a regimen most appropriate to the child (Tables 16a and 16b).

Table 16a: Choosing the NRTI to be used in combination with 3TC:

NRTI	Pros	Cons
ZDV (Preferred NRTI if Hb \geq 8g/dl)	<ul style="list-style-type: none"> - ZDV causes less lipodystrophy and lactic acidosis than d4T - ZDV does not need refrigeration 	<ul style="list-style-type: none"> - ZDV has more initial gastrointestinal (GI) side effects - Large volume of ZDV liquid is often poorly tolerated - Severe anemia and neutropenia can occur. CBC monitoring before and after treatment is recommended.
ABC	<ul style="list-style-type: none"> - ABC causes the least lipodystrophy and lactic acidosis - ABC has little hematologic toxicity and is well tolerated - ABC does not need refrigeration - ABC has good efficacy 	<ul style="list-style-type: none"> - ABC is associated with potentially fatal hypersensitivity in 3% of children - ABC is more expensive than ZDV and d4T and is not widely available in generic form
D4T	<ul style="list-style-type: none"> - d4T causes less GI side effects and anemia than ZDV 	<ul style="list-style-type: none"> - d4T causes more lipodystrophy, lactic acidosis and peripheral neuropathy - d4T liquid needs refrigeration.

Notes:

- 3TC is used in all 3 combinations as it has excellent record of efficacy, safety and tolerability. However, it has a low threshold for drug resistance development.
- ZDV is the preferred choice. However, should the child have Hb < 8g/dl, ABC or d4T should be considered.
- Because of the risk of lipodystrophy with long term-use D4T, consider switching d4T to ZDV (if Hb \geq 8g/dl)

Table 16 b: Choosing the NNRTI agent to use in combination with 2 NRTIs

1NNRTI	Pros	Cons
NVP	<ul style="list-style-type: none"> - NVP can be given to children at any age - NVP does not have teratogenic effect - NVP is available in both pill and liquid formulations. Both do not need refrigeration. - NVP is part of several three-drug fixed dose combinations that can be used in older children 	<ul style="list-style-type: none"> - NVP has higher incidence of rash than EFV. NVP rash may be severe and life-threatening - NVP is associated with rare but potentially life-threatening risk of hepatotoxicity - For adolescent girls, the risk of NVP associated hepatotoxicity or serious rash increases with CD4 > 250 cells/mm³. - Rifampicin lowers NVP level more than EFV
EFV	<ul style="list-style-type: none"> - EFV causes less rash and hepatotoxicity than NVP. Rash that occurs is generally mild. - EFV level is 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, EFV capsule can be opened and added to liquid or small amount of food 	<ul style="list-style-type: none"> - EFV can only be used in children age ≥ 3 years old or weigh ≥ 10 kg - Transient CNS disturbance can occur in 26-36% of children; therefore, EFV should be avoided in children with a history of severe psychiatric illness. - EFV has teratogenic effect and should be avoided in adolescent girls with potential for pregnancy. - EFV is not available in liquid formulation.

Notes:

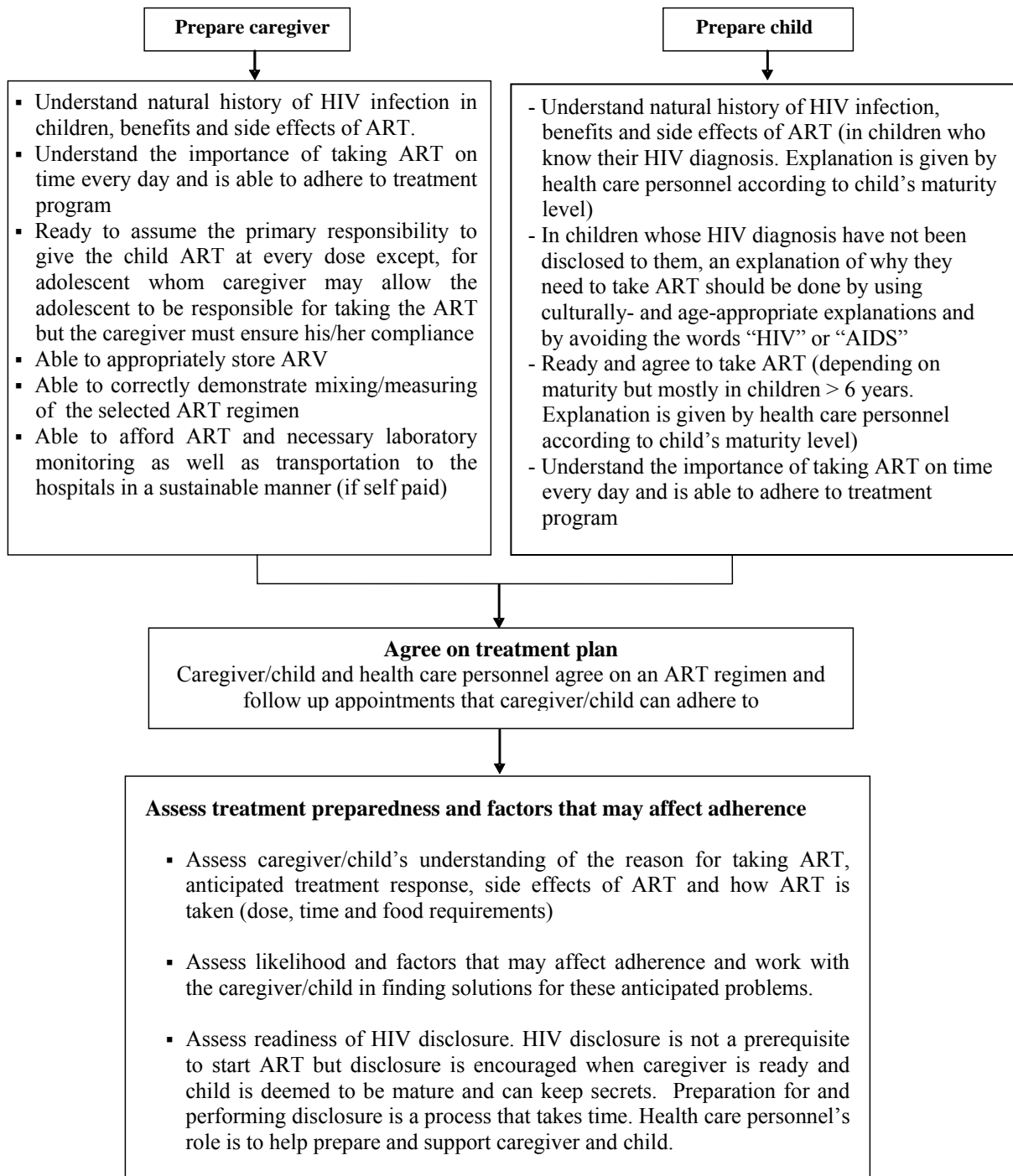
- Children who were exposed to NVP single dose as part of prevention-of-mother-to-child transmission program are at higher risk for NNRTI resistance development but there is currently no data on whether response to subsequent ART with NNRTI-based regimens is compromised. Therefore, at this time, 2NRTI+NNRTI regimen is considered the recommended regimen for these children.

2.2 Preparing to start ART in children: laying the groundwork for ensuring long-term compliance

Ideally, expert counselors and support staff should be available to properly assess treatment preparedness and give extensive counseling to the family (and child if old enough) about the implications of initiating ARV treatment and need for strict

adherence. Starting ART is not an emergency. Beginning ARV therapy when the child/caregiver is not ready can result in poor adherence and ART resistance can emerge quickly. Figure 8 outlines the process for evaluating treatment preparedness.

Figure 8. Assessment and counseling for ART preparedness



MONITORING AND ADHERENCE COUNSELLING FOR CHILDREN ON ANTI-RETROVIRAL THERAPY

The response to ART and side-effects of treatment need to be monitored. If % CD4 or CD4 count measurements are available, they should be followed every 3 months and give information on successful response to therapy or its failure and therefore need for changing therapy (Chapter XIII). If CD4 levels are not available, clinical parameters and are used (Fig. 10). Caregivers should be educated about danger signs of illness and potential toxicities and given clear guidelines on when to seek emergency versus routine care. The next visit after starting ART should be scheduled within a week to ensure that there are no problems or issues to be resolved. Table 17 summarizes current recommendations on monitoring of children after initiation of ART.

Table 17: Monitoring children on ART

Items	Before or at ART initiation	Month (M) 1	M 2	M 3	M4	M5	M 6	Every 2-3 months	Symptom-directed
Clinical evaluation: history and physical exam (including neurodevelopment)	X	X	X	X	X	X	X	X	X
Weight, height	X	X	X	X	X	X	X	X	
Calculation of ART dose ¹	X	X	X	X	X	X	X	X	
Concomitant medications ²	X	X	X	X	X	X	X	X	
Check ART adherence ³		X	X	X	X	X	X	X	
Hb and WBC ⁴	X								X
Full chemistry ⁵									X
CD4% or count ⁶	X							X*	X

Notes

* If signs of clinical progression of disease are seen, CD4 should be done earlier

- The child should be seen again within a week of starting ART to resolve any problems
- If the child has missed visit, attempts should be made to call or visit the child's home.
- In addition to these suggested appointments, caregivers should be encouraged to bring the child in if he/she is sick and especially during the first few months of ART when the child may experience ART side effects and intolerance.

1. Children may have rapid weight and height gain after ART in addition to expected normal growth; therefore, re-calculation of ART dose should be done at every visit. Under dosing of ART can lead to resistance development.

2. Concomitant drugs should be asked at every visit to assure that the child is on appropriate cotrimoxazole dosing (if indicated) and is not taking drugs that have potential drug interactions with ART (Annex E)
3. ART adherence assessment can be done by asking questions about missed dose and times the child take ART. Performing pill count is time consuming but may be a better measurement of adherence, if done correctly.
4. Hemoglobin (Hb) and white blood cell count (WBC) monitoring may be considered in children on ZDV at 1, 2 and 3 months
5. Full chemistry includes but not restricted to liver enzymes, renal function, glucose, lipids, amylase, lipase, serum electrolytes. Monitoring depends on symptoms and regimens. Regular liver enzymes monitoring during the first three months of treatment may be considered for certain children using nevirapine-based regimens, in particular for adolescent girls with CD4 cell > 250 cells/mm³ and infants and children co-infected with hepatitis B or hepatitis C virus, or other hepatic disease.
6. TLC is not suitable for monitoring of therapy; therefore, cannot be substitute for CD4. If CD4 is not available, clinical monitoring alone is used

1. ENSURING LONG-TERM ADHERENCE AND GOOD RESPONSE TO ART

A team effort of healthcare provider, counselor, outreach support service provider, caregiver and child is required to ensure long term adherence and good response to ART. Compassionate care should be provided in a supportive and non-threatening atmosphere and efforts made to understand the family's and the child's social and medical needs.

Figure 9. Ensuring long-term adherence and good response to ART

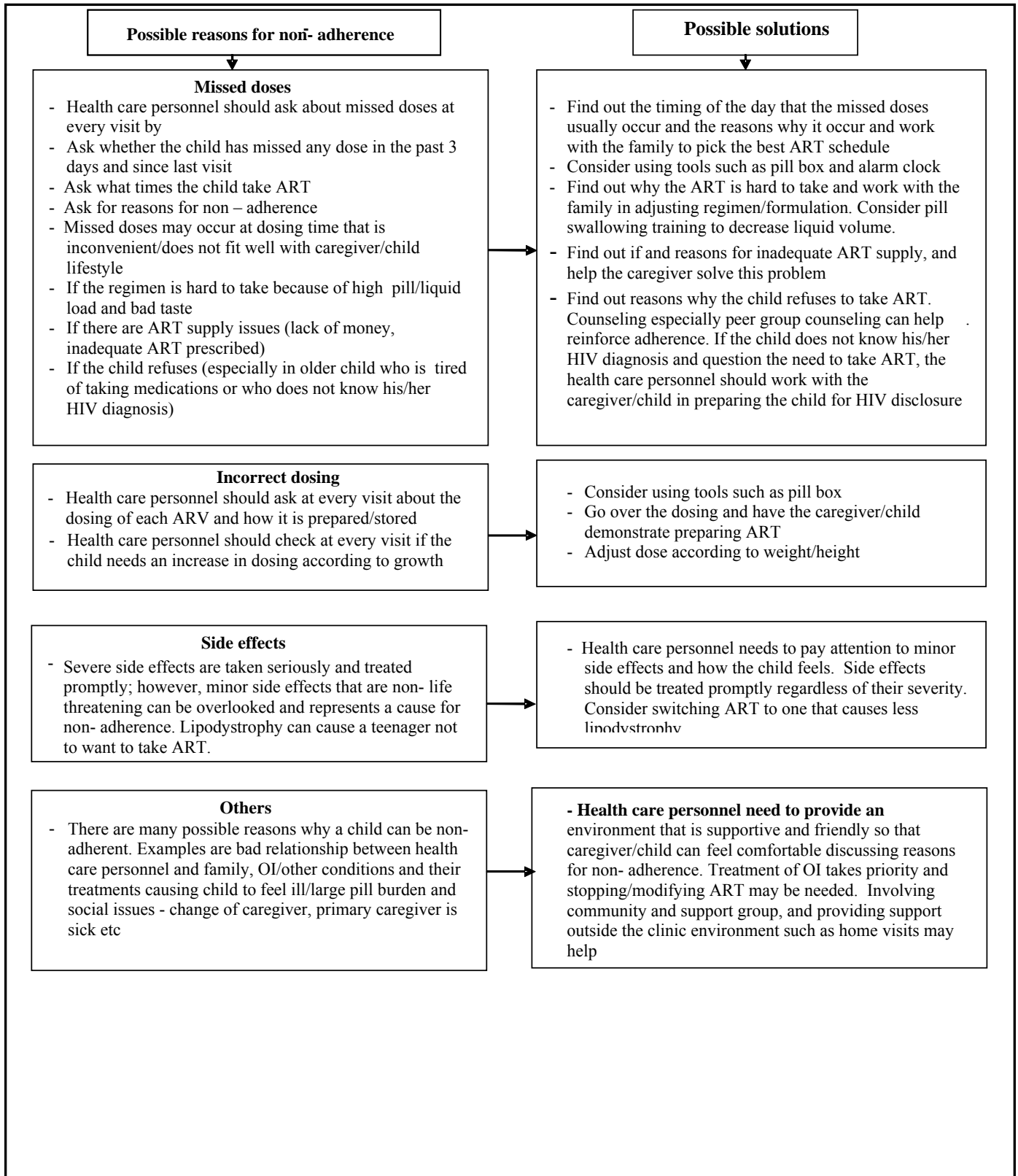
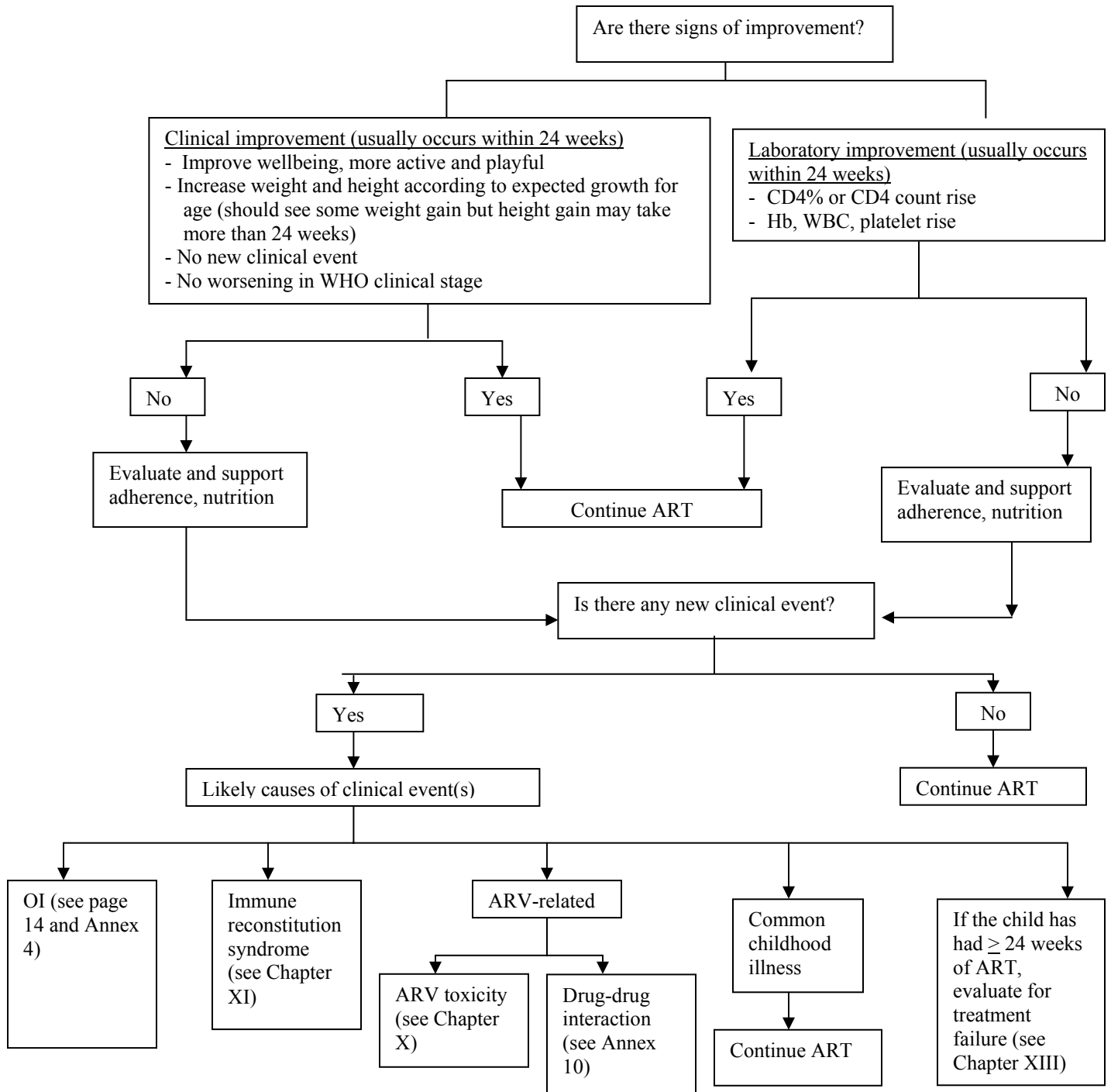


Figure 10: Evaluating response to ART



ANTIRETROVIRAL DRUG TOXICITY

Differentiating between complications of HIV disease and toxicity secondary to ARV drugs can be difficult. Alternative explanations for the toxicity must be excluded before assuming the toxicity is secondary to the ARV drug. Alternative explanations for an observed toxicity could include a concurrent infectious process (for example, common childhood illnesses including hepatitis A virus infection or malaria in a child with severe anaemia), or a reaction to a non-ARV drug that is being given concurrently with the ARV drugs (such as isoniazid-induced hepatitis in a child on tuberculosis treatment or cotrimoxazole-induced rash in a child receiving cotrimoxazole preventive therapy). Adverse reactions that have a non-ARV drug etiology do not require change of the ARV drug. ***However, because of the risk of potentially life threatening hepatotoxicity associated with NVP, hepatic dysfunction of any etiology requires discontinuation of NVP.***

The full spectrum of ARV toxicities observed in adults has also been reported in children. However, some toxicities are less common in children than in adults (e.g., NVP-related symptomatic hepatotoxicity is rare in children), while others are more common in children than adults (e.g., EFV-related rash).

Drug-related adverse events can be acute, occurring soon after the drug was administered; subacute, occurring within 1-2 days of administration; or late, occurring after prolonged drug administration. Additionally, adverse events can vary in severity from mild to severe and life-threatening. Experience with ARV drugs has led to recognition of several types of distinct adverse drug effects that may be most common with certain ARV drugs or drug classes, including:

- Hematologic adverse events from drug-induced bone-marrow suppression, most commonly seen with ZDV therapy (anemia, neutropaenia, and more rarely, thrombocytopaenia);
- Mitochondrial dysfunction, primarily seen with the NRTI drugs, including lactic acidosis, hepatic toxicity, pancreatitis, and peripheral neuropathy (the NRTIs differ in their ability to affect mitochondrial function, with d4T having greater toxicity than ZDV, and 3TC or ABC even less so);
- Lipodystrophy and metabolic abnormalities, primarily seen with d4T, and the PI drugs, and less but also with other certain NRTI drugs (abnormalities include fat maldistribution and body habitus changes; hyperlipidaemia; hyperglycaemia, insulin resistance, and diabetes mellitus; and osteopaenia, osteoporosis, and osteonecrosis);
- Allergic reactions such as skin rashes and hypersensitivity reactions, more common with the NNRTI drugs but also seen with certain NRTI drugs, such as ABC.

Toxicity can be monitored clinically on the basis of child/guardian reporting and physical examination, and assessed also through a limited number of laboratory investigation tests, depending on the specific ARV combination regimen that is utilized.

The management of the patient and the decision about the potential need to stop drugs or to substitute² a new ARV drug for the drug associated with the toxicity largely depends on the ability to attribute the toxicity to a specific ARV drug in the treatment regimen and on the severity of the toxicity symptoms (Table 18 and Annex 9). Given the limited number of ARV drugs and drug combinations available in Pakistan for use in children, it is preferable to make drug substitutions where feasible, so that premature switching to completely new alternative regimens is minimized, and also to restrict drug substitutions to situations where toxicity is severe or life-threatening (Table 18, Annex 9).

As a general principle, *mild toxicities* do not require discontinuation of therapy or drug substitution, and symptomatic treatment may be given (e.g., antihistamines for a mild rash). Some *moderate* or *severe* toxicities may require substitution of the ARV drug associated with toxicity with a drug in the same ARV class but with a different toxicity profile, but do not require discontinuation of all ART. *Severe, life-threatening toxicity* may require discontinuation of all ARV drugs and initiation of appropriate supportive therapy (such as intravenous fluids) depending on the toxicity, with substitution of another drug for the drug associated with the toxicity once the patient is stabilized and the toxicity is resolved (see Annex 8 and Annex 9). NNRTI drugs have a much longer half-life than NRTIs, leading to a concern that stopping all drugs simultaneously leads to exposure to drugs from the NNRTI class only. ***However, if the child has a life-threatening toxicity, all ARV drugs should be stopped simultaneously until the patient is stabilized.***

Clinical examination can also detect toxicities that are not life-threatening and that may appear late (months to years after therapy has been started), such as lipodystrophy. In such consultation with an HIV expert is recommended for management.

Regardless of their severity, adverse events may affect adherence to therapy. A "proactive approach" to managing toxicity is recommended. Discussing the potential side effects of the ART regimen prior to therapy initiation and during the early stages of treatment with the child and his/her caregiver, as well as support during minor and moderate adverse events, can increase the likelihood of adherence to therapy (see Chapter IX and Figures 8 and 9). Most ARV drug toxicities are time-limited and symptoms resolve while ART is being continued. The child and his/her caregiver should be familiar with signs of toxicities that are serious and require immediate contact with the provider and potential drug discontinuation. This is particularly important for toxicities that can be life-threatening if the ARV drug is not discontinued, such as NVP-associated Stevens Johnson Syndrome or symptomatic hepatitis or ABC-associated hypersensitivity reaction.

Sometimes ARV toxicity can be confused with the *syndrome of immune reconstitution (Immune Reconstitution Syndrome or IRS)* which may occur in children with advanced HIV, soon after initiation of ART. IRS represents an exaggerated response to infections the child may already be harboring. It is important to distinguish IRS from drug toxicity. IRS and its diagnosis are covered in Chapter XI.

² Substitution is the exchange of one drug in a (first-line) regimen for another (first-line regimen) drug; this is different from switching a drug because of treatment failure when all drugs of a regimen are changed to a different (second - line) regimen .

Table 18. 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 (Annex 8 and Annex 9):* 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 substitution for the offending drug) when patient is stabilized^a;
 - *Severe reactions:* Substitute the offending drug without stopping ART^a;
 - *Moderate reactions:* Consider continuation of ART as long as feasible; if patient does not improve on symptomatic therapy, consider single drug substitutions^a;
 - *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.

Notes:

- a. For substitution options, refer to Table 19
- b. Management of severe life-threatening toxicity is described in Annex 8.
- c. Severity grading is in Annex 9.
- d. Most ARV drug toxicities are not severe and can be managed by giving supportive treatment. Minor side effects can lead to non-adherence; therefore, health care professionals must counsel patients and provide supportive treatment.
- e. ARV drug toxicities that usually occur within the first 3 months include
 - i. GI toxicities including nausea, vomiting, and diarrhea. These usually occur within the first few days and weeks.
 - ii. Anemia from ZDV. Asymptomatic mild anemia is common. Other causes of anemia should be evaluated and treated. If there is severe anemia (Hb < 7.5 g/dl), ZDV should be switched to either ABC or d4T.
 - iii. Rash and liver toxicity particularly from NVP usually occur within the first 4 weeks of treatment. NVP lead-in dose is used in order to lower the risk of toxicity. Non severe rash and liver toxicity can be followed and supportive care can be given. Severe rash and liver toxicity (ALT > 5 ULN) can be life threatening and NVP should be substituted (see annex G).

- iv. CNS toxicity from EFV usually occurs during the first month and can be self-limiting.
- v. ABC hypersensitivity usually occurs within the first 6 weeks and can be life threatening. ABC must be stopped and never re-challenged.
- f. ARV drug toxicity that usually occur after 3 months
 - i. Lactic acidosis can occur at any time and is particularly associated with d4T use. Severe lactic acidosis can be life threatening.
 - ii. Lipodystrophy is particularly associated with d4T use and can cause permanent disfiguring.

1. SUBSTITUTING WITHIN A FIRST-LINE ANTIRETROVIRAL DRUG REGIMEN IN INFANTS AND CHILDREN FOR DRUG TOXICITY

When the toxicity is related to an identifiable drug in the regimen, the offending drug can generally be replaced with another drug from the same class that does not have the same adverse effect, e.g. substitution of d4T for ZDV for anemia. Given the limited number of ARV drug options available, drug substitutions should be limited to situations where toxicity is severe or life-threatening (see Annex 9), and substitution of drugs from the PI class for toxicity reasons should be avoided if possible. Table 19 lists the usual ARV substitution options for adverse events for the recommended combination first-line regimens.

For some life-threatening toxicities, it may not be possible to identify an optimal substitute drug. For example, for NVP-associated Stevens Johnson Syndrome, most clinicians would avoid substituting another NNRTI drug due to the potential for class-specific toxicity. This would require a change to either a triple NRTI regimen (e.g., substituting a third NRTI, such as ABC, for NVP), or substituting a protease inhibitor ARV drug for NVP, thereby introducing a drug class usually reserved for second-line regimens.

Table 19. Severe toxicities in infants and children associated with specific first-line antiretroviral drugs and potential first-line drug substitutions

First-line ARV drug ^a	Most frequent significant toxicity for the ARV drug	Suggested first-line ARV drug substitution
ABC	Hypersensitivity reaction	ZDV
ZDV	Severe anemia or neutropaenia ^{b,c}	d4T or ABC
	Lactic acidosis	ABC
	Severe gastrointestinal intolerance ^d	d4T or ABC
d4T	Lactic acidosis	ABC ^e
	Peripheral neuropathy	ZDV or ABC
	Pancreatitis	
	Lipoatrophy/metabolic syndrome ^f	

EFV	Persistent and severe central nervous system toxicity ^g	NVP
	Potential teratogenicity (adolescent girl in 1 st trimester pregnancy or potential of pregnancy)	
NVP	Acute symptomatic hepatitis ^h	EFV ⁱ
	Hypersensitivity reaction	Preferred substitution by NRTI to: <ul style="list-style-type: none"> • a third NRTI (disadvantage, may be less potent) or <ul style="list-style-type: none"> • PI (disadvantage, premature start of 2nd line ARV drug)^k
	Severe or life-threatening rash (Stevens-Johnson Syndrome ⁱ)	

Notes:

- a. 3TC - associated pancreatitis has been described in adults but is considered very rare in children.
- b. Exclude malaria.
- c. Defined as severe haematological abnormality that can be life-threatening and that is refractory to supportive therapy.
- d. Defined as severe, refractory gastrointestinal intolerance that prevents ingestion of ARV drug regimen (e.g., persistent nausea and vomiting).
- e. ABC is preferred in this situation; however, if ABC is not available ZDV may be used.
- f. Substitution of d4T typically may not reverse lipoatrophy. In children, ABC or ZDV can be considered as alternatives.
- g. Defined as severe central nervous system toxicity such as persistent hallucinations or psychosis.
- h. Symptomatic NVP-associated hepatic toxicity is very rare in HIV-infected children prior to adolescence.
- i. EFV is not currently recommended for children <3 years of age or < 10kg, and should not be given to post pubertal adolescent girls who are either in 1st trimester of pregnancy or are sexually active and not using adequate contraception.
- j. Severe rash is defined as extensive rash with desquamation, angioedema, or serum sickness-like reaction; or a rash with constitutional findings such as fever, oral lesions, blistering, facial oedema, conjunctivitis; Stevens-Johnson Syndrome can be life-threatening. For life-threatening rash, most clinicians would not substitute EFV due to the potential for NNRTI-class specific toxicity.
- k. The premature introduction of the PI class of drugs in first-line regimens leads to limitations in the choice of drugs in the event of treatment failure (i.e. second-line regimens; see Chapter XIII).

IMMUNE RECONSTITUTION SYNDROME (IRS)

IRS is an exaggerated immune response to antigens or organisms. It is primarily seen in adults and less commonly in children who have very low CD4 counts when starting ARV. IRS is important to clinically differentiate from treatment failure because the symptoms may be similar. Table 20 describes the syndrome and management of IRS.

Table 20: Immune Reconstitution Syndrome

What is IRS?

- IRS is an exaggerated immune response to antigens or organisms. The related organisms could be mycobacteria (e.g. *M. tuberculosis*, nontuberculosis mycobacteria), viruses (herpes zoster, herpes simplex), or fungus (*Cryptococcus neoformans*).

Who is at risk of development of IRS?

- It usually occurs in a child with low baseline CD4 or WHO clinical stage 3 or 4 before initiation of ART. The incidence rate of IRS could be as high as 15-25%.

When does IRS develop?

- IRS usually occurs during the first 6 months after initiation of ART, however it is common to manifest during the first month. During initial period of ART, antiretroviral drugs cause rapid decline of HIV viral load and rapid rise of CD4, therefore brisk immune response to antigen is developed.

What are the common manifestations of IRS?

- There are 2 types of IRS
 - **“Worsening type”** Clinical worsening of a previously treated opportunistic infections e.g.
 - worsening of respiratory symptoms and/or chest x-ray finding in a child with previously treated pulmonary tuberculosis,
 - severe headache in a child with previously treated cryptococcal meningitis
 - **“Unmasking type”** Unmasking of a previously subclinical infection with exaggerated inflammatory response e.g.
 - suppurative lymphadenitis from *Mycobacterial* infection
 - development of abscess at BCG vaccination site

How to manage IRS?

- Antiretroviral drugs should be continued.
- For “unmasking type”, the appropriate anti-infective agents are needed.
- In most cases the symptoms of IRS resolve after a few weeks, however some reactions can be severe or life-threatening that require a short course of steroid treatment; e.g. IRS from pulmonary tuberculosis with acute respiratory distress syndrome (ARDS), IRS from *M.avium* complex infection with high-grade fever and severe abdominal pain, IRS from *Cryptococcal* meningitis with severe increase intracranial pressure.

Immune reconstitution syndrome can be confused with several other clinical events also observed in children with advanced HIV disease, such as opportunistic infections, ARV-related toxicity, or HIV disease clinical progression. Table 21 describes some common events, and their differential diagnosis.

Table 21. Differential diagnosis of common clinical events during the first 6 months of start of ART

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

ANTIRETROVIRAL THERAPY FOR HIV- INFECTED CHILDREN WITH TUBERCULOSIS (TB)

Children with HIV infection have significantly increased susceptibility to infection with *Mycobacterium tuberculosis*. Younger children have a very high risk of developing rapidly progressive TB disease, while older children with latent TB can develop reactivation disease. Isoniazid preventive therapy is recommended for HIV-infected children if living in high TB prevalence areas and there is documented household contact of TB patients, once active TB disease is excluded (Dosage in Annex 6).

Diagnosis of TB disease in young children is difficult. WHO case definitions and diagnostic approach in children is summarized in Annex 3.

The co-management of TB and HIV, and especially the treatment of HIV infection is complicated by the potential for multiple drug interactions, particularly rifampicin drug interactions with the NNRTI and PI agents. These drugs have similar routes of metabolism and elimination, and extensive drug interactions may result in sub-therapeutic ARV drug levels. Toxicity profiles of medications are also overlapping.

The same anti-tuberculosis drug regimens and dosages (isoniazid, rifampicin, pyrazinamide, and ethambutol or aminoglycoside) are used as for non-HIV-infected children. Duration of treatment is also similar.

1. ART CONSIDERATIONS IN CHILDREN WITH TB WHO ARE NOT YET ON ART

In HIV-infected children with confirmed or presumptive TB disease, initiation of TB treatment must receive priority. ART is indicated for children with Clinical Stage 3 pulmonary TB and Clinical Stage 4 extra-pulmonary TB. However, CD4 levels are very helpful in determining the urgency of initiation of ART. Treatment with ARVs can be delayed in children with CD4 measurements above the threshold values (Figure 7), whereas earlier initiation of ART is more critical in children with low CD4 levels. The potential for immune reconstitution syndrome (see Chapter XI) should be considered in children, especially those with low CD4 levels. Table 22 presents recommendations for the timing and choice of ART in HIV-infected infants and children.

Table 22. Recommendations for the timing of ART following initiation of TB treatment with rifampicin-containing regimen in HIV-infected infants and children

Clinical stage of child with TB (as an event indicating need for ART)	Timing of ART following initiation of TB treatment (rifampicin-containing regimen) ^a	Recommended ARV Regimen
WHO Paediatric Clinical Stage 4 ^b	<ul style="list-style-type: none"> ▪ Start ART soon after TB treatment (between 2 and 8 weeks following start of TB treatment) 	<p><u>In children < 3 years:</u></p> <ul style="list-style-type: none"> ▪ Preferred: triple NRTI first-line regimen (d4T or AZT + 3TC + ABC)
WHO Paediatric Clinical Stage 3 ^c	<p>Clinical criteria alone:</p> <ul style="list-style-type: none"> ▪ Start ART soon after TB treatment (between 2 and 8 weeks following start of 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 ^a, it may be reasonable to delay initiation of ART. 	<p>Alternative: Standard first-line regimen of 2 NRTI + NVP^d</p> <p><u>In children >3 years^e:</u></p> <ul style="list-style-type: none"> ▪ Preferred: triple NRTI first-line regimen (d4T or AZT + 3TC + ABC) ▪ Alternative: Standard first-line regimen of 2 NRTI + EFV^f <p>Following completion of TB treatment it is preferable to remain on the ART regimen as outlined above.</p>
	<p>If CD4 available:</p> <ul style="list-style-type: none"> ▪ Evaluate possibility to delay initiation of ART depending on assessment of clinical status and CD4, and clinical and immunological response to TB therapy: <ul style="list-style-type: none"> ○ <u>Severe and advanced immunodeficiency^g:</u> initiate ART soon after TB treatment (between 2-8 weeks following start TB treatment) ○ <u>Mild or no immunodeficiency^h:</u> Initiation of ART may be delayed until after completion of TB therapy; monitor closely response to TB therapy and re-assess for ART after TB therapy; if no improvement, consider starting ART. 	<ul style="list-style-type: none"> ▪ Regimens as recommended above ▪ Where ART can be delayed until after completion of TB treatment, initiation with a standard 2 NRTI + NNRTI first line regimen (Table 4) is recommended.

Notes:

- a. Administration of cotrimoxazole prophylaxis is important in children with TB/HIV co-infection.
- b. All children with Paediatric Clinical Stage 4 should be initiated on ART regardless of CD4 criteria.
- c. Except for lymph node TB.
- d. Careful clinical monitoring with laboratory support if available is recommended where NVP is administered concurrently with rifampicin.
- e. Due to lack of data the ranking of preferred or alternative ARV regimen is not a consensus recommendation.
- f. EFV is not currently recommended for children <3 years of age or < 10kg
- g. Severe immunodeficiency as per Table 10
- h. Mild or not significant immunodeficiency is assumed at CD4 levels above those levels defining advanced immunodeficiency (see Table 10).

2. CONSIDERATIONS FOR HIV-INFECTED CHILDREN WITH TB WHO ARE ALREADY ON ART

In children already on ART, and who are diagnosed with TB, ART should be continued. However, the ARV regimen should be reviewed and may need adjustment to ensure optimal treatment of both TB and HIV and to decrease the potential for toxicity and drug interactions. Recommendations are summarized in Table 23.

Table 23. Recommendations for the co-management of TB and HIV in infants and children diagnosed with TB while receiving first 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 2 NRTI + NNRTI first-line regimen diagnosed with TB	TB due to primary infection (consider at any time during ART, depending on exposure to TB)	Continue ART but assess for need for change in ART regimen - response to TB therapy should be used to evaluate need for change	<ul style="list-style-type: none"> ▪ Substitute NNRTI to triple NRTI first-line regimen ZDV or D4T + 3TC+ABC <i>or</i> <ul style="list-style-type: none"> ▪ Continue on standard 2 NRTI + NNRTI first-line; if on NVP^b substitute to EFV^c if the child is 3 years or older
	TB as part of immune reconstitution syndrome (consider in first 3 months of ART) ^e		
	TB as a sign of treatment failure of first-line regimen (consider after at		

	least 24 weeks of ART)		line regimen ^d
	TB as a sign of treatment failure of second-line regimen		<ul style="list-style-type: none"> ▪ Stop ART until completion of TB therapy ▪ Consider consultation with experts for construction of salvage regimen^d

Notes:

- a. Administration of cotrimoxazole preventive therapy is important in children with TB/HIV co-infection.
- b. Careful clinical and laboratory monitoring needs to be ensured where NVP is administered concurrently with rifampicin.
- c. EFV is not currently recommended for children <3 years of age or < 10kg
- d. Little data are available to guide ART recommendations, research is urgently needed.
- e. IRS usually self-limited and symptoms improve after 10-14 days. Occasionally severe reactions require short course treatment with steroids

TREATMENT FAILURE

ARV treatment failure may be due any one or a combination of the following:

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

Clinical criteria, supported, where possible, with CD4 criteria, are used in order to define treatment failure. When treatment failure is confirmed, switching to a new second-line regimen becomes necessary. Switching a regimen for a failure should not be confused with substitution of a single drug for toxicity (see Chapter 10).

It should not be concluded, on the basis of clinical criteria, that an ARV regimen is failing until the child in question has had a reasonable trial on the therapy, i.e. the child should have received the regimen for at least 24 weeks, and adherence to therapy has been assessed and considered to be optimal, Immune Reconstitution Syndrome has been considered, and that any inter-current opportunistic infections have been treated and resolved. Additionally, before considering changing treatment due to growth failure, it should be ensured that the child receiving adequate nutrition.

1. CLINICAL DEFINITION OF TREATMENT FAILURE

In children on ART, the main clinical indications to switch therapy are the development of new or recurrent stage 3 or 4 events at least 24 weeks after starting therapy with a first-line regimen. Of note are:

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

2. IMMUNOLOGICAL DEFINITION OF TREATMENT FAILURE

Immunological treatment failure can be differentiated based on initial immunological response to ART. Treatment failure is usually characterized by a drop of the CD4 to values at or below their age-related CD4 threshold used for initiation of treatment, after initial

immune recovery following initiation of ART. It is also possible that children on ART may persist at or below their age-related CD4 threshold for initiation of treatment despite an adequate trial of therapy (e.g., at least 6 months of ART). Thus, defining treatment failure based on immunological values relies on previous CD4 values. Immunological criteria for defining treatment failure are supplemental to clinical criteria (Table 24).

Table 24: Immunological (CD4) criteria to guide decision making on switching to a second-line regimen^{a, b}

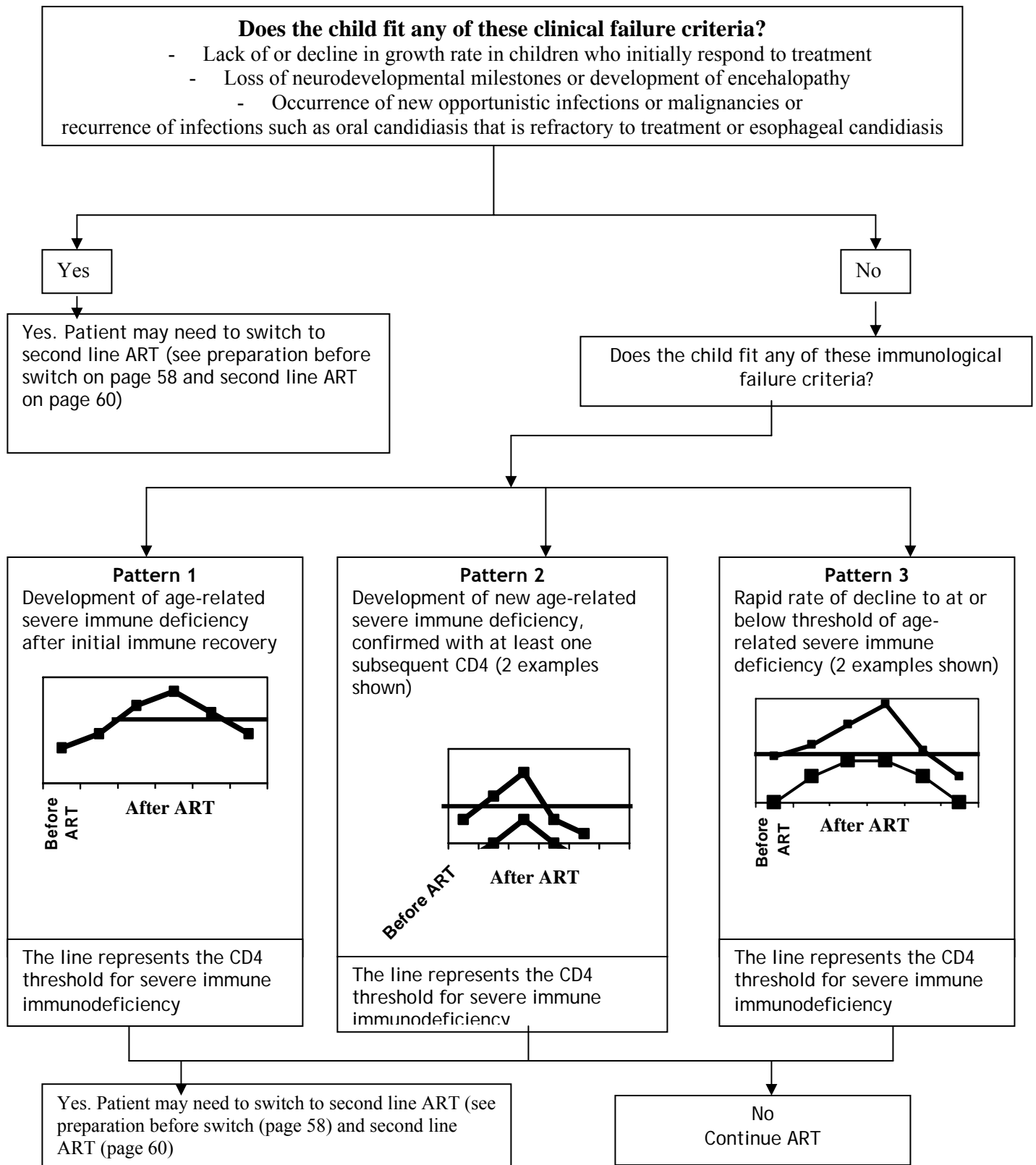
<ul style="list-style-type: none"> ▪ Development of age-related severe immunodeficiency after initial immune recovery^c; ▪ Development of new age-related severe immunodeficiency, confirmed with at least one subsequent CD4 measurement^c; ▪ Rapid rate of decline to at or below threshold of age-related severe immunodeficiency^c.
<ul style="list-style-type: none"> 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 10; use of %CD4 in children < 5 years of age and absolute CD4 count after 5 years of age is preferred. If serial CD4 values are available, the rate of decline should be taken into consideration.

3. DECISION-MAKING REGARDING SWITCHING TO SECOND-LINE REGIMENS USING CLINICAL AND IMMUNOLOGICAL CRITERIA

Children with new Clinical Stage 4 conditions should be considered for switching therapy regardless of CD4 values. However, CD4 measurements are very helpful in deciding the need to switch therapy in children who develop new Stage 3 conditions, and in children who are clinically well, but may have progressive immunological destruction due to a failing regimen. In children on ART who are clinically well, switching a regimen should only be considered if two or more CD4 values below the age-related threshold for severe immunodeficiency are obtained. In such children, if the CD4 value begins to approach the age-related threshold for severe immunodeficiency, increased clinical and CD4 follow-up is warranted. A regimen switch is not recommended in children at Clinical Stages 1-3 where CD4 values drop but remain above their age-related threshold.

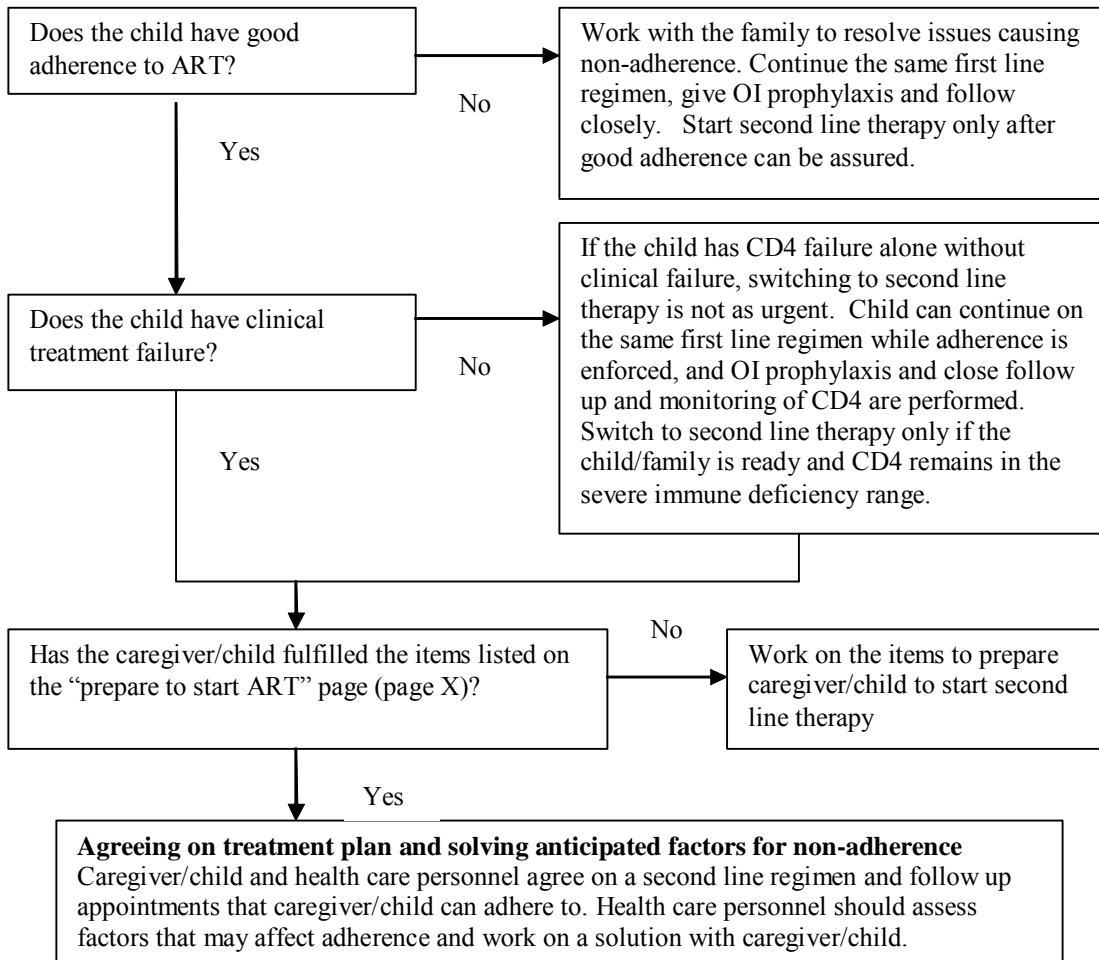
Figure 11 presents an algorithmic approach to guide decision-making in children in whom treatment failure is being considered.

Figure 11. Algorithm for decision-making for need for second-line regimen in HIV-infected children with suspected treatment failure



3.1 Plan before switching to second line regimen

Switching to second line regimen is not an emergency. It is important to ensure that the child is on appropriate prophylaxis for opportunistic infections. A failing regimen usually retains some anti HIV activity; therefore, in general, a child should continue the failing regimen until he/she is ready to switch to second line regimen.



4. RECOMMENDATIONS FOR SECOND-LINE REGIMENS

The entire regimen should be changed from a first-line to a second-line combination in the event of treatment failure. The new second-line regimen should preferably include at least three new drugs, one or more of them from a new class, in order to increase the likelihood of treatment success, minimize the risk of cross-resistance, and be based upon drugs that retain activity against the child's virus strain. Designing potent and effective second-line regimens for infants and children is particularly difficult because of the current lack of experience with use of second-line regimens in children and the limited formulations available for use in children. *Therefore, the importance of choosing potent and*

effective first-line regimens and maximizing their durability and effectiveness by optimizing adherence cannot be emphasized enough.

Referral to an HIV expert is highly recommended for evaluation of treatment failure and choice of second-line regimen before switching ARV in children.

Table 25. Recommended second-line regimens in infants and children in the event of treatment failure of first-line regimens

Recommended 2 nd line regimen: boosted PI component + 2 RTI components (NRTI/NNRTI)			
1 st line regimen at failure	Preferred 2 nd line regimen		
	RTI components (NRTI/NNRTI)		PI component ^a
2 NRTI^b + 1 NNRTI			
ZDV <i>or</i> d4T - containing -----	ddI ^c + ABC -----	plus	LPV/r ^e <i>or</i> SQV/r ^f <i>or</i>
ABC - containing	ddI ^c + ZDV		<i>or</i>
Triple NRTI	ddI ^c + EFV ^d <i>or</i> NVP		NFV ^g
<p>Notes:</p> <ul style="list-style-type: none"> a. PI components are listed in order of potency/acceptability; b. Continuation of 3TC in second line regimens may be considered; c. ddI may not need to be taken on an empty stomach in children; d. EFV is not currently recommended for children <3 years of age or < 10kg, and should be avoided in post pubertal adolescent girls with potential for pregnancy; e. LPV/r is available co-formulated as solid and liquid; however, liquid requires refrigeration f. SQV/r should not be used in children or adolescents weighing less than 25kg; requires refrigeration g. NFV has advantage of not requiring refrigeration and is preferred PI agent if refrigeration is a problem.; it should be taken with food to improve bioavailability and high doses are needed in young children (e.g., >150 mg/kg per day). 			

MANAGEMENT OF COMMON CHILDHOOD ILLNESSES IN HIV-INFECTED CHILDREN

HIV infected children suffer frequent episodes of common childhood illnesses such as acute respiratory infections and diarrhea. WHO and UNICEF have developed evidence-based guidelines on the Integrated Management of Childhood Illnesses (<http://www.who.int/child-adolescent-health/publications/pubIMCI.htm>) which have been adapted by Pakistan. Management of these infections in HIV-infected children should follow the same principles as in children without HIV infection. However, some pathogens are seen much more frequently in HIV-infected children (e.g. PCP as a cause of severe ARI, cryptosporidium as a cause of chronic diarrhea, the yeast cryptococcus as a cause of meningitis) or cause much more severe infection (e.g. disseminated TB and varicella-zoster infections, thrush). These factors should be kept in mind during assessment and management.

1. SYNDROMIC APPROACH FOR MANAGEMENT OF COMMON OPPORTUNISTIC INFECTIONS

The following sections outline the syndromic management of common presenting illnesses and opportunistic infections (OI) in children with HIV.

Further information on common problems is given in the Annexes listed below.

Annex 2. Table of Diarrheal disease pathogens and their treatment

Annex 3. Diagnosis of TB

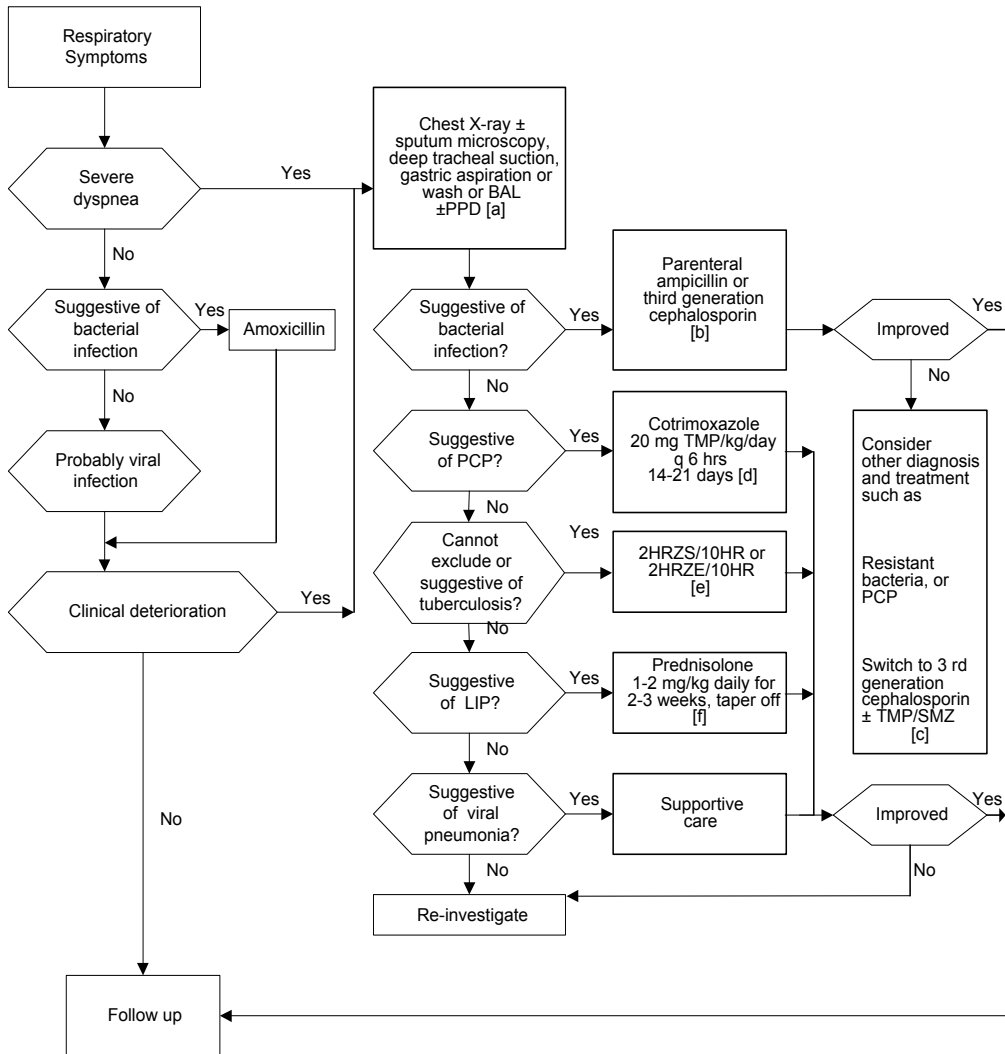
Annex 4. Diagnosis and Management of Opportunistic infections

Annex 5. Neurological abnormalities in HIV-infected children

Annex 6. Primary and Secondary OI prevention

1.1 RESPIRATORY INFECTIONS

Figure 4. Syndromic Approach to Respiratory Infections



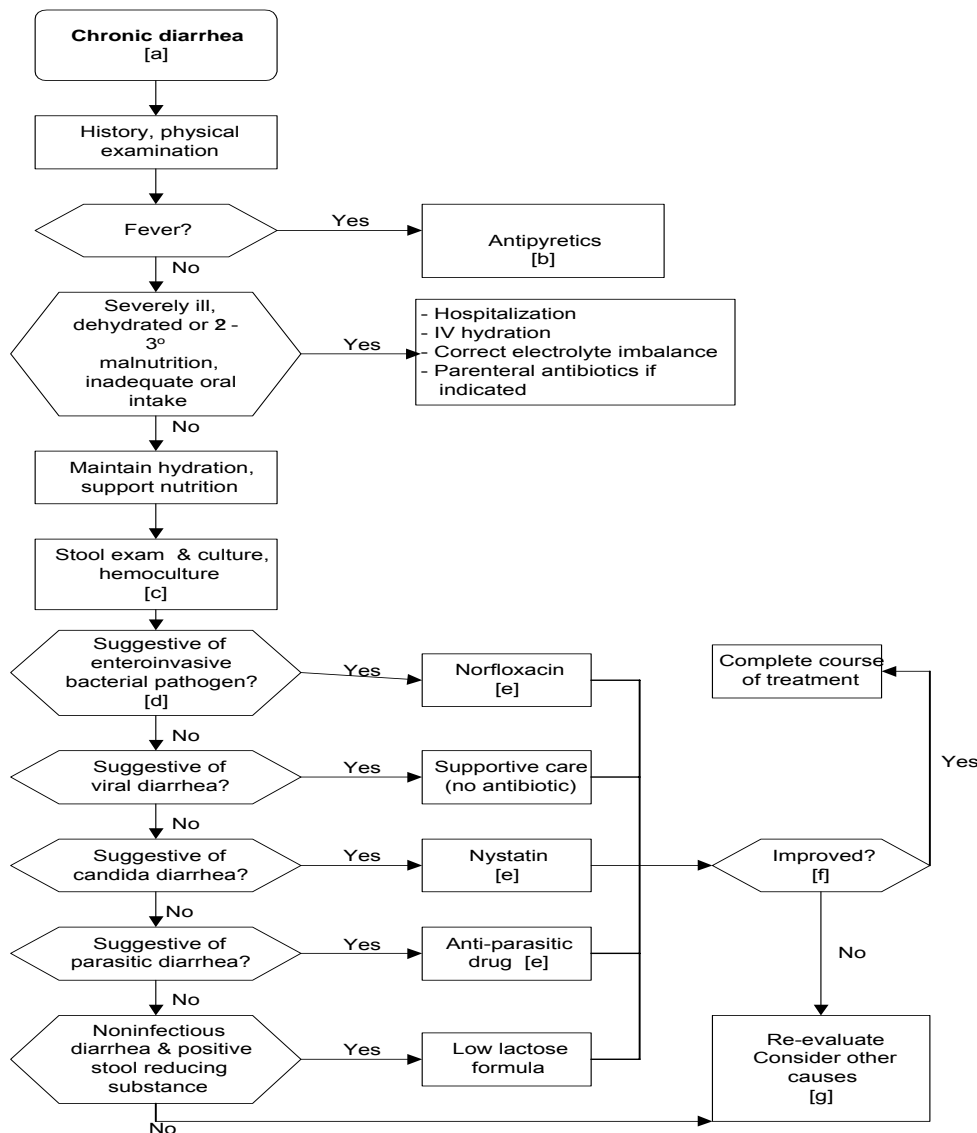
Notes:

- A chest X-ray should be performed, if available.
Bacterial pneumonia: Lobar or patchy infiltrates
PCP: bilateral interstitial infiltrates
Primary tuberculosis: enlarged hilar or paratracheal lymph nodes with pulmonary infiltration
Lymphoid interstitial pneumonitis: persistent bilateral reticulonodular interstitial infiltrates
The presumptive diagnosis (based on chest X-ray) should be substantiated through clinical signs and additional investigations where possible, e.g. microscopy of sputum and pleural effusion
- Ampicillin 100 mg/kg/day IV/IM every 6 hours.
- Third generation cephalosporins: cefotaxime 100-150 mg/kg/day IV every 8 hours or ceftriaxone IV/IM 50-75 mg/kg q.d. for at least 10 days.

- d. PCP is the most serious disease in HIV infected children. In children presenting with acute respiratory distress and no history of taking primary prophylaxis, PCP is most likely. High-dose TMP-SMZ treatment must be initiated immediately. Steroid reduces mortality in severe case of PCP. In case of TMP-SMZ intolerance alternative treatments are dapsone + trimethoprim or primaquin + clindamycin.
- e. Treatment of active tuberculosis: During the first two months, the recommended regimen for young infants and children is the once-daily combination of INH 10 mg/kg, rifampicin 10-15 mg/kg, pyrazinamide 15-30 mg/kg, and streptomycin 15 mg/kg maximum 1g/day (use ethambutol 15-20 mg/kg/day instead of streptomycin in older children). After 2 months, continue INH and rifampicin for the remaining treatment period. Six-month therapy may be justified in pulmonary tuberculosis with prompt response to treatment, otherwise 12-month treatment is recommended.
- f. Lymphoid interstitial pneumonitis (LIP) requires treatment only where symptoms of hypoxemia are present. Prednisolone 1-2 mg/kg daily can be used, the dose should be tapered as allowed by clinical response.

1.2 CHRONIC DIARRHEA

Figure 5. Syndromic Approach to Chronic Diarrhea

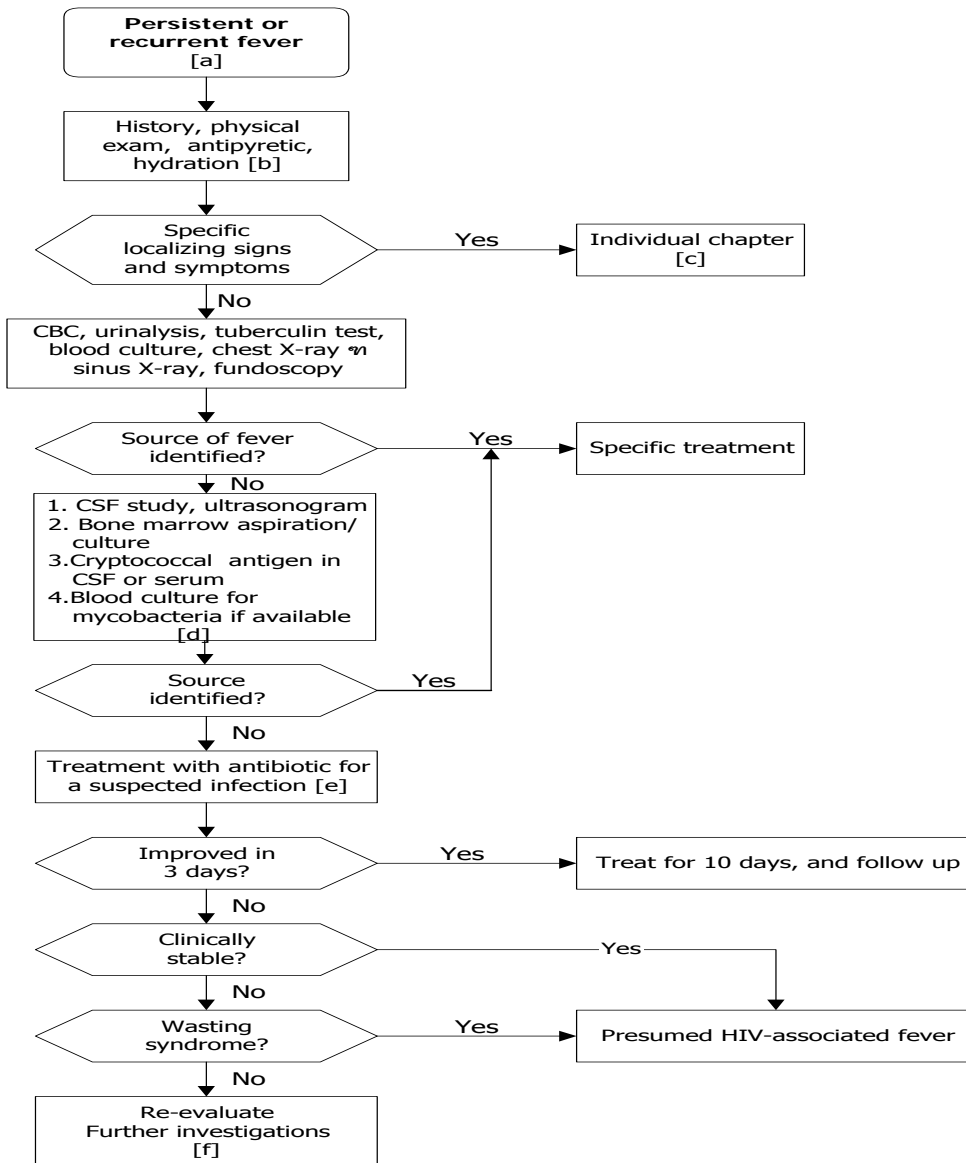


Notes:

- a. Definition of chronic diarrhea: Liquid stools (>3 times/day) for ≥ 14 days in children with symptomatic HIV infection.
 - Acute diarrhea can occur in symptomatic HIV-infected children. The management of acute diarrhea should follow Pakistan IMCI guidelines
- b. Look for and treat other infections. Possible causes of fever include concurrent other infection e.g otitis media, urinary tract infection, pneumonia. See also approach for persistent or recurrent fever.
- c. Microscopy is done to identify *Candida*, *Cryptosporidium*, *Microsporidia*, and parasites that can cause persistent diarrhea. Faecal smears stained with modified acid fast and modified trichrome stains should be performed. Look for blood and neutrophils in faecal smear. These findings can support the diagnosis of some bacterial infections (e.g. *Shigella*, *Salmonella*, *Campylobacter*).
- d. Stool culture may identify *Salmonella*, *Shigella* and *Vibrio cholera* as well as other bacterial pathogens.
- e. Blood culture is indicated if the child is febrile or toxic. Cefixime or ceftriaxone or ciprofloxacin should be used if typhoid fever is suspected (norfloxacin has poor oral bioavailability). *Salmonella*, *Mycobacterium avium* complex and other bacteria are frequently isolated from blood cultures of HIV-infected children.
- f. See Annex 2 for drug dosage
- g. The child should be examined again after 2 days in case of any of the following circumstances: being initially dehydrated, less than 1 year old, persistence of blood in the stool, or no improvement of symptoms. Improvement is defined as follows: weight gain, disappearance of fever and blood in the stool, passage of fewer stools and improved appetite.
- h. Persistent diarrhea is a common presentation in HIV-infected children. If the child is not severely ill (no blood in the stool, afebrile, not dehydrated, not malnourished), observe the child while maintaining hydration and nutrition. Other causes of diarrhea include mucosal damage, bacterial overgrowth, bile acid diarrhea, or CMV infection. Empirical treatment with oral neomycin or colistin plus cholestyramine may relieve symptoms. HIV infection itself may cause diarrhea, which may be successfully treated with antiretroviral therapy (ART).

1.3 PERSISTENT OR RECURRENT FEVER

Figure 6. Approach to Persistent or Recurrent Fever



Notes:

- a. Fever is defined as body temperature of 37.5 °C axilla, 38.0 °C oral, 38.5 °C rectal.
 - Persistent fever: Fever for more than 5 days duration.
 - Recurrent fever: Fever for more than one episode over a period of 5 days.
- b. Children may also have fever as a consequence of intercurrent common childhood illnesses, endemic diseases, and serious bacterial or opportunistic infection, neoplasms and/or HIV itself. Under many of these circumstances the fever will be associated with specific localizing signs and symptoms.
- c. Follow specific IMCI guidelines for management.

- d. CNS infections may have persistent or recurrent fever without abnormal neurological sign. Cranial and/or abdominal ultrasonogram might be beneficial. Bone marrow culture may give better yield than routine blood culture. Mycobacteremia can be easily detected by automated culture system.
- e. In case of persistent high fever (body temperature of 38.5°C axilla, 39°C oral or 39.5°C rectal) and bacterial infection is suspected, empirical treatment with cefotaxime 100-150 mg/kg/day every 8 hours or ceftriaxone 50-75 mg/kg/day every 12-24 hours may be considered. If the fever subsides but a source is not identified, treatment can be terminated after 7-10 days.
- f. CT, MRI may be indicated

ANTIRETROVIRAL REGIMENS FOR PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HIV

The following table (Table 26) summarizes the current recommendations and the preferred regimen to be used for PMTCT in Pakistan and is based on the most recent guidelines from WHO issued in 2006. Although the regimen is complex, it has the advantages of increased efficacy and low risk of development of resistance to nevirapine in the mother. In many situations, complex prophylactic ARV regimens may not be possible, and alternative, simpler regimens are listed in Annex 12 (also see PMTCT – Clinical Guidelines for Pakistan, NACP 2006).

Table 26: Preferred Antiretroviral Regimens for Prevention of Mother to Child Transmission of HIV

	Maternal HAART Indicated ¹	Maternal HAART Not Indicated ⁴
Mother		
Antepartum	HAART ²	ZDV starting at 28 weeks gestation or as soon as feasible thereafter
Intrapartum	HAART	SD NVP ⁵ + ZDV/3TC
Postpartum	HAART	ZDV/3TC x 7 days
Infant	ZDV x 7 days ³	SD NVP + ZDV x 7 days ³

¹ Maternal Highly-Active Anti-retroviral Therapy (HAART) indicated: HAART is recommended for all women with WHO clinical stage IV disease regardless of CD4 cell count; all with WHO clinical stage III disease if no CD4 count available, or women with CD4 count <350 if CD4 count available; and women with WHO clinical stage I or II disease and CD4 count <250. HAART should be initiated as soon as required during pregnancy (including first trimester), should be continued during labor, and maintained postpartum.

² First line HAART for pregnant women is ZDV + 3TC + NVP or d4T+3TC+NVP (see adult ART guidelines and text).

³ If the mother receives less than 4 weeks of HAART or ZDV during pregnancy, 4 weeks, instead of 1 week, of infant ZDV is recommended

⁴ Alternative regimens for situations in which complex regimens cannot be administered are delineated in Appendix 12.

ANNEXTURES

ANNEX 1

PRESUMPTIVE AND DEFINITIVE CRITERIA FOR RECOGNIZING HIV/AIDS-RELATED CLINICAL EVENTS IN INFANTS AND CHILDREN WITH ESTABLISHED HIV INFECTION^a

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

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

Clinical event	Clinical diagnosis	Definitive diagnosis
Severe recurrent presumed bacterial pneumonia	Cough with fast breathing, chest indrawing, nasal flaring, wheezing, and grunting. Crackles or consolidation on auscultation. Responds to course of antibiotics. Current episode plus one or more in previous 6 months.	Confirmed by isolation of bacteria from appropriate clinical specimens (induced sputum, BAL, lung aspirate).
Acute necrotizing ulcerative gingivitis or stomatitis, or acute necrotizing ulcerative periodontitis	Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odour, and rapid loss of bone and/or soft tissue.	None.
Symptomatic LIP	No presumptive diagnosis.	Diagnosed by CXR: bilateral 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.
Chronic HIV-associated lung disease (including bronchiectasis)	History of cough productive of copious amounts of purulent sputum (bronchiectasis only), with or without clubbing, halitosis, and crepitations and/or wheezes on auscultation;	Confirmed by CXR may show honeycomb appearance (small cysts) and/or persistent areas of opacification and/or widespread lung destruction, with fibrosis and loss of volume.
Unexplained anaemia (<8g/dl), or neutropenia (<1000/mm ³) or chronic thrombocytopenia (<50 000/ mm ³)	No presumptive diagnosis.	Diagnosed on laboratory testing, not explained by other non-HIV conditions, or not responding to standard therapy with haematinics, antimalarials or anthelmintics as outlined in IMCI.
Clinical Stage 4		
Unexplained severe wasting, stunting or severe malnutrition not adequately responding to standard therapy	Persistent weight loss not explained by poor or inadequate feeding, other infections and not adequately responding in two weeks to standard therapy. Characterized by: visible severe wasting of muscles, with or without oedema of both feet, and/or weight-for-height of -3 SDs, as defined by WHO IMCI guidelines.	Confirmed by documented weight loss of >-3 SD +/- oedema
Pneumocystis pneumonia (PCP)	Dry cough, progressive difficulty in breathing, cyanosis, tachypnoea and fever; chest indrawing or stridor. (Severe or very severe pneumonia as in IMCI). Usually of rapid onset especially in infants under six months of age. Response to high-dose co-trimoxazole +/- prednisolone.	Confirmed by: CXR typical bilateral perihilar diffuse infiltrates; microscopy of induced sputum or BAL or NPA, or histology of lung tissue.
Recurrent severe presumed bacterial infection, e.g. empyema, pyomyositis, bone or joint infection, meningitis but excluding pneumonia	Fever accompanied by specific symptoms or signs that localize infection. Responds to antibiotics. Current episode plus one or more in previous 6 months.	Confirmed by culture of appropriate clinical specimen.
Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration or visceral at any site)	Severe and progressive painful orolabial, genital, or anorectal lesions caused by HSV infection present for more than one month.	Confirmed by culture and/or histology

Clinical event	Clinical diagnosis	Definitive diagnosis
Oesophageal candida (or candida of trachea, bronchi or lungs).	Chest pain and dysphagia (difficulty in swallowing), odynophagia (pain on swallowing food and fluids), or retrosternal pain worse on swallowing (food and fluids) responds to specific treatment. In young children, suspect particularly if oral candida observed and food refusal occurs and/or difficulties/crying when feeding.	Confirmed by macroscopic appearance at endoscopy, microscopy of specimen from tissue or macroscopic appearance at bronchoscopy or histology.
Extrapulmonary/disseminated TB	Systemic illness usually with prolonged fever, night sweats, weight loss. Clinical features of organs involved, e.g. sterile pyuria, pericarditis, ascites, pleural effusion, meningitis, arthritis, orchitis. Responds to standard anti-TB therapy.	Confirmed by positive microscopy showing AFB or culture of Mycobacterium TB from blood or other relevant specimen except sputum or BAL. Biopsy 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.	Not required but may be confirmed by : <ul style="list-style-type: none"> • typical red-purple lesions seen on bronchoscopy or endoscopy; • dense masses in lymph nodes, viscera or lungs by palpation or radiology; • 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: progressive floaters in field of vision, light flashes and scotoma; 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.	Definitive diagnosis required for other sites. Histology. CSF polymerase chain reaction (PCR).
CNS toxoplasmosis with onset at age over 1 month.	Fever, headache, focal neurological signs, convulsions. Usually responds within 10 days to specific therapy.	Not required but confirmed by computed tomography (CT) scan showing single/multiple lesions with mass effect/enhancing with contrast.
Extrapulmonary cryptococcosis including meningitis	Meningitis: usually sub acute, fever with increasing severe headache, meningism, confusion, behavioural changes that responds to cryptococcal therapy.	Confirmed by CSF microscopy (India ink or Gram stain), serum or CSF CRAG or culture.
HIV encephalopathy	At least one of the following, progressing over at least two months in the absence of another illness: <ul style="list-style-type: none"> - 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. 	Confirmed by brain CT scan or MRI demonstrating atrophy and basal ganglia calcification and excluding other causes.
Disseminated mycosis (coccidiomycosis, histoplasmosis, penicilliosis)	No presumptive diagnosis.	Diagnosed by: <ul style="list-style-type: none"> Histology: usually granuloma formation. Isolation: antigen detection from affected tissue; culture or microscopy from clinical specimen or blood culture.

Clinical event	Clinical diagnosis	Definitive diagnosis
Disseminated mycobacteriosis, other than TB	No presumptive 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	No presumptive diagnosis.	Confirmed in children with chronic diarrhoea lasting longer than one month by microscopic examination.
Chronic Isospora	No presumptive diagnosis.	Confirmed in children with chronic diarrhoea by microscopic examination.
Cerebral or B cell non-Hodgkin lymphoma	No presumptive diagnosis.	Diagnosed by CNS imaging: at least one lesion with mass effect on brain scan; histology of relevant specimen
Progressive multi focal leukoencephalopathy (PML)	No presumptive diagnosis.	Diagnosed by MRI or CT scan, and biopsy. Viral PCR for Jacob Creutzfeldt virus.
Notes: a. Diagnosis of HIV infection according to recommendations in Section IV.		

ANNEX 2

Treatment of common diarrheal pathogens in children with HIV infection

Etiology	Treatment
<u>BACTERIA:</u>	
<i>Salmonella</i> (non-typhoidal)	Ciprofloxacin 20 mg/kg/day , div. bid for 3-7 days*
<i>Shigella</i>	Ciprofloxacin 20 mg/kg/day , div. bid for 3-days
<i>Escherichia coli</i>	No antibiotic
<i>Campylobacter jejuni</i>	Erythromycin 50 mg/kg/day qid for 5 days Or ciprofloxacin 20-30 mg/kg/day bid for 5 days
<i>Mycobacterium avium complex</i>	Clarithromycin 15 mg/kg/day bid plus Ethambutol 15-25 mg/kg/ q.d. plus rifabutin 6 mg/kg OD
<i>M. tuberculosis</i>	Standard treatment for tuberculosis
<i>Yersinia enterocolitica</i>	TMP-SMZ (TMP 8mg/kg/day, SMZ 40 mg/kg/day) bid for 5 days
<u>VIRUS:</u>	
<i>Cytomegalovirus</i>	Supportive treatment
<i>Rotavirus</i>	Supportive treatment
<u>PROTOZOA:</u>	
Cryptosporidium	No therapy proven efficacious, spontaneous resolution may occur after antiretroviral therapy
<i>Isospora belli</i>	TMP-SMZ (TMP 16-20 mg/kg/day) qid for 10 days then bid for 3 weeks
<i>Giardia lamblia</i>	Metronidazole 15 mg/kg/day per oral tid for 5 days
<i>Entamoeba histolytica</i>	Metronidazole 35-50 mg/kg/day per oral tid for 10 days
<i>Microsporidia</i>	Albendazole 20 mg/kg/day bid x 4 weeks
<u>PARASITE:</u>	
<i>Strongyloides</i>	Albendazole 10 mg/kg OD x 3 days (maximum 400 mg/dose)
<u>YEAST:</u>	
<i>Candida albicans</i>	Nystatin 100,000 IU per oral tid for 5-7 days for mild case Alternative: ketoconazole 5 mg/kg/dose OD or bid or fluconazole 3-6 mg/kg OD (also for moderate to severe case)

- Cefixime, or IV ceftriaxone (if toxic) should be used in children with suspected bloodstream infection due to *Salmonella* because of high rates of reduced susceptibility to fluoroquinolones in Pakistan
- Persistent diarrhea is a common presentation in HIV-infected children. If the child is not severely ill (no blood in the stool, afebrile, not dehydrated, not malnourished), observe the child while maintaining hydration and nutrition. Other causes of diarrhea include mucosal damage, bacterial overgrowth, bile acid diarrhea, or CMV infection. Empirical treatment with oral neomycin or colistin plus cholestyramine may relieve symptoms. HIV infection itself may cause diarrhea, which may be successfully treated with antiretroviral therapy (ART).

Approach to HIV-infected child with suspected tuberculosis

Case Definition of TB (From WHO Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children 2006 and Pakistan NTP Guidelines)

- **Pulmonary tuberculosis, sputum smear-positive**
 - a. two or more initial sputum smear examinations positive for AFB, **or**
 - b. one sputum smear examination positive for AFB plus radiographic abnormalities consistent with active pulmonary tuberculosis as determined by a clinician, **or**
 - c. one sputum smear positive for AFB plus sputum culture positive for *M. tuberculosis*.

Children with smear-positive disease are more likely to be adolescent patients or children of any age with severe intrathoracic disease.

- **Pulmonary tuberculosis, sputum smear-negative**

Case of pulmonary TB that does not meet the above definition for smear-positive TB. This group includes cases without smear result, which should be exceptional in adults but are relatively more frequent in children.

Note. In keeping with good clinical and public health practice, diagnostic criteria for pulmonary TB should include:

- At least three sputum specimens negative for AFB, **and**
- Radiographic abnormalities consistent with active pulmonary TB, **and**
- No response to a course of broad spectrum antibiotics, **and**
- Decision by a clinician to treat with a full course of tuberculosis chemotherapy.

- **Extrapulmonary TB**

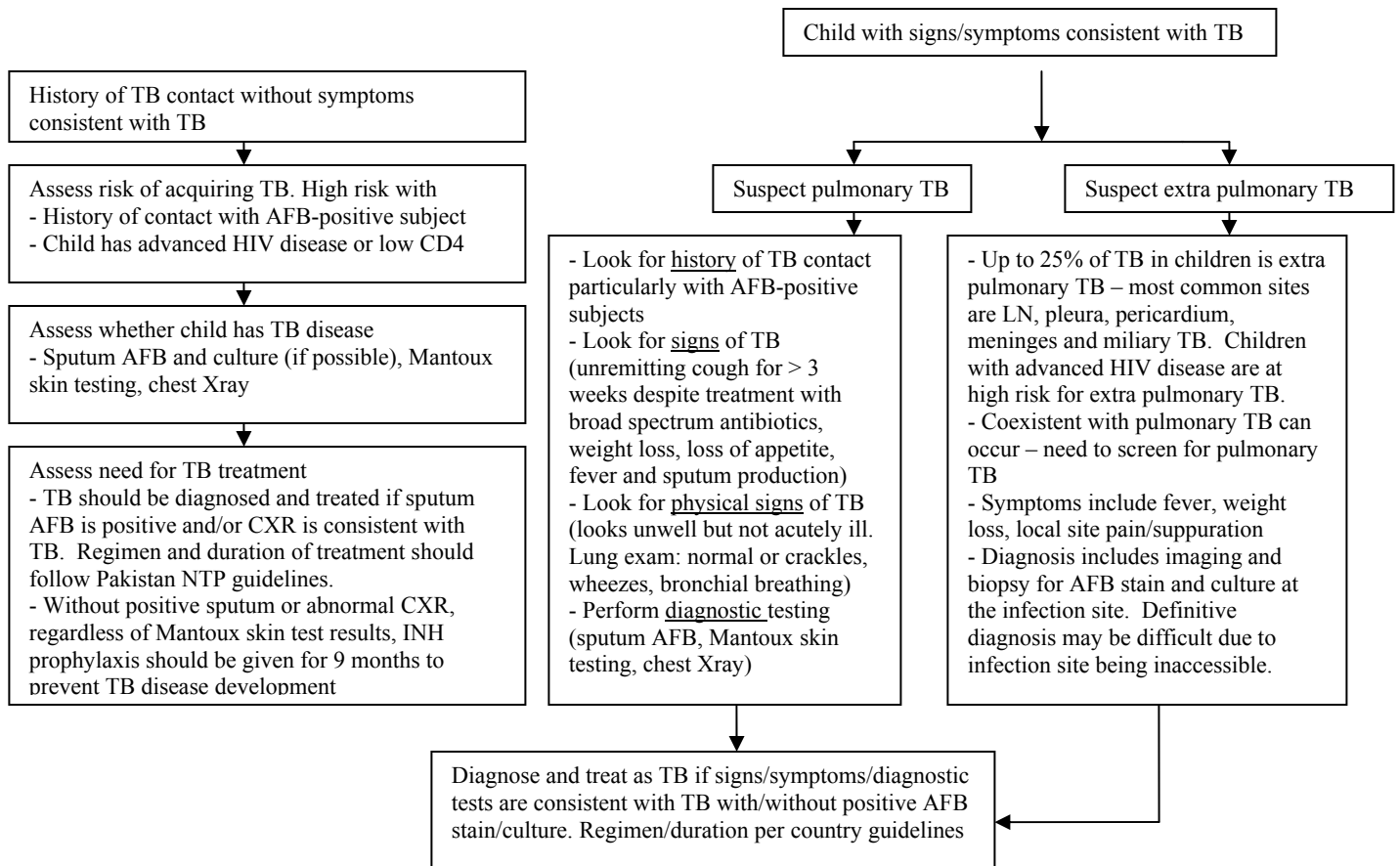
Children with only extrapulmonary TB (i.e. TB of organs other than the lungs) should be classified under this case definition. Children who have both pulmonary and extrapulmonary TB should be classified under the case definition of pulmonary TB.

Note: Sputum collection is often difficult in children < 6-8 years of age. Early morning gastric lavage can be used in young children. AFB stain should be done on 3 consecutive days. Mantoux skin testing has limited value as false negative reaction is common in children with HIV, < 1-2 years and malnourished. A reaction of ≥ 5 mm confirms TB infection in a child with HIV. CXR typically shows nodal enlargement and cavitation (in older children)

The presence of 3 or more of the following should strongly suggest the diagnosis of TB:

- Chronic symptoms suggestive of TB
- Physical signs highly suggestive of TB
- A positive tuberculin skin test
- Chest radiograph suggestive of TB

Diagnostic Approach to TB in children with HIV



ANNEX 4

Clinical diagnosis and management of common opportunistic infections in HIV-infected children

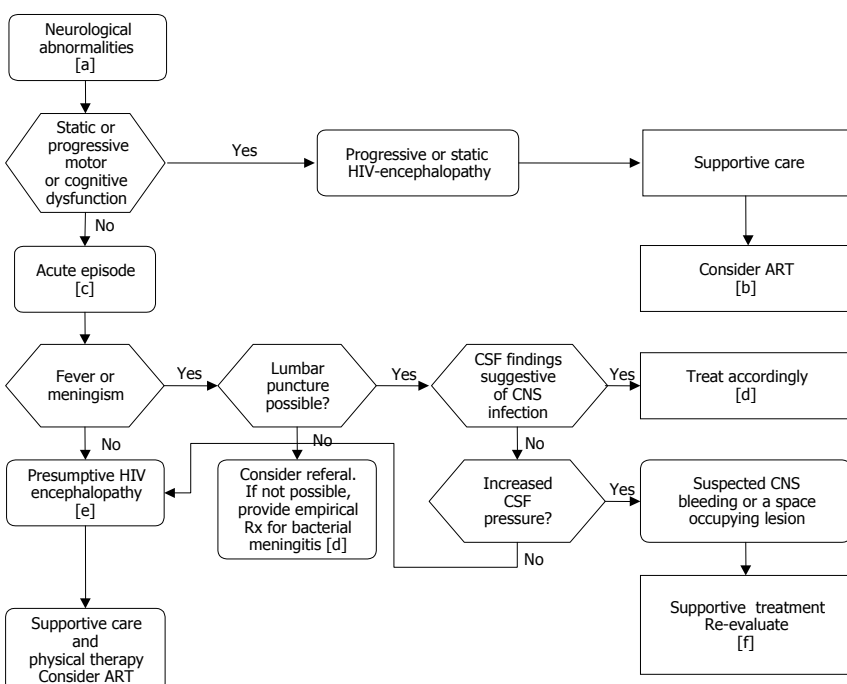
Modified from Treating Opportunistic Infections Among HIV-Exposed and Infected Children-CDC, NIH and IDSA recommendations- December 3, 2004 (www.aidsinfo.nih.gov)

Opportunistic infections	Clinical manifestations	Diagnosis	Treatment
<i>Mycobacterium avium</i> complex (MAC)	Fever, night sweats, weight loss, fatigue, chronic diarrhea and abdominal pain. Laboratory finding; neutropenia, elevations in alkaline phosphatase or lactate dehydrogenase.	Definitive diagnosis: isolation of organism from blood or specimens from normally sterile sites. Histology demonstrating macrophage-containing acid-fast bacilli is a suggestive finding.	HAART should be provided to restore immune function. Treatment with at least 2 drugs; Clarithromycin 7.5-15 mg/kg twice daily (max 500 mg/dose) plus ethambutol 15-25 mg/kg/day once daily (max 1 g/dose). Consider adding a third drug e.g. rifabutin, amikacin or ciprofloxacin in severe case. Duration of treatment: at least 12 months
<i>Pneumocystis pneumonia</i> (PCP)	Dry cough, tachypnea, dyspnea, cyanosis	Chest X-ray: bilateral diffuse parenchymal infiltrates with "ground-glass" or reticulogranular appearance. Associated with a high level of lactate dehydrogenase (LDH). Microscopy of induced sputum by bronchoalveolar lavage (BAL): GMS stain-stains cyst wall in brown or black, Wright stain: stains the trophozoites and intracystic sporozoites in pale blue.	TMP/SMX 15-20 mg/kg/day of TMP in 3-4 divided dose for 21-day course
Candidiasis	Oral candidiasis: creamy white curdlike patches that can easily be scraped off with inflamed underlying mucosa.	Oral candidiasis: KOH preparation demonstrate budding yeast cells Esophageal candidiasis: Barium swallow show cobblestone appearance. Endoscopy show small white raised plaques to elevated	Oral candidiasis Clotrimazole oral troches 10 g OR Nystatin 400,000-600,000 units 5 times daily 7-14 days Oral fluconazole 3-6 mg/kg once daily 7-14

	Esophageal candidiasis: odynophagia, dysphagia, or retrosternal pain.	confluent plaques with hyperemia and extensive ulceration.	days Esophageal candidiasis Oral fluconazole 3-6 mg/kg once daily 14-21 days
Penicilliosis	Persistent fever, anemia, hepatomegaly, generalized lymphadenopathy and translucent umbilicated papules which may resemble molluscum. Laboratory finding; anemia, and/or thrombocytopenia	Definitive diagnosis: isolation of organism from blood, bone marrow aspiration or specimens from normally sterile sites. Wright stain of skin scraping shows basophilic, spherical or oval yeast-like organisms with clear central septation (diameter 3-8 μ m)	Induction therapy: Amphotericin B (0.7-1.5 mg/kg/day) for 2 weeks Consolidation therapy: Itraconazole 5-6 mg/kg/dose twice daily for 8 weeks Maintenance therapy: Itraconazole 3-6 mg/kg/day
Cryptococcosis	Meningoencephalitis form: fever, headache, altered mental status, nuchal rigidity Disseminated form: persistent fever with translucent umbilicated papules which may resemble molluscum.	Elevated intracranial pressure and elevated CSF protein and mononuclear pleocytosis. Cryptococcal antigen can be detected in CSF or serum by latex agglutination test. Wright stain of skin scraping shows budding yeast.	Induction therapy: Amphotericin B (0.7-1.5 mg/kg/day) plus flucytosine (25 mg/kg/dose four times daily) for 2 weeks Consolidation therapy: Fluconazole 5-6 mg/kg/dose twice daily for 8 weeks Maintenance therapy: Fluconazole 3-6 mg/kg/day
Herpes simplex	HSV gingivostomatitis: fever, irritability, superficial painful ulcers in the gingival, oral mucosa and perioral area. HSV encephalitis: fever, alteration of consciousness, abnormal behavior.	HSV gingivostomatitis: use clinical diagnosis. HSV encephalitis is diagnosed by detection of HSV DNA by PCR in the CSF.	HSV gingivostomatitis: oral acyclovir 20 mg/kg/dose three times daily OR intravenous acyclovir 5-10 mg/kg/dose three times daily for 7-14 days Disseminated HSV or encephalitis: intravenous acyclovir 10 mg/mg/dose or 500 mg/m ² /dose three times daily for 21 days
Herpes zoster virus	Primary varicella infection: Generalized pruritic vesicular rash Herpes zoster: Painful rash	Use clinical diagnosis. Giemsa staining (Tzanck preparation) of cell scrapings from lesions: multinucleated giant cells is suggestive of VZV but is also	Primary varicella infection: intravenous acyclovir 10 mg/mg/dose or 500 mg/m ² /dose three times daily for 7 days in children with moderate to severe

	with fluid-filled blisters, dermatomal distribution	observed with HSV infection	immunosuppression. Oral form should be used only in a child with mild immunosuppression. Herper zoster: Oral acyclovir 20 mg/kg/dose four times daily (max 800 mg/dose) for 7 days
CMV infection	CMV retinitis: Young HIV-infected children are frequently asymptomatic and discovered on routine examination. Older children present with floaters or loss of vision. Extraocular CMV disease; e.g. CMV colitis, CMV esophagitis, CMV pneumonitis, CMV hepatitis.	Diagnosis of CMV retinitis is based on clinical appearance with white and yellow retinal infiltrates and associated retinal hemorrhages. Extraocular CMV disease: recover of virus from tissues or histopathology demonstrates characteristic "owl's eye" intranuclear inclusion bodies or positive staining with CMV monoclonal antibodies in biopsy specimens.	Ganciclovir intravenous 5 mg/kg/dose twice daily for 14-21 days followed by lifelong maintenance therapy.
Cryptosporidium	Subacute or chronic watery diarrhea often associated with cramps, nausea and vomiting	Modified Kinyoun acid-fast stain of stool: small oocyst (4-6 um in diameter)	Effective HAART is the only treatment that controls persistent cryptosporidiosis. Supportive care with hydration, correction of electrolyte abnormalities, and nutritional supplementation. Nitazoxanide is approved for treatment (age 1-3 years 100 mg twice daily, age 4-11 year 200 mg twice daily)

Approach to HIV-infected children with neurological abnormalities



- A. **Definition: Progressive encephalopathy:** Progressive decline in motor, cognitive, or language function, evidence of loss or increasing delay in developmental milestone achievement; onset can be as early as the first year of life but can occur at any time. **Static encephalopathy:** Motor dysfunction and other developmental deficits of varying severity that are non-progressive as documented on serial neurological and developmental examination. **Acute episodes:** Acute onset of seizures, focal neurological abnormalities (e.g. toxoplasmosis) or meningism (e.g. cryptococcal meningitis, bacterial meningitis, tuberculous meningitis or cytomegalovirus encephalitis). A careful history and physical examination including neurological examination and development examination are particularly important because management of acute episodes will differ from that of progressive or static encephalopathy.
- B. ART regimens should include either ZDV or d4T due to high CNS penetration.
- C. The acute episode can occur in a previously healthy HIV-infected child or can superimpose on HIV encephalopathy. For empirical treatment prior to identification of bacterial pathogen, cefotaxime 200-300 mg/kg/day every 6-8 hours, is recommended.
- D. If a pathogen is identified, treatment is recommended in the common opportunistic infections (Annex 4).
- E. If there is a focal neurological deficit, neuroimaging scan is needed to exclude cerebral infarction, hemorrhage or lymphoma etc., before HIV encephalopathy can be diagnosed.
- F. Perform neuroimaging e.g. CT scan if available. In acquired toxoplasma infection, CT scan demonstrates multiple hypodense masses with ring enhancement. In CNS lymphoma, CT scan usually demonstrates an isodense or hypodense single lesion that enhances with contrast. Brain atrophy on CT scan is more indicative of HIV encephalopathy. Other possible causes of neurological abnormality in HIV-infected children are CMV encephalitis, CNS tuberculoma, or progressive multifocal leukoencephalopathy

ANNEX 6

GUIDELINES FOR PRIMARY AND SECONDARY OI PROPHYLAXIS IN CHILDREN

6 A. Guidelines for primary OI prophylactic treatment in children

Organism	When to Give Treatment	Drug Regimen
PCP	<p>For HIV-exposed children: CTX prophylaxis is universally indicated, starting at 4-6 weeks after birth & maintained until cessation of risk of HIV transmission and exclusion of HIV infection.</p> <p>For children with confirmed HIV Age < 1 year: CTX prophylaxis indicated regardless of CD4 percent or clinical status.³ Age 1-5 years: WHO stages 2, 3 & 4 regardless of CD4 percent OR Any WHO stage and CD4 <25% Age ≥ 6 years: Any WHO clinical stage & CD4 < 350 OR WHO stage 3 or 4 & any CD4 level</p>	<p>Cotrimoxazole: suspension (200mgSMX, 40mgTMP), pediatric tab (100mgSMX, 20mgTMP), single strength adult tab (400mgSMX, 80TMP)</p> <p>See Annex 6 C for Dosing Table</p> <ul style="list-style-type: none"> • Alternative <ol style="list-style-type: none"> 1. Dapsone 2 mg/kg once daily <p>or</p> <ol style="list-style-type: none"> 2. Dapsone 4 mg/kg once weekly
TB	<p>All children who exposed to active TB cases, particularly household contact, regardless of CD4 (Need to exclude clinical disease by physical exam and CXR)</p>	<ul style="list-style-type: none"> • For known INH-sensitive strain or unknown <p>Recommended</p> <ol style="list-style-type: none"> 1. INH (10-15 mg/kg) (max 300 mg) daily for 9 months <p>or</p> <ol style="list-style-type: none"> 2. INH (20-30 mg/kg) (max 900 mg) twice weekly for 9 months
MAC	<p>CD4 <50 in > 6 year-old CD4 < 75 in 2-6 year-old CD4 < 500 in 1-2 year-old CD4 < 750 in < 1 year-old Stop when CD4 level above threshold for > 3 months</p>	<ul style="list-style-type: none"> • Recommended <ol style="list-style-type: none"> 1. clarithromycin 7.5 mg/kg/dose (max 500 mg) twice daily <p>or</p> <ol style="list-style-type: none"> 2. azithromycin 20 mg/kg (max 1200 mg) once weekly <p>Alternative</p> <p>Azithromycin 5 mg/kg (max 250 mg) once daily</p>

6 B. Guidelines for secondary prophylaxis to prevent recurrence of opportunistic infections in children

<u>Opportunistic Infection</u>	<u>When to Give Treatment</u>	<u>Drug Regimen</u>
PCP	Children who have a history of PCP should be administered prophylaxis for life to prevent recurrence. The safety of discontinuing secondary prophylaxis among HIV-infected children has not been studied extensively.	As for primary prophylaxis
TB	Not recommended	
MAC	Children with a history of disseminated MAC should be administered lifelong prophylaxis to prevent recurrence. The safety of discontinuing secondary prophylaxis among HIV-infected children has not been studied extensively.	<i>Recommended</i> Clarithromycin 7.5 mg/kg/dose (max 500 mg) twice daily plus ethambutol 15 mg/kg/dose (max 800 mg) daily Alternative Azithromycin 5 mg/kg/dose (max 250 mg) plus ethambutol 15 mg/kg/dose (max 800 mg) daily
<i>Cryptococcus neoformans</i> <i>Coccidioides immitis</i>	Children who have a history of cryptococcal meningitis should be administered prophylaxis for life to prevent recurrence. The safety of discontinuing secondary prophylaxis among HIV-infected children has not been studied extensively.	Recommended Fluconazole 3-6 mg/kg/once daily Alternative Itraconazole 2-5 mg/kg once daily
<i>Histoplasma capsulatum</i> <i>Penicillium marneffeii</i>	Children who have a history of histoplasmosis/penicilliosis should be administered prophylaxis for life to prevent recurrence. The safety of discontinuing secondary prophylaxis among HIV-infected children has not been studied extensively.	Itraconazole 2-5 mg/kg once daily
<i>Toxoplasma gondii</i>	Children who have a history of cerebral toxoplasmosis should be administered prophylaxis for life to prevent recurrence. The safety of discontinuing secondary prophylaxis among HIV-infected children has not been studied extensively.	Recommended Sulfadiazine 85-120 mg/kg/day divided into 2-4 times/day plus pyrimethamine 1 mg/kg (max 25 mg) once daily plus leucovorin 5 mg every 3 days Alternative Clindamycin 20-30 mg/kg/day in 4 divided doses daily plus pyrimethamine and leucovorin as above Alternative TMP-SMX 8-10 mg/kg

6 C. COTRIMOXAZOLE PROPHYLAXIS DOSING TABLE

DOSE	Syrup (40mg/ 200mg)	Paediatric tablet (20 mg/100 mg)	Single Strength Adult Tablet (80 mg/400mg)	Double Strength Adult Tablet (160 mg/800 mg)
< 6 months 20 mg TMP/100 mg SMX	2.5ml	1	n/a	n/a
6 months – 5 years 40 mgTMP/200mg SMX	5 ml	2	1/2	n/a
> 6 – 14 years 80 mg TMP/400 mg SMX	10 ml	4	1	1/2
> 15 years (or >35 kg) 160 mg TMP/800 mg SMX	n/a	n/a	2	1

ANNEX 7

SUMMARY OF FORMULATIONS AND DOSAGES OF ANTIRETROVIRAL DRUGS FOR CHILDREN

Name of drug	Formulations	Pharmacokinetic data available	Age (weight), dose and dose frequency	Other comments
<i>Nucleoside analogue reverse transcriptase inhibitors</i>				
Zidovudine (ZDV)	Syrup: 10 mg/mL Capsules: 100 mg; 250 mg Tablet: 300 mg	All ages	< 4 weeks: 4 mg/kg/dose twice daily 4 weeks to 13 yrs: 180 – 240 mg/m ² /dose twice daily Maximum dose: ≥13 yrs: 300 mg/dose twice daily	Large volume of syrup not well tolerated in older children, Syrup needs storage in glass jars and is light sensitive Can give with food Doses of 600 mg/m ² /dose per day required for HIV encephalopathy Capsule can be opened and contents dispersed or tablet crushed and contents mixed with small amount of water or food and immediately taken (solution is stable at room temperature) Do not use with d4T (antagonistic antiretroviral effect)
Lamivudine (3TC)	Oral solution: 10 mg/mL Tablet: 150 mg	All ages	< 30 days: 2 mg/kg/dose twice daily ≥30 days or < 60 kg: 4 mg/kg/dose twice daily Maximum dose: > 60 kg: 150 mg/dose twice daily	Well tolerated Can give with food Store solution at room temperature (use within one month of opening) Tablet can be crushed and

Name of drug	Formulations	Pharmacokinetic data available	Age (weight), dose and dose frequency	Other comments
				contents mixed with small amount water or food and immediately taken
Fixed-dose combination of ZDV plus 3TC	No liquid available Tablet: 300 mg ZDV plus 150 mg 3TC	Adolescents and adults	Maximum dose: > 13 yrs or > 60 kg: 1 tablet/dose twice daily (should not be given if <30 kg weight)	Ideally, tablet should not be split Tablet can be crushed and contents mixed with small amount of water or food and immediately taken At weight <30 kg, ZDV and 3TC cannot be dosed accurately in tablet form
Stavudine (d4T)	Oral solution: 1 mg/mL Capsules: 15 mg, 20 mg, 30 mg, 40 mg	All ages	< 30 kg: 1 mg/kg/dose twice daily 30 to 60 kg: 30 mg/dose twice daily Maximum dose: > 60 kg: 40 mg/dose twice daily	Large volume of solution Keep solution refrigerated; stable for 30 days; must shake well. Needs to be stored in glass bottles. Capsules can be opened up and mixed with small amount of food or water (stable in solution for 24 hours if kept refrigerated) Do not use with ZDV (antagonistic antiretroviral effect)
Didanosine (ddI, dideoxyinosine)	Oral suspension paediatric powder/ water: 10 mg/mL. In many countries needs to be made up with additional	All ages	< 3 months: 50mg/m ² /dose twice daily ^a 3 months to < 13 yrs: 90-120 mg/m ² /dose twice daily or 240 mg/m ² /dose once daily Maximum dose:	Keeps suspension refrigerated; stable for 30 days; must be shaken well Administer on empty stomach, at least 30 minutes before or 2 hours after eating

Name of drug	Formulations	Pharmacokinetic data available	Age (weight), dose and dose frequency	Other comments
	antacid Chewable tablets: 25 mg; 50 mg; 100 mg; 150 mg; 200 mg Enteric-coated beadlets in capsules: 125 mg; 200 mg; 250 mg; 400 mg		≥13 yrs or > 60 kg: 200 mg/dose twice daily or 400 mg once daily	If tablets dispersed in water, at least 2 of appropriate strength tablets should be dissolved for adequate buffering Enteric-coated beadlets in capsules can be opened and sprinkled on small amount of food
Abacavir (ABC)	Oral solution: 20 mg/mL Tablet: 300 mg	Over age 3 months	< 16 years or < 37.5 kg: 8 mg/kg/dose twice daily Maximum dose: > 16 years or ≥37.5 kg: 300 mg/dose twice daily	Can give with food Tablet can be crushed and contents mixed with small amount water or food and immediately ingested MUST WARN PARENTS ABOUT HYPERSENSITIVITY REACTION ABC should be stopped permanently if hypersensitivity reaction occurs
<i>Non-Nucleoside reverse transcriptase inhibitors</i>				
Nevirapine (NVP)	Oral suspension: 10 mg/mL Tablet: 200 mg	All ages	15 to 30 days: 5 mg/kg/dose once daily x 2 weeks, then 120 mg/m ² /dose twice daily x 2 weeks, then 200 mg/m ² /dose twice daily > 30 days to 13 yrs: 120 mg/m ² /dose once daily for 2 weeks, then 120-200 mg/m ² /dose twice daily Maximum dose:	If rifampicin co-administration, avoid use Store suspension at room temperature; must shake well Can give with food Tablets are scored and can be divided into two equal halves to

Name of drug	Formulations	Pharmacokinetic data available	Age (weight), dose and dose frequency	Other comments
			> 13 yrs: 200 mg/dose once daily for first 2 weeks, then 200 mg/dose twice daily	give a 100 mg dose; can be crushed and combined with small amount of water or food and immediately administered MUST WARN PARENTS ABOUT RASH. Do not dose escalate if rash occurs (if mild/moderate rash, hold drug; when rash cleared, restart dosing from beginning of dose escalation; if severe rash, discontinue drug)
Efavirenz (EFV)	Syrup: 30 mg/mL (note: syrup requires higher doses than capsules, see dosing chart) Capsules: 50 mg, 100 mg, 200 mg	Only for children over 3 years of age or weighs > 10 kg	Capsule (liquid) dose: 10 to 15 kg: 200 mg (270 mg = 9 mL) once daily 15 to < 20 kg: 250 mg (300 mg = 10 mL) once daily 20 to < 25 kg: 300 mg (360 mg = 12 mL) once daily 25 to < 33 kg: 350 mg (450 mg = 15 mL) once daily 33 to < 40 kg: 400 mg (510 mg = 17 mL) once daily Maximum dose: ≥40 kg: 600 mg once daily	Capsules may be opened and added to food but have very peppery taste; however, can mix with sweet foods or jam to disguise taste Can give with food (but avoid after high fat meals which increase absorption by 50%) Best given at bedtime, especially in the first 2 weeks, to reduce central nervous system side effects
<i>Protease inhibitors</i>				
Nelfinavir (NFV)	Powder for oral suspension (mix with liquid): 200 mg	All ages However, extensive	< 1 yr: 50mg/kg/dose three times daily or 75mg/kg/dose twice daily	Powder is sweet, faintly bitter, but gritty and hard to dissolve; must be reconstituted

Name of drug	Formulations	Pharmacokinetic data available	Age (weight), dose and dose frequency	Other comments
	<p>per level teaspoon (50 mg per 1.25 mL scoop): 5 mL</p> <p>Tablet: 250 mg (tablets can be halved; can be crushed and added to food or dissolved in water)</p>	<p>pharmacokinetic variability in infants, with requirement for very high doses in infants < 1 yr</p>	<p>> 1 yr to < 13 yrs: 55 to 65 mg/kg/ dose twice daily</p> <p>Maximum dose: ≥13 yrs: 1250 mg/dose twice daily</p>	<p>immediately prior to administration in water, milk, formula, pudding, etc. – do not use acidic food or juice (increases bitter taste); solution stable for 6 hours</p> <p>Because of difficulties with use of powder, use of crushed tablets preferred (even for infants) if appropriate dose can be given</p> <p>Powder and tablets can be stored at room temperature</p> <p>Take with food</p> <p>Drug interactions (less than ritonavir-containing protease inhibitors)</p>
<p>Lopinavir/ritonavir, (LPV/r)</p>	<p>Oral solution: 80mg/mL lopinavir plus 20 mg/mL ritonavir</p> <p>Note : oral solution contains 42% alcohol</p> <p>Capsules: 133.3 mg lopinavir plus 33.3 mg ritonavir</p>	<p>6 months of age or older</p>	<p>>6 months to 13 years: 225 mg/m² LPV/57.5 mg/m² ritonavir twice daily ^a or weight-based dosing:</p> <p>7-15 kg: 12mg/kg LPV/3 mg/kg ritonavir/dose twice daily</p> <p>15-40 kg: 10 mg/kg lopinavir/5 mg/kg ritonavir twice daily</p> <p>Maximum dose: > 40 kg: 400 mg LPV/100 mg ritonavir (3 capsules or 5 mL) twice daily</p>	<p>Preferably oral solution and capsules should be refrigerated; however, can store at room temperature up to 25°C (77°F) for 2 months; at temperature >25°C (77° F), drug degrades more rapidly</p> <p>Liquid formulation has low volume but bitter taste</p> <p>Capsules large</p> <p>Capsules should <i>not</i> be crushed or opened, but must be</p>

Name of drug	Formulations	Pharmacokinetic data available	Age (weight), dose and dose frequency	Other comments
				swallowed whole Should be taken with food
Saquinavir/r	Soft gel capsule : 200mg Hard gel capsule : 200 mg and 500mg	> 25 kg	Approved dosing in adults: SQV1000mg/RTV100mg twice daily There is no data in children. For children weight > 25kg, the approved adult dosing can be used. If possible, monitoring of SQV level is recommended	Capsules large Capsules should <i>not</i> be crushed or opened, but must be swallowed whole Should be taken with food

ANNEX 8

SERIOUS ACUTE AND CHRONIC TOXICITIES DUE TO ARV DRUGS THAT MAY REQUIRE THERAPY MODIFICATION: CLINICAL PRESENTATION, LABORATORY ABNORMALITIES, AND IMPLICATIONS FOR ART MANAGEMENT ^a

Possible clinical manifestations (Most common ARV drug(s) associated with the toxicity)	Possible laboratory abnormalities ^b	Implications for antiretroviral drug treatment
<i>Acute Serious Adverse Reactions</i>		
Acute Symptomatic Hepatitis (NNRTI class, particularly NVP, more rarely EFV; NRTIs or PI class)		
<ul style="list-style-type: none"> ▪ Jaundice ▪ Liver enlargement ▪ Gastrointestinal symptoms ▪ Fatigue, anorexia ▪ May have hypersensitivity component (rash, fever, systemic symptoms), usually occurs within 6-8 weeks ▪ May have accompanying lactic acidosis (see below) if secondary to NRTI drug 	<ul style="list-style-type: none"> ▪ Elevated transaminases ▪ Elevated bilirubin 	<ul style="list-style-type: none"> ▪ Discontinue all ARV until symptoms resolve ▪ If possible, monitor transaminases, bilirubin ▪ If receiving NVP, NVP should <u>NOT</u> be readministered to the patient in future ▪ Once symptoms resolve, either <ul style="list-style-type: none"> ○ restart ART with change to alternative ARV (if on NVP regimen, this is required); or ○ restart current ART regimen with close observation; if symptoms recur, substitute an alternative ARV^c
Acute Pancreatitis (NRTI class, particularly d4T, ddI; more rarely 3TC)		
<ul style="list-style-type: none"> ▪ Severe nausea and vomiting ▪ Severe abdominal pain ▪ May have accompanying lactic acidosis (see below) 	<ul style="list-style-type: none"> ▪ Elevated pancreatic amylase ▪ Elevated lipase 	<ul style="list-style-type: none"> ▪ Discontinue all ARVs until symptoms resolve ▪ If possible, monitor serum pancreatic amylase, lipase ▪ Once symptoms resolve, restart ART with substitution of an alternative NRTI, preferably one

		without pancreatic toxicity ^c
Hypersensitivity Reaction (ABC or NVP)		
<ul style="list-style-type: none"> ▪ <i>ABC</i>: Combination of acute onset of both respiratory and gastrointestinal symptoms after starting ABC, including fever, fatigue, myalgia, nausea, vomiting, diarrhea, abdominal pain, pharyngitis, cough, dyspnea; rash (usually mild) may or may not occur; progressive worsening of symptoms soon after receives ABC dose, usually occurs within 6-8 weeks ▪ <i>NVP</i>: Systemic symptoms of fever, myalgia, arthralgia, hepatitis, with or without rash 	<ul style="list-style-type: none"> ▪ Elevated transaminases ▪ Elevated eosinophil count 	<ul style="list-style-type: none"> ▪ Immediately discontinue all ARVs until symptoms resolve ▪ NVP or ABC should <u>NOT</u> be readministered to the patient in future ▪ Once symptoms resolve, restart ART with substitution of an alternative ARV for ABC or NVP^c
Lactic Acidosis (NRTI class, particularly d4T)		
<ul style="list-style-type: none"> ▪ Generalized fatigue and weakness ▪ Gastrointestinal features (nausea, vomiting, diarrhoea, abdominal pain, hepatomegaly, anorexia, poor weight gain and/or sudden unexplained weight loss) ▪ May have hepatitis or pancreatitis (see above) ▪ Respiratory features (tachypnea and dyspnea) ▪ Neurological symptoms (including motor weakness). 	<ul style="list-style-type: none"> ▪ Increased anion gap ▪ Lactic acidosis ▪ Elevated aminotransferase ▪ Elevated CPK ▪ Elevated LDH 	<ul style="list-style-type: none"> ▪ Discontinue all ARVs until symptoms resolve ▪ Symptoms associated with lactic acidosis may continue or worsen despite discontinuation of ART ▪ Once symptoms resolve, restart ART with substitution of an alternative NRTI with lower mitochondrial toxicity risk (eg. ABC or AZT)^c
Severe Rash/Stevens Johnson Syndrome (NNRTI class, particularly NVP, less common EFV)		
<ul style="list-style-type: none"> ▪ Rash usually occurs during first 6-8 weeks of treatment ▪ <i>Mild to moderate rash</i>: erythematous, maculopapular, confluent, most often on the body and arms, with no systemic symptoms 	<ul style="list-style-type: none"> ▪ Elevated aminotransferases 	<ul style="list-style-type: none"> ▪ 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 <u>NOT</u> be readministered to the patient

<ul style="list-style-type: none"> ▪ <i>Severe rash:</i> 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 		<p>in the future</p> <ul style="list-style-type: none"> ▪ 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 (ZDV)		
<ul style="list-style-type: none"> ▪ Severe pallor, tachycardia ▪ Significant fatigue ▪ Congestive heart failure 	<ul style="list-style-type: none"> ▪ Low haemoglobin 	<ul style="list-style-type: none"> ▪ If refractory to symptomatic treatment (e.g., transfusion), discontinue ZDV only and substitute an alternative NRTI^c
Severe neutropenia (ZDV)		
<ul style="list-style-type: none"> ▪ Sepsis/infection 	<ul style="list-style-type: none"> ▪ Low neutrophil count 	<ul style="list-style-type: none"> ▪ If refractory to symptomatic treatment (e.g., transfusion), discontinue ZDV only and substitute an alternative NRTI^c
<i>Chronic Late Serious Adverse Reactions</i>		
Lipodystrophy/Metabolic Syndrome (d4T; PIs)		
<ul style="list-style-type: none"> ▪ Fat loss and/or fat accumulation in distinct regions of the body: <ul style="list-style-type: none"> ○ 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 	<ul style="list-style-type: none"> ▪ Hypertriglyceridaemia; ▪ Hypercholesterolaemia; ▪ Low HDL levels ▪ Hyperglycaemia 	<ul style="list-style-type: none"> ▪ Substitution of ABC or ZDV for d4T may prevent progression of lipoatrophy ▪ Substitution of an NNRTI for a PI may decrease serum lipid abnormalities

Severe Peripheral Neuropathy (d4T, ddl; more rarely 3TC)		
<ul style="list-style-type: none"> ▪ Pain, tingling, numbness of hands or feet; refusal to walk ▪ Distal sensory loss ▪ Mild muscle weakness and areflexia can occur 	<ul style="list-style-type: none"> ▪ None 	<ul style="list-style-type: none"> ▪ Stop suspect NRTI only and substitute a different NRTI that is not associated with neurotoxicity^c ▪ Symptoms may take several weeks to resolve
<p>Notes:</p> <p>a. Alternative explanations for the toxicity must be excluded before it is concluded it is secondary to the ARV drug. Note: This table does not describe detailed clinical toxicity management, only management of the ART regimen.</p> <p>b. All laboratory abnormalities may not be observed.</p> <p>c. See Table 19 (page X) for recommended antiretroviral drugs substitutions.</p> <p>ARV – antiretroviral drug; ART – antiretroviral therapy; CPK - creatinine phosphate kinase; LDH - lactate dehydrogenase; HDL - high-density lipoprotein; NRTI – nucleoside analogue reverse transcriptase inhibitor; NNRTI – non-nucleoside reverse transcriptase inhibitor; PI – protease inhibitor</p>		

ANNEX 9

SEVERITY GRADING OF SELECTED CLINICAL AND LABORATORY TOXICITIES MOST COMMONLY SEEN WITH RECOMMENDED ANTIRETROVIRAL DRUGS FOR CHILDREN

PARAMETER	MILD	MODERATE	SEVERE	SEVERE, POTENTIALLY LIFE-THREATENING
GENERAL GUIDANCE TO ESTIMATING SEVERITY GRADE				
Characterization of symptoms and general guidance on management	Symptoms causing no or minimal interference with usual social & functional activities ^a : No therapy needed, monitor	Symptoms causing greater than minimal interference with usual social & functional activities: May require minimal intervention and monitoring	Symptoms causing inability to perform usual social & functional activities: Requires medical care and possible hospitalization	Symptoms causing inability to perform basic self-care functions ^c : Requires medical or operative intervention to prevent permanent impairment, persistent disability, or death
HAEMATOLOGY <i>Standard International Units are listed in italics</i>				
Absolute neutrophil count	750 – <1,000/mm ³ <i>0.75 x10⁹ – <1 x10⁹/L</i>	500 – 749/mm ³ <i>x10⁹ – 0.749x10⁹/L</i> <i>0.5</i>	250 – 500/mm ³ <i>0.25 x10⁹ – 0.5x10⁹/L</i>	<250/mm ³ <i><0.25x10⁹/L</i>
Haemoglobin (child >60 days of age)	8.5 – 10.0 g/dL <i>1.32 – 1.55 mmol/L</i>	7.5 - <8.5 g/dL <i>– <1.32 mmol/L</i> <i>1.16</i>	6.5 – <7.5 g/dL <i>1.01 – <1.16 mmol/L</i>	< 6.5 g/dL <i>< 1.01 mmol/L</i> Or severe clinical symptoms due to anaemia (e.g., cardiac failure) refractory to supportive therapy
Platelets	100,000-<125,000/mm ³ <i>100x10⁹ – 125x10⁹/L</i>	50,000-<100,000/mm ³ <i>50x10⁹ – <100x10⁹/L</i>	25,000-<50,000/mm ³ <i>25x10⁹ – <50x10⁹/L</i>	<25,000/mm ³ <i>< 25x10⁹/L</i> Or bleeding
GASTROINTESTINAL				
Laboratory				
ALT (SGPT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
AST (SGOT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN

PARAMETER	MILD	MODERATE	SEVERE	SEVERE, POTENTIALLY LIFE-THREATENING
Bilirubin (>2 weeks of age)	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN
Lipase	1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	> 5.0 x ULN
Pancreatic amylase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN
Clinical				
Diarrhoea ≥ 1 year of age	Transient or intermittent episodes of unformed stools OR increase of ≤ 3 stools over baseline per day	Persistent episodes of unformed to watery stools OR increase of 4 – 6 stools over baseline per day	Grossly bloody diarrhoea OR increase of ≥ 7 stools per day OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
< 1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR hypotensive shock
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR aggressive rehydration indicated (e.g., IV fluids)	Persistent nausea with no or minimal oral intake resulting in dehydration with aggressive rehydration indicated
Pancreatitis	NA	Symptomatic AND hospitalization not indicated (other than emergency treatment)	Symptomatic AND hospitalization not indicated (other than emergency treatment)	Life-threatening consequences (e.g., circulatory failure, haemorrhage, sepsis)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

PARAMETER	MILD	MODERATE	SEVERE	SEVERE, POTENTIALLY LIFE-THREATENING
ALLERGIC/DERMATOLOGIC				
Acute systemic allergic reaction	Localized urticaria (wheals) lasting a few hours	Localized urticaria with medical intervention indicated OR mild angioedema	Generalized urticaria OR angioedema with medical intervention indicated OR symptomatic mild bronchospasm	Acute anaphylaxis OR life-threatening bronchospasm or laryngeal oedema
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic Epidermal Necrolysis (TEN)
NEUROLOGIC				
Alteration in personality-behaviour or in mood ^b	Alteration causing no or minimal interference with usual social & functional activities ^b	Alteration causing greater than minimal interference with usual social & functional activities ^b	Alteration causing inability to perform usual social & functional activities ^b AND intervention indicated	Behaviour potentially harmful to self or others OR life-threatening consequences
Altered Mental Status	Changes causing no or minimal interference with usual social & functional activities ^b	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities ^b	Onset of confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities ^b	Onset of delirium, obtundation, or coma

PARAMETER	MILD	MODERATE	SEVERE	SEVERE, POTENTIALLY LIFE-THREATENING
Neuromuscular weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR minimal muscle weakness causing no or minimal interference with usual social & functional activities ^b	Muscle weakness causing greater than minimal interference with usual social & functional activities ^b	Muscle weakness causing inability to perform usual social & functional activities ^b	Disabling muscle weakness causing inability to perform basic self-care functions OR respiratory muscle weakness impairing ventilation
Neurosensory alteration (including painful neuropathy)	Asymptomatic with sensory alteration on exam OR minimal paraesthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paraesthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paraesthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paraesthesia causing inability to perform basic self-care functions ^c
OTHER LABORATORY PARAMETERS <i>Standard International Units are listed in italics</i>				
Cholesterol (fasting, paediatric <18 years old)	170 - < 200 mg/dL <i>4.40 - 5.15 mmol/L</i>	200 - 300 mg/dL <i>5.16 - 7.77 mmol/L</i>	> 300 mg/dL <i>> 7.77 mmol/L</i>	NA
Glucose, serum, high: Nonfasting	116 - < 161 mg/dL <i>6.44 - 8.89 mmol/L</i>	161 - < 251 mg/dL <i>8.89 - 13.89 mmol/L</i>	251 - 500 mg/dL <i>13.89 - 27.75 mmol/L</i>	> 500 mg/dL <i>> 27.75 mmol/L</i>
Glucose, serum, high: Fasting	110 - < 126 mg/dL <i>6.11 - 6.95 mmol/L</i>	126 - < 251 mg/dL <i>6.95 - 13.89 mmol/L</i>	251 - 500 mg/dL <i>13.89 - 27.75 mmol/L</i>	> 500 mg/dL <i>> 27.75 mmol/L</i>
Lactate	< 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences or related condition present	Increased lactate with pH < 7.3 with life-threatening consequences (e.g., neurological findings, coma) or related condition present
Triglycerides (fasting)	NA	500 - < 751 mg/dL <i>5.65 - 8.49 mmol/L</i>	751 - 1,200 mg/dL <i>8.49 - 13.56 mmol/L</i>	> 1,200 mg/dL <i>> 13.56 mmol/L</i>

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

ULN - upper limit of normal

Notes:

- a. Values are provided for children in general except where age groups are specifically noted.
- b. Usual social and functional activities in young children include those that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc).
- c. Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement, walking or using hands).

ANNEX 10

DRUG INTERACTIONS WITH ANTIRETROVIRAL AGENTS

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

ARV	NVP	EFV	LPV/r	NFV	SQV
			ketoconazole		no data (RTV treatment dose can increase ketoconazole level 3-fold)
Fluconazole	↑NVP Cmax, AUC, Cmin by 100% No change in fluconazole level Possible increase hepatotoxicity with co-administer requiring monitoring of NVP toxicity	No data	No data	No data	No data
Intraconazole	No data	No data	↑Itraconazole level Do not exceed 200mg/day itraconazole	No data but potential for bidirectional inhibition, monitor toxicities	Bidirectional interaction has been observed. May need to decrease itraconazole dose. Consider monitor SQV level (especially if given unboosted with RTV)
Oral contraceptives	↓Ethinyl estradiol by 20%. Use alternative or additional methods	↑Ethinyl estradiol by 37%. Use alternative or additional methods	↓Ethinyl estradiol level by 42% Use alternative or additional methods	↓levels of norethindrone by 18% and ethinyl estradiol by 47%	No data for unboosted SQV. RTV treatment dose can ↓level of ethinyl estradiol by 41%
Lipid lowering agents					
Simvastatin, Lovastatin	No data	↓Simvastatin level by 58% EFV level unchanged Adjust simvastatin dose according to lipid response, not to exceed the maximum	Potential large ↑ statin level Avoid concomitant use	↑ Simvastatin AUC by 505% Potential large ↑ lovastatin AUC Avoid concomitant use	Potential large ↑ statin level Avoid concomitant use

ARV	NVP	EFV	LPV/r	NFV	SQV
		recommended dose			
Atorvastatin	No data	↓Atorvastatin AUC by 43% EFV level unchanged Adjust atorvastatin dose according to lipid response, not to exceed maximum recommended dose	↑Atorvastatin AUC 5.88 fold Use lowest possible starting dose with careful monitoring	↑Atorvastatin AUC 74% Use lowest possible starting dose with careful monitoring	↑ Atorvastatin level by 450% when use as SQV/RTV Use lowest possible starting dose with careful monitoring
Pravastatin	No data	No data	↑Pravastatin AUC 33% No dose adjustment needed	No data	↓Pravastatin level by 50% No dose adjustment needed
Anticonvulsants					
Carbamazapine, Phenobarbital, phenytoin	Unknown. Use with caution Monitor anticonvulsant levels	Use with caution. One case report showed low EFV levels with phenytoin Monitor anticonvulsant and EFV levels	↑Carbamazapine from RTV Both phenytoin and LPV/r levels ↓ For all, avoid concomitant use or monitor LPV/anticonvulsant levels	Unknown but may decrease NFV level substantially Monitor NFV/anticonvulsant levels	Unknown for unboosted SQV but may markedly ↓ SQV level Monitor SQV/anticonvulsant levels

ANNEX 11

Case I: A 6-month old HIV-exposed male infant was brought into the clinic by his mother. She delivered the baby vaginally. Both she and her baby received NVP single dose. She is breastfeeding the baby. This is the first clinic visit.

Step 1: Assessment at first visit (Page 13)

Identify risk factor of HIV infection: This child is at risk of HIV infection via mother to child transmission. The use of NVP single dose reduces the transmission risk by 50% but the breast feeding increases the transmission risk by about 10%.

Identify signs and symptoms of HIV, opportunistic infections, growth and nutritional status: The child is cachectic and his weight and length is below 3SD. He has tachypnea and dry cough.

Concomitant medication: the child is not on cotrimoxazole. Cotrimoxazole should have been started at age 6 weeks of age at a dosing of 6-8mg/kg trimethoprim once daily. Risk of having *Pneumocystis jiroveci* pneumonia is higher because of lack of prophylaxis (page 17).

Perform laboratory HIV diagnostic testing: at age 6 months, the diagnostic method is HIV DNA or HIV RNA PCR.

Step 2: Identification of OI and diagnosis of HIV (Chapters IV and V and Annex 4)

The infant is admitted to the hospital and given a presumptive diagnosis of *Pneumocystis jiroveci* pneumonia. Chest X-ray shows bilateral perihilar diffuse infiltration. Gomori's methanamine silver stain does not show cysts. The infant is promptly given oral high-dose cotrimoxazole (trimethoprim 5mg/kg/day, sulfamethoxazole 25mg/kg/day) 4-times a day for 3 weeks along with supportive care. The infant improves after this treatment. After completion of 3 weeks of high dose cotrimoxazole, he is given cotrimoxazole prophylaxis at a dosing of 8mg/kg trimethoprim once daily.

HIV DNA PCR, or HIV RNA PCR is not available; therefore, confirmation of HIV diagnosis is not possible at this time. When the child is 18 months of age, HIV antibody testing can be done to confirm HIV diagnosis.

Step 3: Assessment of ART needs in the absence of confirmed HIV diagnosis (Page 28)

Without HIV diagnosis confirmation, ART should only be started if a child fits the WHO presumptive diagnosis of severe HIV disease. It is possible that this child will fit this diagnosis because the child has a diagnosis of an AIDS-indicator condition (Probable *P. jiroveci* pneumonia). In order to make a presumptive diagnosis of severe HIV disease, HIV antibody testing is done which is positive. CD4 is 10% which is within the severe immune suppression range. ART should be started and preferably after completion of *Pneumocystis jiroveci* pneumonia treatment in order to lower the risk of immune reconstitution syndrome. ART initiation is not an emergency and assessment of caregiver's readiness is crucial. In order to assure adherence to therapy, a team effort is required (page 40).

Step 4: Choosing ART

Because this infant is younger than 3 years of age and weighs less than 10 kgs, the WHO and NACP recommended first line regimen is 2NRTIs plus NVP. He has anemia with hemoglobin of 8.5g/dl; therefore, for the 2NRTIs, d4T is selected instead of ZDV, to be taken with 3TC. He is exposed to NVP which may put him at risk for NVP resistance; however, data on whether this would affect treatment outcome is not available; therefore, the preferred first line regimen is NVP-based ART.

Case II: A 6 year-old boy with recurrent otitis media and pruritic papular eruptions and CD4 178 cells/mm³ has been referred to your clinic.

Step 1: Assessment after HIV diagnosis is confirmed (Page 14 and 19)

Staging of HIV disease using clinical criteria: recurrent otitis media and pruritic papular eruptions are WHO stage 2 conditions or mild HIV disease (Table 4).

Staging of HIV disease using immunological criteria: His CD4 of 178 cells/mm³ is considered severe immune suppression (Table 10).

Staging of HIV disease using total lymphocyte count is not needed as CD4 is available.

Cotrimoxazole prophylaxis: This child is not on cotrimoxazole prophylaxis but should be on it as he has signs of WHO stage 2 and his CD4 is < 200 cells/mm³.

Assess whether the child fits ART initiation criteria: the child has had only one CD4 which is within the severe immune suppression range. As CD4 can fluctuate depending on health status at the time of testing, a repeat CD4 is recommended prior to starting ART in children who do not have clinical criteria to start ART (WHO stage 3 or 4).

Concomitant medication: the child is not on any medication.

Assess signs and symptoms for opportunistic infections: the child does not have these.

Assess growth and nutritional status: the child has normal growth and is on a balanced diet. His Hb is 10.2 g/dl.

Assess family situation: the father died of AIDS. The mother is on successful ART. The mother has good general HIV and ART knowledge. The child does not know his HIV status. The child dislikes taking medications. The family has reasonable income and can pay for transportation to clinic visits. They have a refrigerator to store medications.

Step 2: Starting ART (page 28)

This boy does not have clinical criteria to start ART (does not have WHO stage 3 or 4). His repeat CD4 is 180 cells/mm³ which confirms that he has CD4 within the severe immune suppression range and should be started on ART.

Step 3: Choose regimen (page 37)

The preferred regimen is 2NRTI plus 1NNRTI. For 2NRTI, the health care personnel chose ZDV plus 3TC as ZDV is associated with less lipodystrophy than d4T, and there are no contraindications to ZDV (such as severe anemia). The NNRTI chosen is NVP as this the recommended first line NNRTI in Pakistan and the child is older than 3 years. However, his mother is concerned about rash and hepatotoxicity with NVP. She has suffered serious rashes with NVP. Therefore, the regimen selected is ZDV (300mg), 3TC (150mg) and NVP (200mg). He weighs 20 kg and is 110cm tall (body surface area is 0.78 m²) so the dosing of ART should be ZDV 300 mg, 3TC 80mg, NVP 150mg given twice daily. He has to take one tablet of ZDV, half tablet of 3TC and three-fourth tablet of NVP. The mother is informed that the medication has to be given to him on time every day to prevent resistance. The pill is cut using a pill cutter. The child cannot swallow pills and the pill has to be crushed and mixed with water.

Step 4: Preparing family and child for ART (page 40)

Health care personnel's responsibility: Education is provided regarding natural history of HIV in children, and benefits, side effects, and adherence to ART. The pill cutting, crushing and mixing with water is demonstrated to the mother and she is able to perform this task. The best time to take ART is identified after the health care personnel ask about the family daily activities. The best regimen based on the pill load, frequency, lifestyle, dosing is chosen. The mother is given a phone number that she can contact a staff 24 hours if she has questions.

Caregiver's responsibility: the mother understands and is ready to adhere to the treatment program.

Children's responsibility: the medication is shown to the child and he is asked whether he agrees to take the medication. When he asks why he has to take this medication, it is explained to him that this medication will make him strong because it will help kill germs in his body that can make him sick. The child continues to receive support while on ART.

Case III: A 5 year old child with presumed pulmonary TB and CD4 8% is referred to your clinic.

Step 1: Diagnosis of OI, staging of HIV disease and initiation of ART/cotrimoxazole

The child has poor appetite and poor weight gain, low grade fevers, chronic non-productive cough, generalized lymphadenopathy. There is no history of recent tuberculosis contact in the family. Physical examination showed a chronically ill cachectic child with bilateral crackles on lung exam. Chest Xray showed bilateral hilar adenopathy and infiltration. The child cannot produce sputum. Tuberculin skin test was not performed. A diagnosis of presumed pulmonary tuberculosis is made. The child's weight and height are below 2 SD. He has poor appetite and bad dental hygiene. He does not have chronic diarrhea.

Pulmonary tuberculosis puts him in WHO stage 3 (Table 4). His CD4 of < 15% is considered severe immune suppression (Table 10). Staging of HIV disease using total lymphocyte count is not needed as CD4 is available. This child should be on cotrimoxazole prophylaxis as he has signs of WHO stage 3 disease and his CD4 is < 15%. By clinical criteria (WHO stage 3), the child may start ART; however, with pulmonary TB, delay ART initiation may be considered if CD4 is not in the severe immunodeficiency range for age. This child does have CD4 in the severe immunodeficiency range (CD4 < 15%); therefore, he should start ART. Both parents have passed away. He lives with his grandparents.

Step 2: Starting TB treatment (Chapter XII)

A regimen of isoniazid, rifampicin, ethambutol and pyrazinamide was started. The child improved within 2 weeks with better appetite, no fever and less cough. The 4-drug TB regimen was continued for 2 months then it was switched to a 2-drug regimen with isoniazid and rifampicin. The plan is to continue this regimen to complete 9 months of treatment according to Pakistan guidelines.

Step 3: Choose when to start ART and choose regimen (page 53)

This child has presumed pulmonary TB and severe immune deficiency (CD4 < 15%); therefore, ART should be initiated. In children with HIV and TB co-infection, ART should be started 2-8 weeks after anti-TB treatment is started. In this case, ART is started 8 weeks after anti-TB treatment as there is no urgency in starting ART since the child shows a clear clinical improvement following anti-TB treatment. The delay in starting ART after anti-TB treatment is to lower the chance of overlapping toxicity of ART and anti-TB medications and of immune reconstitution syndrome.

Normally, the preferred regimen is 2NRTI plus 1NNRTI but in children, who are starting ART after rifampicin-based anti-TB treatment, a triple NRTI regimen with d4T or ZDV plus 3TC plus ABC is recommended due to the lack of drug interaction of these drugs with anti-TB medications. However, in this health care facility, ABC is not available because of its high cost; therefore, the alternative regimen with 2NRTI plus EFV was selected. Rifampicin can lower EFV drug level by 25%. At this time, there is no data on whether adjustment of EFV dose is needed. In this case, standard dosing of EFV was used in combination with ZDV plus 3TC. NRTIs are not affected by rifampicin and can be selected similarly to non-TB cases.

Step 4: Preparing family and child for ART (page 40)

The caregiver is prepared and understands the need to start ART. The caregiver is also counseled on the signs and symptoms of immune reconstitution syndrome and the overlapping toxicity of ART and anti-TB medications.

Case IV. A 6-year-old girl developed painful vesicles at left chest wall 4 weeks after initiation of ARV

Step 1: Assess whether it is ARV-related toxicity

- She received ZDV+3TC+NVP regimen. The common NVP-associated rash is an erythematous maculopapular rash distributed at face or trunk. The onset of rash usually occurs during first 2- 8 weeks. Rash developed in this child is a painful group of vesicles distributed at left chest wall along dermatomal distribution. The most likely diagnosis is a herpes zoster.

Step 2: Assess whether it is a treatment failure

- She received ARV less than 24 weeks, therefore it is not counted as a sign of ARV treatment failure. She should continue same antiretroviral therapy.

Step 3: Assess whether it is a new opportunistic infection or immune reconstitution syndrome

- It is most likely immune reconstitution syndrome, because it occurs during the first month after ART. Immunological assessment to document CD4 response should be performed if available. Current CD4 is 8%, 153 cell/mm³, which is rapidly increase from 3%, 38 cell/mm³ prior to initiation of ARV treatment.
- She should continue same ARV regimen and oral acyclovir 20 mg/kg/dose four times daily for 7 days.

Case V: A 10-year-old HIV-infected girl who received ART (a regimen containing ZDV plus 3TC plus NVP) for 3 years presented with oral candidiasis.

Step 1: Evaluate adherence to ARV

- Her mother is responsible for giving ARV to a child. She admits that during the past 6 months, she forgot to give ARV to a child 2-3 times a week. The adherence problem is a most common cause of treatment failure.

Step 2: Assessment whether a child has failure of first-line regimen using clinical and immunological criteria

- The child has taken ARV for longer than 24 weeks and develops new opportunistic infection, therefore she meets clinical failure criteria.
- CD4 count should be performed if available. The CD4 count is 12%, 180 cells/mm³. The previous CD4 count performed last year was 20%, 350 cells/mm³. There is a significant decline of CD4 from peak level and CD4 count also falls in severe immunodeficiency category. The child meets immunological failure criteria.

Step 3: Switch to second line regimen

- Before change ARV to second line regimen, make sure that a child can adhere to second-line regimen.
- The options available for second line regimens are ddi+ABC+NFV or ddi+ABC+ LPV/r or ddi+ABC+SQV/r.

ANNEX 12

I. DRUG DOSAGES FOR PMTCT PROPHYLACTIC REGIMENS FOR WOMEN ON HAART

- HAART should be continued during labor, delivery, and post-partum period (see adult guidelines)
- Infants should receive 1 week of ZDV syrup 4 mg/kg twice a day
- If the mother receives less than 4 weeks of HAART during pregnancy, infant ZDV dosing should be extended to 4 weeks

II. DRUG DOSAGES FOR PMTCT PROPHYLACTIC REGIMENS FOR WOMEN NOT ON HAART

Regimen	Woman			Infant
	Antenatal	Intrapartum	Postpartum	
If complex prophylactic ARV regimens for PMTCT are possible				
ZDV plus SD NVP	ZDV 300 mg twice a day starting at 28 weeks or as soon as possible thereafter ¹	ZDV 600 mg at onset of labour	ZDV 300 mg twice a day	SD NVP 2mg/kg oral suspension or 6mg immediately after birth
Plus ZDV/3TC tail		Plus SD NVP 200 mg at onset of labour	Plus 3TC 150 mg at onset of labour and every 12 hours until delivery ²	PLUS 3TC 150 mg twice a day for 7 days ²
If complex prophylactic ARV regimens for PMTCT are not possible				
Single-dose NVP		SD NVP 200 mg at onset of labour		SD NVP 2mg/kg oral suspension or 6mg immediately after birth ⁴

¹If no antepartum prophylaxis has been given, the intrapartum and postpartum components of complex regimens can still be given. This is the preferred option in this situation, rather than SD NVP regimens. ZDV to infants should be given for 4 weeks.

² If **conditions to deliver the intervention exists**, a seven-day tail of ZDV + 3TC given to the mother after delivery should be given to reduce the emergence of NVP resistance.

³ If **the mother receives less than 4 weeks of ZDV** during pregnancy, infant ZDV dosing should be extended to 4 weeks

⁴If possible, ZDV syrup should be added to the infant regimen for 4 weeks in the dosage of 4 mg/kg twice daily

III. DOSAGES FOR COMMON HAART DRUGS IN PREGNANT WOMEN

Drug	Formulation	Dose	Adverse events
Zidovudine (ZDV or AZT)	300 mg tablet	300 mg bid	Anemia, neutropenia, GI intolerance, headache, insomnia, myopathy, lactic acidosis (rare)
Lamivudine (3TC)	150 mg tablet	150 mg bid	Minimal toxicity Lactic acidosis with hepatic steatosis (rare)
Stavudine (d4T)	30 mg capsule	30 mg bid	Pancreatitis, peripheral neuropathy, lactic acidosis with hepatic steatosis (rare)
Nevirapine (NVP)	200 mg tablet	200 mg od for 14 days, then 200 mg bid	Rashes, Stevens-Johnson's Syndrome, hepatitis, life-threatening hepatotoxicity
Efavirenz (EFV)	200 mg capsule	600 mg od at bed-time	Dizziness, somnolence, insomnia, confusion, agitation, elevations in liver enzymes, skin rash

ANNEX 13

USEFUL INTERNET LINKS

<http://www.who.int/hiv/en/>
<http://www.who.int/3by5/about/en/>
http://www.who.int/3by5/publications/documents/arv_guidelines/en/
http://www.who.int/hiv/pub/prev_care/pub18/en/
<http://www.who.int/hiv/pub/mtct/guidelines/en/>
<http://www.unaids.org>

<http://www.who.int/medicines>
<http://www.medscape.com/home/topics/aids/aids.html>
<http://www.aidsinfo.nih.gov/guidelines/>

<http://www.cdc.gov/hiv/treatment.htm>
<http://www.fda.gov/oashi/aids/hiv.html>
<http://www.aidsinfo.nih.gov>
<http://www.clinicaloptions.com/hiv.aspx>
<http://www.who.int/child-adolescent-health/publications/pubimci.htm>
<http://www.bayloraids.org>
<http://www.hopkins-aids.edu/>
<http://hivinsite.ucsf.edu/insite>
<http://www.aidsmap.com>
<http://www.aidsmeds.com/>
<http://aids.org>

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- HIV Curriculum for the Health Professional, Baylor International Pediatric AIDS Initiative, 3rd ed., 2006.
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- Pocketbook of Hospital Care for Children – Guidelines for the management of common illnesses with limited resources. WHO 2005.

