

Integrated Management of Childhood Illness (IMCI)

**Manual on
Paediatric HIV Care
and Treatment
for District Hospitals**



**Departments of Child and Adolescent Health and Development
(CAH) and HIV/AIDS**

Manual on Paediatric HIV Care and Treatment for District Hospitals



**World Health
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Development Process

HIV is increasingly affecting the health and welfare of children and undermining hard-won gains in child survival in some of the highly affected countries. Recent estimates from UNAIDS suggest that, globally, about 2.1 million children younger than 15 years of age have HIV. The roll out of paediatric HIV care and treatment is faced with three challenges: lack of appropriate paediatric ARV formulations, delayed infant HIV diagnosis, and lack of skills of health professionals to manage cases. The manual is expected to address the third challenge. It is an addendum to the “Pocket book of Hospital Care for Children,” as well as to IMAI and IMCI guidelines. WHO initiated the collaborative development of this manual because existing guidelines, including the “Pocket Book of Hospital care of Children,” were found inadequate to provide specific guidance for the complex management of paediatric HIV at district hospitals.

The Department of Child and Adolescent Health and Development, in collaboration with the HIV /AIDS department, planned the development of several second-level or referral level manuals, including the paediatric addendum, during 2006. The materials are targeted at doctors, but can be used by clinical officers or experienced nurse clinicians in some settings. The paediatric manual is designed to guide management on paediatric ART and opportunistic infections. It is not designed to teach tertiary level care, but to support care in the health centres and beyond.

The first technical consultation took place from February 27-March 3, 2006 where experts of different organizations contributed to the initial outline of the manual. The participants were selected from different regions of the world and represented important players in the area of paediatric HIV. The experts used existing WHO guidelines, other published and unpublished materials, and their own professional experiences to shape the manual.

The following steps were taken mostly on consensus regarding manual contents:

- Agree on a minimum competency list for second-level care and primary-level care
- Agree from which existing policies and guidelines the content will come
- Distribute tasks to small groups to draft the first chapters
- Circulate first draft among meeting participants for comments, and develop second draft accordingly.

A second technical consultation was organized from 17-19 October, 2006, using the same experts to review the draft chapters and further refine them. This consultation’s primary objective was to simplify the manual and make it reader-friendly without compromising quality.

Furthermore, recommendations from the following 2010 WHO guidelines were recently incorporated:

1. Antiretroviral therapy for HIV infection in infants and children: Towards universal access. Recommendations for a public health approach: 2010 revision.
2. WHO recommendations on the diagnosis of HIV infection in infants and children. 2010 revision.
3. Guidelines for intensified tuberculosis case finding and isoniazid preventive therapy for people living with HIV in resource constrained settings. 2011.
4. Guidelines on HIV and infant feeding 2010. Principles and recommendations for infant feeding in the context of HIV and a summary of evidence.
5. WHO recommendations on management of pneumonia and diarrhoea in HIV-infected infants and children. 2010.

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Duke Gyamerah contributed to the graphic design and layout, and Megan Towle for editing the manual.

Review by date: The manual will need to be revised during 2013 -2015 when new significant research results come about that call for change of the new WHO recommendations. CAH will initiate the revision of the manual.

Introduction to manual

This is a manual for use by doctors, middle-level practitioners (e.g. clinical officers and senior nurses), and other senior health workers who are responsible for the care of young children in developing countries at the first referral level, and who manage HIV-infected children in district hospitals. The manual is not intended for tertiary hospital management. It presents up-to-date clinical guidelines based on a review by subject experts of published evidence for both inpatient and outpatient care in small hospitals, where basic laboratory facilities, essential drugs, and inexpensive medicines are available. The manual is developed by WHO and partners based on evidence-based normative guidelines and a thorough review of field experience with HIV/AIDS treatment provision in resource poor settings. The field of paediatric ART is a fast-changing one. It is therefore planned to revise the manual based on new research, as well as feedback on its use from countries.

The main purpose of the manual is to contribute to universal access to care, treatment, and prevention for HIV/AIDS. HIV is increasingly affecting the health and welfare of children and undermining hard-won gains in child survival in some of the highly affected countries. Recent estimates from UNAIDS suggest that, globally, about 2.1 million children younger than 15 years of age have HIV. In 2009, an estimated 370 000 children were newly infected, mainly through mother-to-child transmission, of whom an estimated half will die without early interventions. Many of the 280 000 children who died in 2009 never received an HIV diagnosis or entered into HIV care. As countries move towards universal access with the decentralization of HIV care, treatment, and prevention for HIV/AIDS, the WHO needs to support them with the tools necessary to improve skills of health care providers at district hospital and health centre levels.

The manual addresses common presentations; the practitioner is advised to consult standard paediatric textbooks for rare presentations of HIV-infected children. The manual could be used in most areas of developing countries but may also be adapted by countries to suit their specific local circumstances. This manual is an addendum to the “Pocket Book of Hospital Care for Children” and is intended for incorporation into the pocket when it is eventually revised. The manual is also intended for use along with the adult second-level IMAI guidelines in settings where the practitioner manages both children and adults.

The manual consists of two parts. The first part deals with the management of HIV-infected children when they present with common illnesses and opportunistic infections.

Part I consist of common presentations, the differential diagnosis in terms of common illnesses, and opportunistic infections:

- Cough or difficult breathing
- Diarrhoea- acute and persistent
- Fever
- Malnutrition, anaemia and other haematological manifestations

Part II consists of HIV specific management, including antiretroviral therapy as well as chronic care, and the key differences between in children and adults.

- Diagnosis of HIV infection in infants and children
- Routine care of HIV-exposed and infected children
- Antiretroviral therapy
- Nutritional support
- Pain management
- Disclosure and psychosocial support

It also contains annexes with paediatric ART formulations and doses, as well as simplified dosing tables.

PART I

Common childhood illnesses in HIV-exposed and infected children

Chapter 1: Cough or Difficult Breathing

Chapter 2: Diarrhoea and other Gastrointestinal Conditions

Chapter 3: Fever

Chapter 4: Malnutrition, Anaemia and other Haematologic Conditions

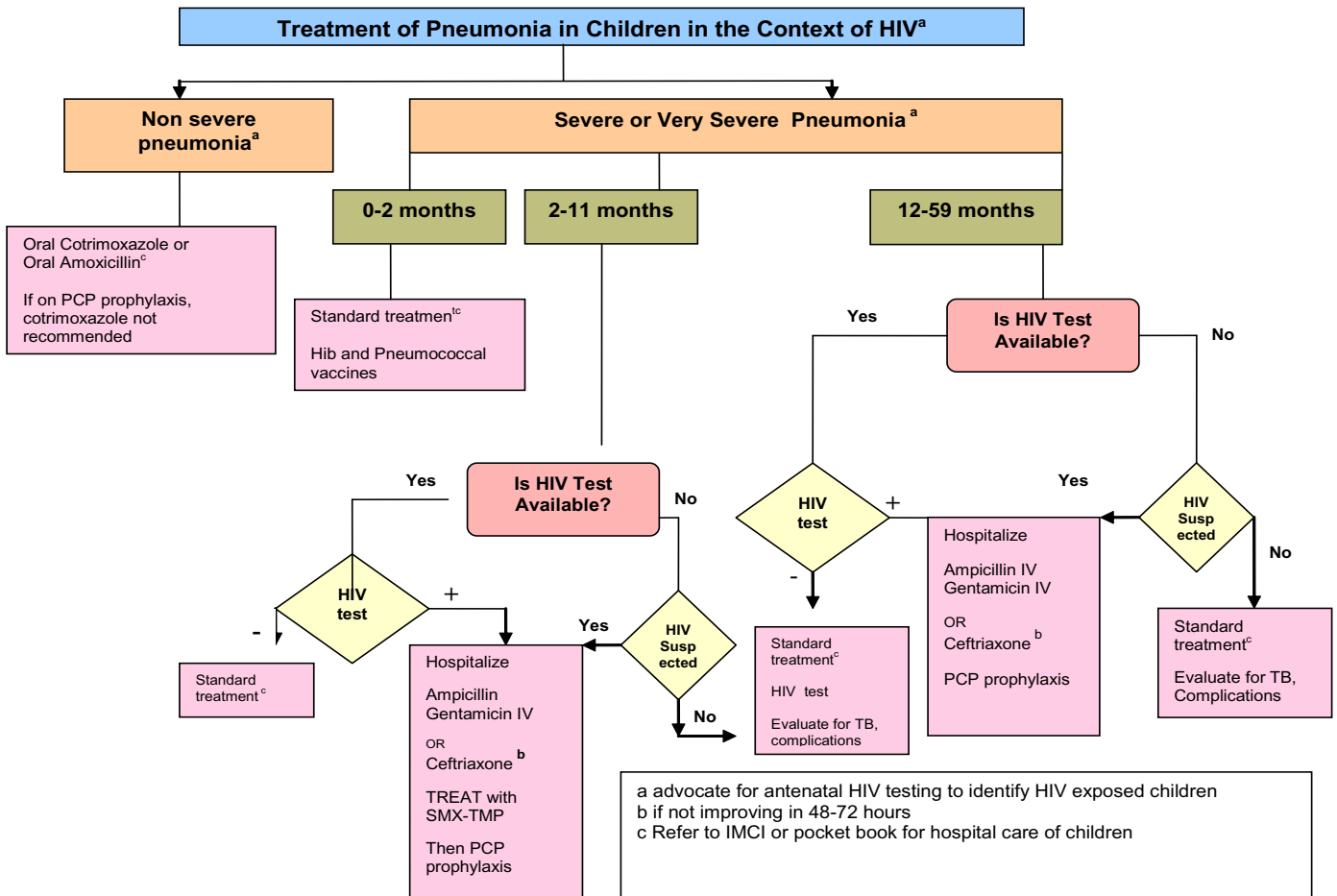
Chapter 1

Cough or difficulty breathing in HIV-exposed and HIV-infected children

1.1 Approach to cough or difficulty breathing for the HIV-infected child

Assess all HIV-infected or HIV-exposed children for danger signs according to IMCI and to chapter 1 of the pocket book of hospital care for children. Obtain history and perform examination outlined in chapter 4 of the pocket book. Antibiotic treatment of severe and very severe pneumonia in HIV-infected infants and children is based on a 2010 WHO recommendation (WHO 2010).

Follow the flow chart below that is applicable to HIV-infected or HIV-exposed infants and children.



In HIV-infected children presenting with cough or difficulty breathing, the following entities should be sought by history, examination and investigations:

Pulmonary causes:

- Pulmonary Tuberculosis,
- Pneumocystis Pneumonia
- Lymphoid Interstitial Pneumonitis
- bacterial pneumonia
- Wheezy bronchitis, bronchial asthma

Non-pulmonary causes:

- Severe anaemia, malaria, sepsis, meningitis

1.2 Differential diagnosis table of an HIV-infected or HIV-exposed child with cough or difficulty breathing

Table 1.2a: Differential Diagnosis of Child with Cough or difficulty breathing

Diagnosis	Features In Favour
Pneumocystis pneumonia (PCP)	<ul style="list-style-type: none"> ◦ Mild fever ◦ Hypoxia and degree of respiratory distress (Fast breathing, Chest retractions) disproportionate to findings on auscultation ◦ On irregular or not on routine Co-trimoxazole (TMP-SMX) prophylaxis
Lymphoid Interstitial Pneumonia LIP	<ul style="list-style-type: none"> ◦ Persistent cough with or without mild-severe exertional breathlessness. ◦ Clubbing, stunted growth, generalized lymphadenopathy, bilateral parotid enlargement, hepatosplenomegaly. ◦ Normal respiratory tract examination or localized bilateral crepitations/rhonchi. ◦ Features of cor pulmonale with evidence of right heart failure (Cough/breathlessness, raised JVP, tender hepatomegaly, bilateral pitting pedal edema, prominent 2nd heart sound on auscultation)
Pulmonary TB	<ul style="list-style-type: none"> ◦ Failure to thrive; ◦ Persistent non-remittent cough (lasting >30 days) ◦ Weight loss ◦ Persistent fever poorly responsive to appropriate antibiotics and antimalarials ◦ Decreased activity/weakness. ◦ Contact with an adult with diagnosed TB or presenting with persistent non-remittent cough, weight loss and persistent fever especially an immediate family member
Bronchiectasis	<ul style="list-style-type: none"> ◦ Persistent cough with productive purulent sputum, hemoptysis ◦ Persistent fever ◦ Clubbing, malnutrition, persistent localized coarse crepitations

1.3 Pneumonia in HIV-infected or exposed children

- HIV-infected/exposed children are at significantly increased risk of developing pneumonia
- History and diagnosis of very severe, severe and non-severe pneumonia is the same in HIV-infected/exposed children as in HIV-negative children (see section 4.2 of the Pocketbook).
- Provide same treatment to HIV-infected/exposed children with pneumonia.
- For severe and very severe pneumonia one should use a combination of Ampicillin or Crystalline Penicillin and Gentamicin as first line. If this fails use ceftriaxone as 2nd line or Ciprofloxacin and Gentamicin.
- In addition, all HIV-exposed/infected children 1-12 mo age with features of pneumonia and severe pneumonia in resource constraint settings should receive additional oral Co-trimoxazole in high doses, TMP 5 mg/kg + SMX 25 mg/kg 4 times/day for 21 days.
- If bacterial pneumonia, response is fast within 3-5 days. Delayed responses only after 5-7 days would favour PCP though other disorders (Foreign body, complicated bacterial pneumonias, asthma, Tuberculosis, inappropriate antibiotics, resistant organisms, underlying LIP, bronchiectasis, etc.) need to be evaluated as usual.

1.4 PCP (*Pneumocystis jiroveci* pneumonia)

If untreated, mortality due to *Pneumocystis jiroveci* (previously *P. carinii*) Pneumonia can be as high as 100%. Therefore it remains imperative to have a high index of suspicion for PCP and to diagnose and treat as early as possible.

- PCP pneumonia is one of the criteria for WHO Clinical Stage 4.
- Response usually takes more than 5 - 7 days of appropriate high dose CTX therapy.

Diagnosis

Suspect PCP in all HIV-infected/exposed children but especially in

- any HIV-infected/exposed infant <12 mo
- an HIV-infected/exposed infant or child irregularly or not on Cotrimoxazole prophylaxis
- in children >12 mo with CD4/CD4% levels of severe immunosuppression

Symptoms

- Subacute or acute onset of non-productive cough and difficulty breathing
- Fever (usually mild)

Signs

- Severe respiratory distress (tachypnea, chest indrawing, hypoxia etc), but disproportionate to findings on auscultation (which usually shows normal breath sounds or bilateral crepitations/rhonchi)
- a drop in Oxygen Saturation on pulse oximeter following exertion.

Chest X-Ray will be falsely negative in 10-20% of proven PCP and will typically show a bilateral diffuse interstitial reticulo-granular (“ground glass”) pattern with no hilar lymphnodes or effusions. PCP may also present with pneumothorax.

Management

1. Co-trimoxazole (Trimethoprim/Sulphamethoxazole combination) High Dose

In settings where HIV prevalence is high, and therefore PCP a most likely cause of pneumonia, only infants who present with features of severe and very severe pneumonia should be given

cotrimoxazole, the empiric treatment for PCP. Cotrimoxazole should not be used for treatment of pneumonia in children older than 12 months, as the chances of severe pneumonia being due to PCP is very small.

- The dose is trimethoprim 5 mg/kg and sulphamethoxazole 25 mg/kg 4 times per day by mouth; minimum duration 21 days;
- If IV route is chosen, 15 mg/kg/day of trimethoprim and 75 mg/kg/day sulphamethoxazole is recommended.
- If there is a severe drug reaction or a history of severe drug reaction to sulphamethoxazole, give TMP 5 mg/kg/dose, 4 times per day PO + Dapsone 100 mg/day PO x 21 days.

2. Corticosteroids (Prednisolone)

Even though the evidence is of low quality, there may be some benefits of using steroids in PCP infected children with:

- severe respiratory distress, with or without IMCI danger signs
- or with $pO_2 < 70$ mmHg in room air
- or A-a gradient > 35 mmHg

Dose:

Oral Prednisolone 0.5 mg/kg/dose, twice daily x 5 days then 0.25 mg/kg/dose, twice daily x 5 days then 0.25 mg/kg/dose, once daily x 5 days.

3. Oxygen

Oxygen should be administered if the child is in respiratory failure (apneic, cyanosed, altered sensorium, bradypneic, jaw breathing, etc.), then oxygen delivery must be optimized and controlled either by intubation or self-inflating bag mask or face mask ventilation where appropriate and feasible.

4. CTX Prophylaxis

CTX prophylaxis should be given to:

- All HIV-exposed from 6 weeks age and should be continued until the HIV infection is confirmed to be absent.
- All HIV-infected children
- Children with a history of PCP
- Children with severe immunosuppression based on CD4.

The CTX prophylaxis dose is based on a standard Trimethoprim dose of 6-8 mg/kg/day once a day. Serious side effects are rare to CTX prophylaxis.

N.B. Details on co-trimoxazole prophylaxis dosages are available in part II.

5. ART

PCP pneumonia is a stage 4 clinical disease – start ART as appropriate (See pages 47 and 71 for indications on when to start ART).

1.5 Lymphoid Interstitial Pneumonitis (LIP)

LIP is a lymphoproliferative, non-infectious pulmonary disorder that is characterized by diffuse infiltration of CD4 lymphocytes, plasma cells, and histiocytes in alveolar septa and along the lymphatics. It is most common in children infected with HIV, especially those aged >2-3 years. Since it is a clinical stage 3 criterion, ART should be started.

Diagnosis

Suspect LIP in any HIV-infected child who has the features below, and obtain a CXR to confirm diagnosis.

Suspect LIP if a child does not respond, or if CXR findings persist and worsen despite appropriate antibacterial and anti-tuberculosis treatment.

Consider LIP in any HIV-exposed/infected child (especially if aged >2-3 years) who is either:

- asymptomatic (but with persistent radiological features) or
- symptomatic with insidious onset of mild but persistent cough, with or without exertional dyspnoea, and breathing difficulty and has:
 - Clubbing, stunted growth, generalized lymphadenopathy, bilateral parotid enlargement,
 - Features of Cor Pulmonale (Cough/shortness of breath, raised JVP, tender hepatomegaly, bilateral pitting pedal oedema, prominent 2nd heart sound) and
 - Hypoxia (Pulse oximeter saturations less than 90%) in whom
 - Chest auscultation
 - May be normal or have
 - Diffuse crepitations or rhonchi.

If possible, obtain a CXR. Suspect LIP if the CXR shows:

- Persistent bilateral reticulonodular interstitial infiltrates prominent in lower lobes or
- Reticular or finely reticulo-nodular interstitial opacities with nodules <3 mm or
- Coarse reticulo nodular opacities with nodules 3-5mm or
- One patchy alveolar opacity; or, a focal alveolar consolidation or
- Persistent hyperinflation or isolated severe bullous lung disease.

Management

1. Bronchodilators:

- Useful in mild-moderate symptomatic children.

2. Corticosteroids (Oral Prednisolone)

- Intermittent Steroids
 - for mild-moderate symptomatic children.
- Long term Steroids
 - when there is persistent hypoxia, exertional dyspnea, or tachypnea. A simple regimen is oral prednisolone 1 mg/kg/dose, three times per day, for 4 weeks then slow taper (alternative days) till hypoxemia resolves and child is relatively asymptomatic. Discontinue if there is no response by 4-6 months, with an appropriate tapering dose.

1.6 Pulmonary Tuberculosis in HIV-infected/exposed children

As the reported seroprevalence of HIV in children with TB ranges from 10 to 60%, it is important to consider TB in a child with proven or suspected HIV. Similarly, the risk of developing TB disease in HIV-infected children in a TB endemic setting is over 20 times higher than in HIV-uninfected children. This explains the high prevalence of HIV infection in children with TB in TB/HIV endemic regions, and the potential of antiretroviral therapy (ART) for reducing the risk of TB.

The clinical presentation of TB in children with suspected or proven HIV can be the same as in HIV-negative children (see, page 102 in the Pocketbook), except for the following points:

- HIV-infected children have an increased risk of developing primary progressive TB because of the associated immune suppression.
- TB tends to progress more rapidly
- Extrapulmonary TB is seen more often in HIV-infected children.
- There is a higher case fatality rate for children with TB and HIV.
- A substantial proportion of deaths in children with TB/HIV occur in the first two months following the commencement of TB treatment
- Diagnosis of TB in an HIV-infected child is more difficult since:
 - The symptoms are often non-specific and may overlap with symptoms of HIV disease itself and other pulmonary manifestations of HIV like PCP, bacterial pneumonia, and LIP.
 - An HIV-infected child is more likely to have a negative skin tuberculin test

Diagnosis

TB screening, prevention, and treatment must be an integral part of early HIV diagnosis in children, which is expanding as part of HIV prevention, care, and treatment. Infants and children living with HIV should routinely be screened for TB, whether or not they are receiving TB prophylaxis or ART as a standard part of their clinical care. It goes without saying that HIV prevention should, when possible, be focused on the family as a whole. Assessing parents and other caretakers for HIV and referring them for treatment and other care could be life-saving for the child.

Look for TB in all children with suspected or confirmed HIV infection. Suspect TB if an HIV-infected child presents with symptoms or signs of TB (see page 102, "Diagnosis").

Investigations

Investigation	Comment
Careful history of TB contact	The infant or child's history of contact with someone with TB (regardless of the type of TB disease) within the home is particularly important, and should motivate the health care worker to screen for TB in the child and among the other family members. History of TB contact is especially important due to poor sensitivity of TST to identify TB infection.
Careful history of symptoms.	Lower specificity: clinical overlap between symptoms of TB and HIV Children living with HIV who have any one of poor weight gain, fever, current cough or contact history with a TB case may have TB and should be evaluated for TB and other conditions. Children living with HIV who do not have poor weight gain,* fever, or current cough are unlikely to have active tuberculosis TB and should be offered IPT regardless of their age

Investigations

Investigation	Comment
Tuberculin Skin Test TST (Mantoux)	<p>Positive when > 5 mm after 48-72 hrs with or without a BCG scar in an HIV infected child. A positive Mantoux test supports the diagnosis, but a negative test does not rule out tuberculosis; a Mantoux test can be falsely negative due to HIV induced anergy.</p> <p>Although a positive TST may indicate infection with mycobacteria, usually <i>Mycobacterium tuberculosis</i>, it is not a reliable marker of TB disease activity.</p> <p>Variable sensitivity is the main limitation of TST in the diagnosis of TB in HIV-infected children. Important clinical causes of false negative results include: severe malnutrition, severe TB disease, and HIV infection. Therefore in settings where it is available, TST may be used in the diagnosis of active TB in children, and also may have a role in screening for latent TB.</p>
Chest X-ray	<p>Variable: normal, non-specific infiltrates or specific: miliary mottling of lung fields; infiltration associated with hilar and/or paratracheal lymphadenopathy; persistent non-resolving features and radiological opacities in spite of an adequate antibiotic trial.</p>
Zeihl-Nielson Stain for Acid Fast Bacilli	<p>Sputum or sputum induced by saline nebulization or gastric aspirate, collected in equal quantity of sodium bicarbonate. Early morning samples, at least 3 consecutive samples to be sent to laboratory irrespective of age.</p>
Absolute CD4 and CD4%	<p>In both adults and children, Pulmonary TB and TB adenitis in HIV positive individuals are WHO Stage 3 Disease while Extra-pulmonary TB is a Stage 4 Disease. All patients with HIV/TB Co-infection should be given ART.</p>

Many times the diagnosis is presumptive, based on a constellation of history of contact, symptoms, signs, and suggestive findings on investigations.

Management

Prevention: important public health measures are the identification and treatment of undiagnosed TB cases among caretakers, and early ART in eligible caretakers and children to prevent TB.

1. Anti-Tuberculosis Therapy (ATT):

- Please refer to section on ART for co-administration of ATT and ART.
- In treating children with HIV/TB coinfection, use national guidelines for treatment of tuberculosis. DOTS is the recommended strategy. Most guidelines recommend that TB in HIV-infected children should be treated with a 6-month Rifampicin-containing regimen, the same in HIV-uninfected children, to reduce the risk of relapse. If there is poor response to therapy, consider alternative diagnosis and assess for causes for failure: poor drug compliance, poor drug absorption, and drug resistance. To reduce recurrence, extend the duration of treatment to 9-12 months if clinical response is inadequate.

a. Problems of simultaneous ATT& ART

- Drug interaction: Rifampicin interacts with metabolism of Nevirapine and Lopinavir & decreases blood levels of both

- Higher risk of side effects like hepatitis, skin rashes, peripheral neuritis
 - Increased pill burden interfering with adherence
- b. Approach to treatment of combined TB and HIV infection:
- Priority is to treat TB first
 - Start ART as soon as tolerated in the first 8 weeks of TB treatment, irrespective of the CD4 count and clinical stage.
 - The preferred first-line regimen for children under 3 years who are taking rifampicin-containing regimen is: 2NRTIs +NVP or a triple NRTI regimen.
 - Preferred first-line regimen for children 3 years old and above who are taking rifampicin-containing regimen for TB is: RTIs +EFV.
 - Preferred first-line ARV for children under 2 years of age who (a) have been exposed to NVP and (b) are taking a rifampicin-containing regimen for TB is a triple NRTI.

2. Co-trimoxazole Prophylaxis

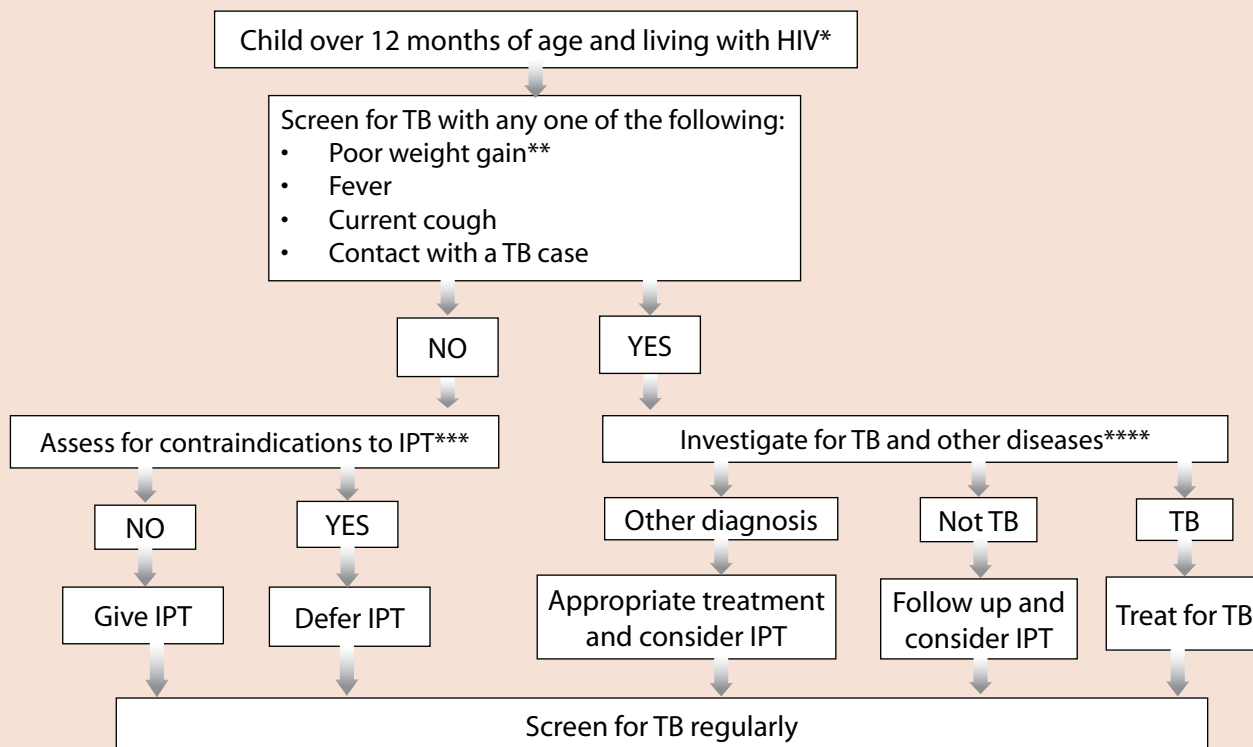
Standard recommendations for CTX prophylaxis (Refer to the section) must be followed.

3. Family Screening

Family screening for tuberculosis is mandatory to actively detect all potential contact cases, especially among immediate family members and other siblings.

4. Isoniazid (INH) Preventive Therapy (IPT)

5. An HIV-positive infant or child with no evidence of TB, especially in resource limited settings with high prevalence of TB, should be given INH preventive therapy to reduce the incidence of TB and death among these children. *INH should be given for 6 months at a dose of 10mgs/kg/day to a maximum of 300mgs per day.* Countries are encouraged to review the WHO guidelines and use them for reducing the incidence of TB and improving survival among HIV-infected children.
 - The guidelines for intensified tuberculosis case finding and isoniazid preventive therapy for people living with HIV in resource limited settings recommend:
 - HIV-positive children over 12 months of age who are unlikely to have active TB on symptom-based screening, and have no contact with a TB case, should receive 6 months of INH preventive therapy (10mg/kg) as part of a comprehensive package of HIV care.
 - Children under 12 months of age, only those children who have contact with a TB case and who are evaluated for TB (using investigations) should receive 6 months IPT if the evaluation shows no TB disease.
 - All HIV-positive children that successfully complete treatment for TB disease should receive INH for an additional 6 months.
 - According to the WHO there is no data regarding the efficacy of IPT for children stratified by degree of immunosuppression. However due to biological plausibility to extrapolate what is known for adults and adolescents to children, the WHO does conditionally recommend the combined use of IPT with ART for all children, and that ART should not be delayed while starting or completing a course of IPT.

Figure 1. Algorithm for TB screening in children more than one year old and living with HIV

* All children and infants less than one year old should be provided with IPT if they have household contact history with a TB case.

** Poor weight gain is defined as reported weight loss, or very low weight (weight-for-age less than -3 z-score), or underweight (weight-for-age less than -2 z-score), or confirmed weight loss (>5%) since the last visit, or growth curve flattening

*** Contraindications include: active hepatitis (acute or chronic) and symptoms of peripheral neuropathy. Past history of TB should not be a contraindication for starting IPT. Although not a requirement to initiate IPT, TST may be done as part of eligibility screening in some settings.

**** Investigations for TB must be done in accordance to existing national guidelines

According to the WHO guidelines, TST is not required to initiate IPT in children and should not be routinely used as part of the process to determine eligibility for IPT. However it has been noted that TST may provide important additional information in assessing a child with suspected TB, especially if there is no positive contact history.

1.7 Bronchiectasis

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

Diagnosis

Symptoms

- Persistent Cough
- Copious purulent sputum production (young children usually swallow the sputum and vomit after bouts of cough).
- Hemoptysis
- Fever (with infectious exacerbations)
- Anorexia
- Failure to thrive

Signs

- Clubbing
- Crepitations localized to the affected area
- Wheeze or rhonchi
- Exertional dyspnea and hypoxemia in severe cases

District level investigations that may support a diagnosis are listed below:

Investigation	Findings
Chest X-ray	Loss of broncho-vascular markings, crowding of bronchi, and loss of lung volume. In more severe forms, cystic spaces, occasionally with air-fluid levels and honeycombing, may occur. Compensatory emphysema of unaffected lung may be seen.
Sputum for Gram stain and culture	Deep throat swab or induced sputum specimens are often difficult to collect in children but may be of assistance in acute exacerbations.

Bronchiectasis should be suspected in the presence of chronic cough, especially with large quantities of purulent sputum associated with postural variations; existing malnutrition; clubbing; and persistent coarse crepitations, and especially if localized it points to a localized chronic suppurative bronchiectasis. Persistent radiological shadows, especially with signs of cysts or honey-combing, support this diagnosis. An essential first step is to rule out foreign body inhalation, aspirations, and complications of past measles or pertussis. Pulmonary TB and LIP may also present as bronchiectasis. Sputum or gastric aspirates for AFB may help in diagnosis of TB bronchiectasis.

Management

- 1. Chest physiotherapy (postural drainage)**
- 2. Bronchodilators**
- 3. Antibiotics**

It is not unusual if 2-4 weeks of parenteral antibiotics are necessary to adequately manage acute exacerbations. The first choice may be Ampicillin (50 mg/kg IM every 6 hours) and Gentamicin (7.5 mg/kg IM once a day)—remembering that gram negative coverage is essential, and antibiotic choice may be changed when identifying organisms and sensitivity where feasible.

- 4. Steroids**

Indicated for an underlying LIP only after treating secondary bacterial infections aggressively and after ruling out or adequately treating pulmonary Tuberculosis.

- 5. HAART**

Start ART, as bronchiectasis is a WHO Clinical Stage 3 criterion.

- 6. Surgical Resection (segmental or lobar)**

If the symptoms are severe or refractory to medical management this would be indicated.

1.8 Cytomegalovirus (CMV) Infection

CMV infections that occur in HIV infected immunocompromised children are usually pneumonia, colitis, meningoencephalitis, or retinitis. CMV belongs to the Herpesviridae DNA family that can be transmitted by direct person-to-person contact, maternal-fetal/child transmission, and through blood product transfusions.

Diagnosis

CMV interstitial Pneumonia

Symptoms

- Fever
- Dry and non productive cough
- Dyspnea, retractions, wheeze, hypoxia

Signs

- Febrile
- Fast breathing, lower chest indrawing
- Rhonchi, scattered crepitations
- Fundus: chorioretinitis (if disseminated CMV infection)

CMV Esophagitis/GastroenteritisSymptoms

- Nausea, vomiting, diarrhea, difficult swallowing
- Abdominal pain
- Gastrointestinal bleeds
- Failure to thrive

Signs

- Abdominal tenderness – epigastrium
- Of Malnutrition

CMV RetinitisSymptoms

- Asymptomatic
- Blurred vision, , blindness
- Strabismus, failure to fix

Signs-Fundus

- White, perivascular infiltrates and hemorrhages
- Decreased visual acuity, visual field defects
- Necrotic, rapidly progressive ‘cottage cheese’ retinitis or ‘ketchup’ retinitis

District level investigations that may support a diagnosis are listed below:

Investigation	Comment
Chest X-ray (Interstitial Pneumonia)	Diffuse and interstitial infiltrates. Also described are peribronchial infiltrates with hyperinflation and nodular pulmonary infiltrates.
Gastrointestinal Endoscopy (Esophagitis/Gastroenteritis)	Linear, localized or punctate ulcers. Hemorrhagic or diffuse erosions in more severe forms. Biopsies showing cytomegalic inclusion cells are diagnostic.
CMV Antibodies	Seroconversion, but unless IgM elevated may not be indicative of active infectious process
CD4 Count/ CD4 %	Useful if CD4 below severe immunosuppression threshold.

Management

- Oxygen
- IV fluids,
- Antibiotics for associated bacterial infections.
- Oral Rehydration for diarrhoea
- ART
- Antiviral
 - CMV pneumonitis: Ganciclovir 7.5 mg/kg twice daily x 14 d.
 - CMV gastroenteritis: Ganciclovir 7.5 mg/kg twice daily x 14 d.
 - CMV retinitis: Ganciclovir 7.5 mg/kg twice daily x 14-21 d. Requires lifetime suppressive therapy.

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Chapter 2

Diarrhoea and other gastrointestinal problems in HIV-infected children

Diarrhoea is probably the most common manifestation of HIV in children, especially in infancy. While most children have acute diarrhoea, some will present with persistent (or chronic) diarrhoea. Persistent diarrhoea is associated with an 11-fold increase of risk of death in HIV-infected infants. Therefore, proper care of HIV-infected children with persistent diarrhoea is essential. The most important aspect of managing diarrhoea is managing dehydration with ORT or IV infusion, depending on the dehydration status (Refer to IMCI guidelines and to chapter 5 of the WHO Pocketbook). HIV-infected children with dehydration should be managed the same as non-HIV infected, including management of any associated malnutrition. In addition, the clinician should treat the underlying cause if there is dysentery (loose stool containing blood), bloody diarrhoea (suggestive of shigella), or if the diarrhoea is suggestive of cholera or giardia.

As in immunocompetent children, the Clinical History and examination must answer the following questions:

- i. Are there danger signs? (IMCI – Ask Look Feel)
- ii. Is there Diarrhoea? (Frequency of stools, consistency of stools)
- iii. Is there Persistent Diarrhoea? (diarrhoea \geq 14 days)
- iv. Is the child dehydrated? (IMCI - Ask Look Feel)
- v. Is there blood in stools? (Diarrhoea containing blood)

2.1 Diarrhoea

Acute diarrhoea should be managed the same as in non-HIV infected children, though as mentioned, HIV-infected children are more prone to persistent diarrhoea.

2.1.1 Persistent Diarrhoea in HIV-infected children

Persistent or chronic diarrhoea is described as diarrhoea (loose or watery stools, \geq 3 times a day) of 14 days or more in duration. The differential diagnosis of persistent diarrhoea in HIV-infected children includes opportunistic infections (viral, bacterial, protozoal, parasites), secondary conditions (allergies, lactose intolerance), HIV-related medication side effects, and nutritional deficiencies. In resource-constrained settings, the available investigations do not usually identify specific pathogens and aetiologies. Therefore, an empirical treatment approach is needed.

The presence of unexplained persistent diarrhoea places an HIV-infected child into WHO Stage 3 disease, thereby making the child eligible for ART.

Appropriate management of diarrhoea in the chronically malnourished child is particularly critical:

- Severely malnourished children have more than an 8-fold risk for mortality than normally nourished children.
- Infectious diseases are the primary cause of mortality in the malnourished

- Undernourishment compromises growth and development, resistance to infections and recovering from disease
- Severe protein energy malnutrition is associated with the depletion of the haematological and lymphocyte subsets, and this depletion is exacerbated by HIV- 1 infection. Cell-mediated immunosuppression is more marked in non-oedematous severe malnutrition, regardless of the HIV status.
- CD4+ percentages are lower in both HIV-positive and HIV-negative children without oedema than in children with oedema.
- Severe malnutrition complicated by diarrhoeal dehydration is commonly seen in tropical and subtropical countries
- Therapy should be adapted to meet the specific disturbances in the dehydrated AND malnourished infant.
- Serum sodium, potassium, zinc, and magnesium levels tend to be low in malnourished children. Protein levels also appear to be low.
- Calories should be provided via slow NGT feeds while replacing fluids and electrolytes through IV infusion. If appetite is poor, begin feeds via NGT early and increase over the next few days

PREVENTION: Caregivers of HIV infected children, particularly those with low CD4 counts, should pay particular attention to hygiene (hand-washing with soap before preparing food and before feeding child) and appropriate disposal of faeces. Caregivers should ensure that the child drinks boiled water, eats only thoroughly cooked meat, and eats cooked or thoroughly washed fruits and vegetables.

All HIV exposed and infected children should also receive cotrimoxazole prophylaxis to reduce morbidity and mortality from diarrhoeal diseases (WHO Guidelines on cotrimoxazole prophylaxis-2006).

Symptoms

- The presence of blood in stools and or small quantity mucoid stool, especially with tenesmus, indicates a probable **colitis**. Typical etiologies of colitis in the HIV infected patient include: Shigella, Ameobiasis, CMV, Campylobacter jejuni, and Clostridium difficile.
- Predominately explosive watery stools associated with steatorrhea, flatulence, and fat malabsorption point to **a small intestinal diarrhoea**. Possible causes include lactose intolerance, Giardia lamblia, MAC, Cryptosporidium, non-typhoid Salmonella, Microsporidia, *Isospora bella* and Campylobacter. Giardia should only be treated if laboratory evidence identifies the protozoa.

Signs

Pay particular attention and look for:

- Dehydration in a child with persistent diarrhoea (Severe Persistent Diarrhoea, page 122 of Pocketbook).
- Signs of vitamin deficiencies:
 - Vitamin A (eye changes like nyctalopia, conjunctival-corneal dryness, Bitot spots),
 - Vitamin D (features of rickets such as widened wrist joints, double malleoli, deformities of lower limbs, rachitic rosary, harrison's sulcus),
 - Vitamin E (Dry rough skin)
 - Vitamin K (ecchymosis, purpura)

- Malnutrition (see chapter 7 of Pocketbook)
- Potbelly due to lax anterior wall muscles
- Rectal prolapse
- Anal excoriations especially if erythematous and associated with explosive watery diarrhoea

Investigations

District level investigations that may support a diagnosis are listed below:

Investigation	Comment
Stool microscopy for WBCs/hpf and specific etiologies	<p><u>Stool WBC/hpf > 10</u> suggests Shigella, Entamoeba histolytica, CMV or Invasive E.coli</p> <p><u>Stool WBC/hpf 0</u> suggests normal or Cryptosporidia, Cyclospora, Giardia, MAC</p> <p><u>Specific organisms</u> may be identified such as giardia lablia and entameoba.</p>
Stool for modified ZN stain	Cryptosporidia, Cyclospora
Stool pH and reducing substances	Stool pH < 5.5 and reducing substances positive suggests lactose intolerance
Stool for ova and cysts	Helminthiasis, Entamoeba Histolytica
CD4 Count/ CD4 %	<p><u>CD4 < 50/cmm:</u> consider Disseminated CMV, Disseminated MAC</p> <p><u>CD4 < 100/cmm:</u> Cryptosporidiosis, chronic Microsporidiosis</p>

In resource-constrained settings, laboratories and diagnostic interventions may not be able to identify exact aetiologies. The following presentation may suggest aetiologies of diarrhoea:

- The presence of blood usually indicates the need for treatment for Shigella (in younger children).
- Persistent diarrhoea may possibly need management of lactose intolerance (low lactose intakes) and specific treatment for giardia and microsporidia.
- The presence of recurrent or prolonged antibiotic use suggests *Clostridium difficile*.
- Drug side effects (ARVs - all PIs and NRTIs except Zidovudine; Antibiotics) are known to cause diarrhoeas.
- Diarrhoeas due to systemic infections (malaria, UTI, sepsis) must be ruled out, especially in malnourished children.

Diagnosis

Since it is difficult to distinguish the different causative agents of persistent diarrhoea without stool culture an empiric approach to treatment is recommended in immunocompromised children with persistent diarrhoea.

2.1.1.1 Empiric management

1) Give the child more fluids than usual using low osmolarity ORS, to prevent dehydration.

- Assess the child with diarrhoea using IMCI (ASK, LOOK, FEEL); classify as no, some, or severe dehydration; and manage accordingly.
- Note clean water may not always be available

- Advise to drink more fluids from onset of diarrhoea
 - Advise on how to make ORS when low osmolarity ORS is not available
 - Encourage children to drink as much as possible - they may not feel thirsty so keep water by bed and encourage small regular sips
- 2) Give supplemental zinc (10 - 20 mg) to the child, every day for 10 to 14 days
- 3) Continue to feed the child to prevent malnutrition (refer the Pocketbook)
- **Encourage children to eat.** If they do not eat during the acute episode they may become malnourished or become more malnourished. **This is very important!**
 - Eat small amounts of readily digestible food
 - After an episode, where possible, advise an extra meal per day for two weeks to help with regaining weight loss
 - Temporarily avoid or change consumption of lactose-containing foods if lactose intolerance present. (see page 124 and 125 of the Pocketbook). Lactose intolerance is suspect when infants/young children predominantly on milk feeds continue to pass explosive, watery stools causing perianal erythematous excoriation very similar to perianal candidiasis. Special diets that are low in lactose or are lactose free may be indicated till the intestinal mucosa recovers.
- 4) ART as indicated
- ART and improvement in the child's immune status may be the only way to improve persistent diarrhoea. It is a recommended treatment in some cases of infectious diarrhoea, e.g cryptosporidium, MAC, microsporidium.
- 5) Multivitamins and Micronutrients
- Give daily Multivitamins and micronutrients for 2 weeks to all HIV exposed and infected children with persistent diarrhoea.
- 6) For diarrhoea with blood:
- Ciprofloxacin (15 mg/kg, 2 times/day for 3 days), OR Pivmecillinam (20 mg/kg, 4 times/day for 5 days), OR Ceftriaxone (50-100 mg/kg, once a day IM for 2-5 days), AND
 - Metronidazole (7.5 mg/kg 3 times a day for 7 days)

Hygiene

- Teach all caregivers of children with HIV to pay particular attention to personal hygiene (handwashing with soap, especially after going to the toilet, after handling stools, and before preparing food and eating), drinking boiled water, eating only thoroughly cooked meat, and eating only cooked or thoroughly washed fruits and vegetables.

If no response do stool investigations

Stool microscopy - 3 specimens on separate days

- Wet mount
- Ova and parasites stain (Giemsa)
- Modified AFB smear
- AFB smear

DO NOT use antimotility agents (Loperamide) in children.

2.2. Hepatitis in HIV-Infected child

Hepatomegaly and mildly elevated liver enzymes are common in HIV infected children, though chronic or progressive liver disease is unusual. Hepatitis could occur in children infected with HIV due to:

1. Co-infections with Virus (Hepatitis A- E, CMV, EBV)
2. Co-infections with MAC and complications of Cryptosporidia..
3. Drug toxicity
4. Fatty liver

Symptoms

- Jaundice, anorexia, nausea/vomiting, fever, right hypochondria pain, pruritus and pale-coloured stools suggest Acute Hepatitis. However, it is important to remember that children may be anicteric.
- In hepatic failure additional symptoms are: altered sensorium, irritability, altered sleep patterns, poor feeding, constructional apraxia, ascites, bleeding manifestations.
- The presence of rash, fever and systemic symptoms usually within 6 - 8 weeks of initiating potentially hepatotoxic ARVs may suggest a hypersensitivity reaction. Fast breathing may suggest lactic acidosis, especially associated with NRTIs.
- The older child may require evaluations for other causes of hepatitis: History of contact (HAV, HBV, HCV, HDV, HEV), past blood transfusions (HBV, HCV, HDV), injectable drug use (HBV, HCV), and sexual activity (HBV).

Signs

- Icterus
- Hepatomegaly or decreasing span of liver size
- In hepatic failure, ascites, asterixis, constructional apraxia, altered sensorium, abnormal reflexes, skin and mucosal bleeds.

Investigations

- Liver function tests (Total/direct serum bilirubin, Serum ALT/AST is essential). Enzymes- ALT/AST- are elevated. Decreasing levels of enzymes, when associated with rising bilirubin, may be ominous and need a clinical correlation.
- Eosinophilia (ie Hypersensitivity reaction)
- Peripheral blood smear for malaria
- HBsAg
- HCV, HAV testing
- Blood glucose
- Prothrombin Time
- Electrolytes (Na, K)

Diagnosis

The presence of jaundice (recently onset) is indicative of an acute hepatitis diagnosis. It is essential to gauge the severity of the dysfunction – ie is there hepatic encephalopathy and coagulopathy?

The recent initiation of ARVs may be a cause (eg NNRTIs, particularly NVP; or PIs, particularly Ritonavir; or NRTIs, particularly 3TC, d4T, ddI, ZDV), as drug-drug interactions may be. Another

possible cause a hepatic dysfunction to be considered is withdrawal of 3TC, FTC, or TDF in a child with HBV coinfection. Among the drug-related causes, the first suspects are ARVs, anti-TB medications (Rifampicin, INH, Pyrazinamide), and others like Fluconazole, Ketoconazole, and Co-trimoxazole. Aetiologies may be co-infections such as Viral Hepatitis (A,B,C,D,E) or Complicated Malaria.

Treatment

- Remove potentially offending medication(s) as per ARV adverse event guidelines
- Supportive Care (monitor, nutrition, rest)
- Hepatic Failure (monitor, intestinal decontamination- lactulose and neomycin, low protein intake, vitamin K, fresh frozen plasma, antibiotics, correction of dyselectrolytemia, antacids/ H2 blockers, oxygen/ ventilation)

Prevention: Vaccination with hepatitis B vaccine for parents and caretakers

2.2.1 ARV related Hepatitis

Caused by NNRTI especially NVP, or less frequently EFV; NRTIs or PIs. Symptomatic NVP-associated hepatotoxicity is very rare prior to adolescence.

Symptoms/signs

As above

Investigations

- ALT/AST:
 - **Mild** 1.25-2.5 times normal, **moderate** 2.6-5 times normal, **severe** 5.1-10 times normal, severe life threatening >10 times upper limit
- Bilirubin (after the neonatal period):
 - **Mild** 1.1-1.5, **moderate** 1.6-2.5, **severe** 2.6-5, severe life threatening >5 times upper limit of normal.

Specific ARV Management

- Determine severity based on clinical and laboratory assessment
- Evaluate concurrent medications, establish association with ARV/non-ARV medication
- Consider other disease processes
- Manage adverse event according to severity
 - Mild: Continue support and monitoring carefully
 - Moderate: Continue ART and if persistent or non improvement consider single ARV substitute.
 - Severe: Substitute the offending agent without stopping ART.
 - Severe, life threatening:
 - Discontinue all ARVs until stabilized and symptoms resolve
 - Monitor liver enzymes, bilirubin
 - Never reintroduce NVP
 - Once symptoms resolve, restart ART with substitute ARV as needed but monitoring carefully
 - Stress adherence and safeguards despite mild-moderate toxicity

2.2.2. HIV and Hepatitis B and C virus co-infections

Of the hepatotropic viruses, hepatitis B and C are the most common causes of chronic hepatitis. The hepatitis A virus causes sporadic acute infections.

With HIV, the incidence of acute and chronic hepatitis is increasing. HIV and HBV or HCV co-infections are common. HBV and HIV have several common features, including how the hepatitis B viral DNA integrates into its host genome once it enters hepatocytes. This prevents the elimination of HBV. The two viruses also have similar mechanisms for developing resistance. The three viruses are transmitted parenterally, vertically, or sexually. HCV and HBV are 10 to 100 times more infectious, respectively, than HIV on blood-to-blood contact. The probability of transmission by needle stick with HBV-contaminated blood is about 30% and for HCV 2-8%, compared to 0.3% after exposure to HIV-contaminated blood.

The most important risk factor for HIV and HBV infection in children is perinatal exposure to an HIV and HBsAg-positive mother. It is estimated that over 95% of HIV-infected individuals (adults and children) have been infected with HBV. About 10-15% of these progress to chronic HBV infection, defined as positive HBsAg for more than 6 months. The risk of HBV infection leading to a chronic infection is higher in children than in adults. In contrast, HCV is poorly transmitted sexually and perinatally in immunocompetent individuals. However, HIV and HCV co-infection is associated with significantly higher levels of hepatitis C viraemia, which increases the risk of perinatal and sexual transmission. An estimated 30-50% of HIV-infected individuals are also infected with HCV. Over 90% of these cases progress to chronic hepatitis, defined by presence of HCV RNA in circulation. In view of the above risk factors, all HIV-infected persons should be evaluated for co-infection with a hepatitis virus and offered anti-hepatitis treatment as appropriate.

Clinical Course and Effect of HIV on HBV and HCV co-infections

Many cases of HBV infection are asymptomatic, especially in children. This is demonstrated by the high proportion of persons who have no history of acute hepatitis, but have high carriage rate of serum markers. In the symptomatic cases, clinical features in the co-infected are similar to those non-HIV-infected, including: elevation of alanine aminotransferase (ALT) levels, malaise, lethargy, anorexia, and jaundice. Some of the children may present with enlarged lymph nodes, joint and skin disorders, anaemia, and kidney complications.

HIV infection accelerates the progression of liver disease during HBV or HCV infection. The risk of liver fibrosis, cirrhosis, Hepatocellular Carcinoma (HCC), and liver-associated mortality is significantly increased in the co-infected. On the other hand, HBV and HCV infections have not been conclusively shown to affect the progression of HIV infection. However, HBV and HCV increase hepatotoxicity from ARV medicines, especially the nucleosides such as stavudine (d4T), didanosine (ddI) and zidovudine (AZT). These substances should be avoided or used with caution in co-infected patients.

Diagnosis

The diagnostic tests used in co-infected patients for HIV, HBV or HCV are the same as for the mono infected patients. Rapid antibody and virological tests are used for diagnosis of HIV in co-infected patients. HBV infection is detected by the presence of HBsAg and or HBeAg, and HCV infection is detected by the presence of HCV antibodies (anti-HCV) and HCV RNA.

Treatment

HBV treatment in HIV co-infected patients is problematic due to the following reasons:

- There is scarcity of controlled trials and therefore lack of evidence-based treatment guidelines
- Weakened immune function impairs treatment success

- Incorporation of HBV DNA in the host genome makes eradication of HBV impossible with the current medicines
- HBV exacerbates hepatotoxicity from ARV medicines
- Overlap in therapeutic agents for both viruses
- HIV and HBV potential to develop drug resistance

The current goals for treating HBV in HIV positive patients are to:

- Achieve sero-conversion from HBeAg to anti-HBe
- Achieve a complete and long-term suppression of HBV DNA
- Achieve normalization of transaminases
- Ensure improvement of liver histology
- Prevent the development of HCC
- Reduce the risk of HBV transmission
- Reduce the risk of ART induced hepatotoxicity.

Treatment should be offered to patients with the following characteristics:

- HBeAg positive
- HBV DNA (>20,000 IU/mL)
- Consistently elevated ALT
- Significant inflammation of the liver as seen on liver biopsy or on use of imaging techniques such as elastometry (Fibroscan), a non invasive method of determining the status of liver architecture.

Type of treatment

Available treatment options for HBV and HIV co-infections include interferons, nucleoside, and nucleotide agents. The interferons are expensive and not easily available. ARV medicines are therefore recommended for treating HIV/HBV co-infections. The nucleoside analogues effective against HBV are Lamivudine (3TC), Emtricitabine (FTC), and Entecavir (ETV); of these, the most available in countries are 3TC and FTC. Nucleotide analogues effective against HBV are Tenofovir (TDF) and Adefovir (ADV), of which TDF is relatively more available.

A combination of TDF and FTC plus NVP is recommended for treating HIV/HBV co-infection.

HCV

The goal of therapy in HCV infection is to achieve **sustained virologic response**. This is defined as an undetectable level of serum HCV RNA six (6) months after completing treatment. A sustained virologic response during both HBV and HCV treatments is associated with the cessation of viral replication. This results in reduced liver injury and possible reversal of fibrosis, and so reduced risk of cirrhosis and hepatocellular carcinoma. The virologic response is also associated with preventing further virus transmission.

HCV has 6 genotypes (numbered 1 through 6). The response to treatment is good with genotypes 2 and 3 (>80%) and relatively less so with genotypes 1 and 4 (45-55%). Little is known about treatment response for genotypes 5 and 6. The factors associated with favourable response to treatment are:

- Genotypes 2 and 3
- Early virologic response (within 12 weeks of treatment)
- HCV RNA less than 800,000 IU/ml,

- None obese patients
- Stable HIV infection

A combination of EFV+2 NRTI is recommended for treating HIV/HCV co-infection.

Prevention

The main components of prevention include:

- Increase coverage of HBV immunization for young children
- Increase uptake of PMTCT by HIV-infected pregnant women.
- Babies born to mothers with chronic hepatitis B should receive hepatitis B immunoglobulin soon after birth, and active immunization as per the national immunization schedule.
- All HIV-infected patients with negative HBV and HAV serology should be vaccinated against these two viruses.

In addition, adult patients should be counselled on measures to prevent further transmission of the viruses such as **safer sex** and **avoidance of needle sharing**.

Those who have co-infection should be educated to avoid situations that would worsen liver disease such as **avoiding the use of herbal medicines**, many of which are hepatotoxic. Hepatotoxic drugs (e.g anti-tuberculous drugs) should be used with caution.

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Chapter 3

Fever in the HIV-Infected child

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

- Children may have acute fever lasting less than 7 days, prolonged fever greater than 7 days, or fever with focus or without focus.
- Clinical examination remains the cornerstone of assessing fever, especially in children.
- If there is fever with a focus (eg. cough, diarrhoea, urinary disturbances, seizures) refer to the appropriate IMCI/IMAI/Pocketbook sections. In addition, both the IMAI and Pocketbook have entire sections on the child with fever that also apply to HIV-infected children.
- Below we will concentrate on the approach to the child with fever and no obvious focus.

3.1 Approach to fever in an HIV-infected child

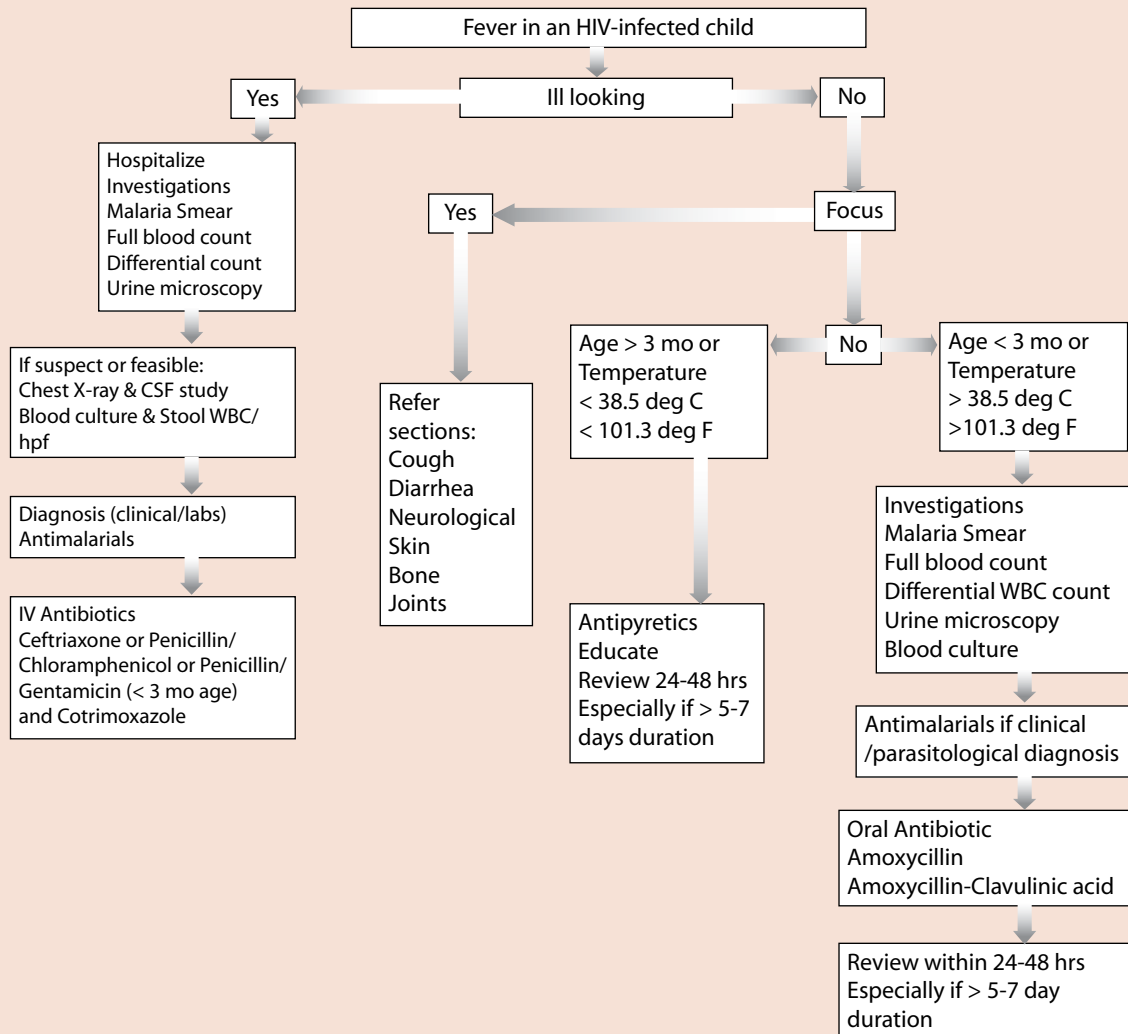
All HIV-infected children should first be assessed for danger signs, as per IMCI and Chapter 1 of the Pocketbook.

History (Ask - IMCI)

- General Danger Signs: Is the child able to drink or breastfeed? Does the child vomit everything? Has the child had convulsions?
- If the main symptom is fever (Recorded as temperature 37.5°C and above or feels hot to touch), search for the focus of infection.
 - Does the child live in or has the child recently travelled through a high risk Malaria or Dengue area?
 - What is the duration of fever?
 - Has the child had a fever and rash within the last 3 months?
 - Does the child have cough or difficult breathing?
 - Does the child have diarrhoea?
 - Does the child have ear pain or discharge?

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

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



Systemic review

Again, finding a focus to treat is the priority for treating fever. A systemic approach is essential, as multiple conditions may be present. Enquiring about the following details is crucial, as it may point to the cause of the fever.

- If the main symptom is fever? (Recorded as temperature 37.5°C and above or feels hot to touch) Refer to IMCI:
- Does the child live in, or recently travelled through, a high risk Malaria or Dengue area?
- Children in high risk Malaria areas need appropriate anti-malarial drugs based on clinical and if possible parasitological diagnosis.
- Duration of fever?
 - Fever greater than 7 days is more likely to be due to bacterial/parasitic infections rather than common viral presentations and as duration is more prolonged *Mycobacterium tuberculosis*, connective tissue disorders and malignancies become priorities.

- Has the child had a fever and rash within the last 3 months?
 - Fever associated with a cold, cough, conjunctivitis that precedes an erythematous macular-papular rash is typical of Measles that may be complicated with secondary bacterial infections and Tuberculosis.
- Does the child have cough or difficulty in breathing?
- Does the child have diarrhoea?
- Does the child have ear pain or discharge?
- Does the child have a headache, vomiting, convulsion, neurological deficits, or altered sensorium?

These symptoms are typically seen in older children with neuro-infection.

- Does the child have fever with chills, burning pain while passing urine, lower abdomen or flank pain?
 - These symptoms are difficult to determine in younger children, but indicate a urinary tract infection.
- Does the child have painful skin lesions, painful joint swellings or painful limbs?
 - Painful skin lesions suggest skin infections (eg. cellulitis) or complicated skin lesions (eg. purpura fulminans, DIC, vasculitis). Painful swollen joint(s) often suggest acute rheumatic fever, septic arthritis, or connective tissue disorders. Painful limbs may point to viral fever, myositis, pyomyositis, or osteomyelitis.
- Does the child have pain in abdomen, vomiting, diarrhoea, or yellow discoloration of eyes/urine?
 - Intestinal obstruction usually will have abdominal distention and billous vomiting. Keep in mind hepatitis, gastritis, drug side effects, and pancreatitis.
- Does the child have bony tenderness or new swellings (neck, axilla, groin, abdomen), with or without pain?
 - Diffuse bony tenderness especially with lymphadenopathy may suggest a lymphoreticular malignancy (eg. Leukemia).
- Does the child have breathlessness, swelling of both feet (bipedal oedema), bleeding gums, or non-blanching skin lesions?
 - Severe anaemia may be a symptom of congestive heart failure or thrombocytopenia, which causes bleeding manifestations involving the gums and skin. Additionally, malaria causes anaemia. Bone marrow suppression may be due to disseminated infections, drug induced aplasia, or malignancy involving the bone marrow.
- Does the child have prolonged fever greater than 2-3 weeks, night sweats or significant weight loss or contact with an adult with the same symptoms including persistent cough?
 - Tuberculosis is a high priority if prolonged fever, night sweats, or significant contact history with suspected tuberculosis. Alternatively, occult bacterial infections (eg. abscesses, pyelonephritis), malignancies, connective tissue disorders, and MAC may have features of prolonged fever and weight loss.
- What is the child's HIV status and latest absolute CD4 count or CD4%? What medications are the child currently taking, and since when—especially co-trimoxazole prophylaxis? Is the child adherent?
 - HIV infection causes atypical clinical presentations of common infections or disorders, and increases the possibility of infections by uncommon organisms. The CD4%/CD4 counts measures the degree of immunosuppression and helps to narrow down possible aetiologies (eg. In severely immunosuppressed individuals, disseminated CMV, extra-pulmonary Cryptococcus, PCP, and MAC). Regular, long-term co-trimoxazole prophylaxis makes

some diagnosis less likely (eg. PCP). While adherent to HAART, immunity will improve and hence IRIS may develop presenting as febrile illnesses (eg. Tuberculosis, CMV).

Physical Examination

- Does the child look ill?

Ill looking might involve: recent onset Irritability, resentful of being handling even by parent/guardian let alone medical team, uncomfortable or uninterested child, poorly responsive to surroundings or persons. If the parent insists that something is wrong or the child is feeding poorly, especially when it comes to liquids, it is important to take their perspective seriously.

- Vital Signs (Heart Rate, Respiratory Rate, Temperature, Blood Pressure, Sensorium)

Tachycardia may indicate circulatory failure due to sepsis. Tachypnea suggests pneumonia, septicemic shock, drug induced side effects, or cardiac failure. Temperature $> 37.5^{\circ}\text{C}$ or hypothermia suggest infections—hypothermia, the latter being more dangerous. A low blood pressure is a sign of decompensated shock. Altered sensorium may suggest neuroinfection or metabolic abnormalities or failure (circulatory or respiratory).

- Anthropometry (Weight, length/height, head circumference)

Documenting weight loss by serial weights and estimating chronic stunting due to chronic ill health by length/height measurements. Non-progressive head circumference measurements in children under 24 months or increasing head size may indicate HIV encephalopathy or hydrocephalus respectively.

- Respiratory Distress (Chest retractions, accessory muscle use, grunting, wheeze, stridor, drooling of saliva, cyanosis, apnea)

Features of respiratory illness associated with fever suggests upper or lower respiratory tract infections. The presence of cardiomegaly, gallop, and hepatomegaly suggests cardiac failure (eg. Pericarditis, cardiomyopathy, myocarditis) as a cause for respiratory distress.

- Circulatory failure (peripheral pulses, colour/temperature of extremities, capillary refill time, Blood pressure, central pulses, sensorium)

Compensated and decompensated shock or circulatory failure may occur in children with septicemia.

- General examination

- Pallor

Anemia may be due to malaria or chronic infections or malnutrition or drug induced- or infection induced- bone marrow suppression.

- Icterus

Hepatitis is commonly infective or drug induced.

- Clubbing

Infections with clubbing are usually respiratory (eg. bronchiectasis, lung abscess, empyema) or associated with Lymphoid Interstitial Pneumonitis (LIP).

- Pedal/sacral edema

Congestive cardiac failure, severe edematous malnutrition, or hypo proteinemia may cause dependent edema.

- Skin - Rash (macular-papular, vesicular, petechiae/purpura/ecchymosis, purpura fulminans), pustules or cellulitis

Viral exanthematous infections, fungal infections, gram negative septicemia, or gram positive infections are causes of skin lesions.

- Lymphadenopathy

Localized lymphadenopathy may suggest infections in the lymphnode drainage area, apart from Extra-pulmonary Lymphnode Tuberculosis. Viral infections or malignancies or persistent generalized lymphadenopathy are other causes.

- Oral cavity (ulcers, thrush, angular cheilitis, glossitis, gingivitis, caries)

Candidiasis, anaerobic infections, and viral infections commonly manifest with oral lesions.

- Eyes (corneal clouding, red eye, pus discharge)

Vitamin A deficiency, bacterial conjunctivitis, and herpes zoster may affect the eyes.

- ENT (Anterior nares, tonsils, posterior pharynx, otoscopy, mastoid swelling)

Coryza, streptococcal throat infections, viral upper respiratory tract infections, otitis media, and mastoiditis may be causes for fever.

- Respiratory

- Tracheal/apical position, percussion impaired/dull/hyper-resonant, vocal resonance/fremitus, auscultation (breath sounds, adventitious sounds)

Among the lower respiratory tract infections, pneumonia due to bacteria are priorities when dealing with the HIV-infected child. Pneumocystis jiroveci pneumonia (PCP) is difficult to exclude as a cause of fever, cough, and difficult breathing. PCP has high rates of mortality and diagnosis is difficult to confirm. Therefore, it may be necessary to treat the HIV-infected or exposed infant and young for PCP, in addition to antibiotics, for a bacterial pneumonia. Differential diagnoses to be considered in the HIV-infected child are Pulmonary Tuberculosis, complicated Bacterial Pneumonia, and Lymphoid Interstitial Pneumonia.

- Abdomen and genitourinary

- Organomegaly, free fluid, palpable masses, flank swelling/tenderness

- Genitalia, Perineum, anus

Cardiovascular

- Heart sounds, murmur, gallop, cardiomegaly, diminished sounds

Musculo-skeletal

- Bony tenderness/swellings, joint swellings or painful restricted movements, or muscle tenderness

- Osteomyelitis, septic arthritis, myositis, pyomyositis, malignancies or connective tissue disorders manifest with the above features.

Neurological

- Tender, stiff neck and/or raised anterior fontanelle

- Sensorium

- Pupil symmetry, reaction

- Facial asymmetry, limitations of eye movements, poor gag reflex

- Motor (Bulk, Tone, Power, Deep tendon reflexes, Babinski reflex)

- Coordination, gait

- Fundoscopy

3.2 Sepsis

The risk of septicaemia is higher in HIV-infected children. Just like fever, aetiology can vary widely so it is critical to be highly suspicious of septicaemia.

Aetiology:

- Bacteremia occurs without any focus OR secondary to infection of the lung, gastrointestinal tract, skin, ear, sinuses, and urinary tract.
- Most common organism is *Streptococcus pneumoniae*
- Others are: nontyphoidal Salmonella spp., Pseudomonas spp., E coli, H influenzae
- Campylobacter jejuni, Listeria monocytogenes, Citrobacter spp., Enterobacter spp S aureus ., Klebsiella spp., Actinomyces israelii
- Predisposing factors: Low CD4 cell count, neutropenia, and the presence of a central Venous catheter
- Complications of bacteremia include septic shock, disseminated intravascular coagulation, and seeding of the pathogens to multiple organs to cause osteomyelitis, meningitis, pneumonia, endocarditis, and pyelonephritis

Symptoms:

- Symptoms of primary focus of infection
 - Assess for pneumonia, meningitis, osteomyelitis, cellulitis,
 - sinusitis (nasal discharge and persistent cough – 2 weeks)
- Fever +/-
- Rigors
- Rapid respiration
- Altered consciousness

Signs:

- Shock (low pulse volume, tachycardia, hypotension, prolonged capillary refill, decreased urine output, altered consciousness)
- Bleeding (DIC) – skin bleeds, GIT bleed
- Skin eruptions

Investigations:

- Blood counts
- Blood culture and sensitivity
- Urine culture
- Chest X-ray
- Platelet count, Prothrombin time, Partial thromboplastin time

Treatment:

- 1 Antibiotics are started based on:
 - local patterns of infection & susceptibility
 - recent antibiotic usage
 - Empirical antibiotics to be started until culture reports are available.

- 2 Modify antibiotic based on culture sensitivity report
- 3 Treat with the appropriate antibiotics for 10 to 14 days.
- 4 Maintain fluid intake and electrolyte balance with intravenous fluids
- 5 Monitor heart rate, blood pressure, urine output and temperature hourly

Setting	Organism suspected	Antibiotic
CD4 count >200 cells/mm ³ and an ANC >500 cells/mm ³	Gram negatives including E.coli, Klebsiella, Salmonella typhi as well as H. influenzae, S.pneumoniae are possible organisms	ceftriaxone 50 mg/kg IM/IV every 12Hr OR Cefotaxime 50 mg/kg IM/IV every 6Hr
CD4 count <50 cells/mm ³ and absolute neutrophil count (ANC) <500 cells/mm ³	Pseudomonas spp	Ceftazidime 75 mg/kg IM/IV every 12Hr
Skin infections/abscess	S. aureus	Methicillin / oxacillin 50 mg/kg IM/IV every 6Hr
Catheter related sepsis	Pseudomonas spp S. aureus S. epidermidis	Ceftazidime 75 mg/kg IM/IV every 12Hr Vancomycin 10 mg/kg IV every 8Hr
Methicillin-resistant Staph aureus in the community	S. aureus	Vancomycin 10mg/kg IV every 8Hr
Neonate, but can affect any child	Listeria	ampicillin 50 mg/kg IV every 6Hr PLUS an aminoglycoside Gentamicin 7.5mg/kg IM/IV once per day OR Amikacin 7.5mg/kg IM/IV every 12Hr

Prophylaxis against bacterial infections:

- Vaccinations against: H. influenzae type b and *Pneumococcus*

Fungal Infections:

- Systemic fungal infections are rare
- Mucosal and cutaneous infection are common
- The most common is Candida

Symptoms/Signs:

- Oral lesions:
 - creamy white lesions on oral mucosa, palate, tonsils
 - raised plaque
 - flat erythematous lesions
 - substernal/abdominal pain/ difficulty in swallowing
- Disseminated- occurs in severely immunosuppressed

- hospital acquired
- central venous catheter is a risk factor

Investigation:

- o KOH preparation for fungal elements
- o Blood culture
- o Retinal examination for endophthalmitis

Treatment:

- o Oral:
 - Nystatin suspension 400,000-600,000 U po 4 times /day – 14 days
 - Clotrimazole trouches 10 mg po 4-5 times / day – 14 days
 - Fluconazole suspension 3-6 mg/kg once per day – 14 days
 - Ketoconazole tabs 5-10 mg/kg twice daily – 14 days
 - itraconazole tabs 2-5 mg/kg twice daily – 14 days
- o Esophageal
 - Fluconazole 3-6mg/kg once daily (max 200mg) – 21 days
 - IV Amphotericin 0.5-1 mg/kg/day if unresponsive to fluconazole
- o Disseminated-
 - Remove central line if present
 - IV Amphotericin 0.5-1 mg/kg/day (given as infusion 0.1mg/ml over 2 hours with adequate hydration before infusion; monitor for renal toxicity)
 - Duration of therapy :2-3 weeks after cultures negative and no systemic signs of sepsis

Other fungal infections known:

- o Cryptococcus, Aspergillus, Histoplasma, Coccidioidomycosis

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Chapter 4

Malnutrition and anaemia including hematologic manifestations

4.1 Malnutrition

Malnutrition is a common condition in HIV-infected children and is a major contributor to mortality. In HIV-infected children, wasting (i.e. very low weight for height/length) is very common and has been associated with shorter child survival.

Severe Acute Malnutrition (SAM)

Severe acute malnutrition develops when the child is not getting enough energy or protein and other nutrients from his food to meet his nutritional needs. A child who has had frequent illnesses, HIV infection, or tuberculosis can also develop severe acute malnutrition. The child's appetite decreases, and the food that the child eats is not used efficiently. A child with severe acute malnutrition may present with severe wasting and/or bilateral oedema (swelling of both feet).

Use IMCI criteria:

For all children:

- Determine weight-for-age
- Look for oedema of both feet

If age up to 6 month:

- Look for visible severe wasting

If age 6 months or above:

- Determine if mid-upper arm circumference (MUAC) less than 11 cm
- If MUAC less than 11 cm, or oedema, assess appetite

Optimal growth of an infant or child, measured in weight and height/length, is a sensitive indicator of HIV disease progression. Severe growth problems in HIV-infected children that are not attributed to inadequate nutritional intake instead point to the need for ART initiation (i.e. growth failure and severe malnutrition/wasting are used as criteria for clinical stage 3 and 4 disease, respectively). Growth is also useful when evaluating the child's response to ART; the potential adverse effects of ARV drugs or opportunistic infections may affect food intake and nutrition in general, resulting in limited growth improvements and/or adherence to therapy.

4.1.1 Nutritional assessment and support

All HIV-infected infants and children should be assessed for nutritional status including weight-for-height, height-for-age, and weight-for-age. Where these cannot be measured, MUAC could be measured to decide nutritional status. As for all infants, HIV-infected infants should be weighed and length measured monthly for the first five years of life, and standardized growth curves used to determine the nutritional status. Thereafter, children should be weighed at each review and full nutritional assessments made every three months, unless the child requires particular attention because of growth problems or special nutritional requirements.

HIV infection is associated with increased energy needs, which requires a proactive approach to nutritional support in HIV-infected children:

- In asymptomatic HIV-infected children, resting energy expenditure is increased by about 10%
- In HIV-infected children experiencing growth failure, energy expenditure is increased between 50% and 100%
- It is recommended to increase the energy intake of HIV-infected infants and children—if they are asymptomatic, by 10% of the RDA for their age and sex, and if they are symptomatic or recovering from acute infections, by 20–30% of the RDA.

Vitamin A supplements should be given in accordance with the WHO-recommended high-dose prevention schedule for children at high risk of vitamin A deficiency.

Identifying the underlying cause of growth failure may provide valuable information on further support strategies. This may include: treating underlying illness (common illnesses should be managed according to IMCI guidelines), evaluating the need to start or switch ART, family education about locally available food choices, and referral to food programmes, preferably with support for the whole family. In addition, selecting specific high-energy, palatable foods for children with conditions that interfere with normal ingestion or digestion (e.g. sore throat or mouth, oral thrush, diarrhoea) may both alleviate symptoms and ensure sufficient energy intake.

4.1.2 ART in severely malnourished children

All children with severe malnutrition are at risk for a number of life-threatening problems and urgently require therapeutic feeding. It is not known at what phase of malnutrition treatment ART should start. Expert opinion therefore suggests that HIV-infected children with severe malnutrition should be stabilized before decisions are made on initiating ART. The initial treatment of severe malnutrition lasts until children have stabilized on this treatment, and their appetites have returned. In HIV-uninfected children the response to initial treatment of severe malnutrition should not take longer than 10 days, but in HIV-infected children the response may be delayed or very limited.

ART is indicated in HIV-infected infants and children by

- unexplained severe malnutrition that is not caused by an untreated opportunistic infection
- lack of response to standard nutritional therapy (i.e. clinical stage 4 disease)

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

4.2 Anaemia

Anaemia occurs in 20 – 70% of HIV-infected children, and more commonly in children with AIDS. Anaemia results from a number of underlying causes.

Definition:

Anaemia can be defined as a reduction in red blood cell mass or blood haemoglobin concentration. In practice, anaemia is most commonly defined by reductions in one or more of the following:

- Chronic infection and diseases (including HIV Infection)
- Poor nutrition
- Autoimmune diseases
- Virus associated conditions (e.g. parvovirus B19 red cell aplasia)
- Adverse drug effects blood loss, especially chronic blood loss, through intestinal hookworm infection haemolysis caused by many conditions, including bacterial infections and malaria

History:

- Patients with inherited aetiologies often present in childhood and may have a positive family history.
- Severity and initiation of symptoms:
 - Patients with chronic anaemia may not be as symptomatic as patients with acute anaemia with similar haemoglobin values.
 - Prior episodes of anaemia may indicate inherited forms, whereas anaemia in a patient with previously documented normal blood counts suggests an acquired aetiology.
- Questions relating to haemolytic episodes:
 - Changes in urine colour, sclera icterus, or jaundice associated with the symptoms of anaemia should be asked.
- Questions about possible blood loss:
 - Bleeding from the gastrointestinal tract should be reviewed, including changes in stool colour, identifying blood in stools, and history of bowel symptoms.
 - Teenagers may have excessive menstrual losses without realizing it
- Common causes of anaemia in children living in low- and middle-income countries are the presence of intestinal nematode infection (e.g., hookworm, whipworm leading to iron deficient anaemia) and malaria leading to haemolytic anaemia.
- Underlying medical conditions: a careful past medical history and review of symptoms should be obtained to elucidate chronic underlying infectious or inflammatory conditions that may result in anaemia.
- Prior drug or toxin exposure
- Questions relating to diet: questions should be primarily aimed at determining iron content in the diet and, to a lesser degree, folate and B12 content. Document the type of diet, type of formula (if iron fortified), and age of infant at the time of discontinuing formula or breast milk. In addition, determine the amount and type of milk the patient is drinking. Specific questions about if the child has symptoms consistent with pica may help to diagnose lead poisoning.
- Birth history: A birth and neonatal history should be obtained, including: infant and mother's blood type, any history of exchange or intrauterine transfusion, and a history of anaemia in the early neonatal period. Gestational age at birth is important, as premature infants may have iron or vitamin E deficiencies that result in anaemia. The presence of jaundice or need for phototherapy may signify the presence of an inherited haemolytic anaemia.
- Developmental milestones: parents should be asked questions to determine if the child has reached age-appropriate developmental milestones. Loss of milestones or developmental delay in infants with megaloblastic anaemia may signify abnormalities in the cobalamin, B12, pathway.
- Family history, race, and ethnicity: any family history of anaemia should be pursued in depth.

Symptoms

Few clinical disturbances occur until the haemoglobin level falls below 7 – 8 g/dl. Below this level pallor becomes obvious in the skin and mucous membranes. Physiologic adjustments include increased cardiac output, increased oxygen extraction, and shunting of blood towards vital organs and tissues.

- Common symptoms of anaemia include lethargy, tachycardia, and pallor.
- Acutely anaemic infants may present with irritability and poor oral intake. In contrast, patients

with chronic anaemia may be well compensated and may not have significant complaints.

- Weakness, tachycardia, shortness of breath on exertion ultimately result from increasingly severe anaemia, regardless of the cause.

Signs

- Pallor mucus membranes and hands
- Tachycardia
- Tachypnoea
- Signs of respiratory distress
- Signs of congestive cardiac failure
- Jaundice and Hepatosplenomegaly: in patients with haemolytic processes.

Investigations

- Full Blood Count (FBC) and blood smear
- Reticulocyte count:
 - An evaluation of the reticulocyte count aids in defining the aetiology of the anaemia.
 - An increased reticulocyte count generally is seen as a normal bone marrow response to ongoing hemolysis or nonchronic blood loss.
 - A low reticulocyte count, which reflects decreased production of red blood cells, is more consistent with bone marrow depression.
- Bone marrow biopsy
- Investigation and management should address both the cause and etiology of anaemia
 - Is anaemia associated with other haematological abnormalities such as Aplastic Anaemia and Leukaemia? If yes, review blood cell indices and bone marrow smear.
 - Is it associated with reticulocytosis? If yes usually a consequence of bleeding or ongoing haemolysis?
 - Is there associated hyperbilirubinaemia? If yes, usually due to haemolysis.
Review peripheral blood smear
 - Is anaemia associated with a lower than appropriate reticulocyte response? If yes: assess red blood cell size

Below you will find tables on pages 40 -41 on investigation and management of anaemia, neutropenia and thrombocytopenia

Common causes and etiology of anemia related to HIV infection can be found below.

Cause of Anemia	Etiology
Poor production of RBCs	<p>HIV infection</p> <ul style="list-style-type: none"> ◦ Anemia of chronic disease ◦ HIV infection of stromal cells <p>Infection</p> <ul style="list-style-type: none"> ◦ CMV, Parvovirus B19, atypical tuberculosis <p>Malignancy</p> <ul style="list-style-type: none"> ◦ Lymphoma, Kaposi's sarcoma <p>Drugs</p> <ul style="list-style-type: none"> ◦ Sulfonamides, dapsone
Destruction of RBCs	<p>Hemophagocytic syndrome</p> <p>Disseminated intravascular coagulation (DIC)</p> <p>Drug associated hemolytic anemia</p>
Ineffective Production of RBCs	<p>Folate and iron deficiency</p> <ul style="list-style-type: none"> ◦ Dietary ◦ Intestinal malabsorption <p>Vitamin B-12 deficiency</p> <ul style="list-style-type: none"> ◦ Intestinal malabsorption ◦ Infection in stomach or intestine

Causes and etiology of neutropenia related to HIV infection.

Causes of Neutropenia	Etiology
Decreased WBC growth factors	<p>Decreased numbers of progenitor cells in the bone marrow</p> <p>Decreased numbers of granulocytes and monocytes</p> <p>Decreased serum levels of GCSF</p> <p>Decreased numbers of neutrophils</p>
Drugs	<p>Antiretrovirals: ZDV, 3TC, ddI, d4T</p> <p>Anti-viral agents: gancyclovir, foscarnet</p> <p>Anti-fungal agents: flucytosine, amphotericin</p> <p>Pneumocystis carinii prophylaxis: sulfanomides, trimethoprim, pentamidine</p> <p>Antineoplastic agents: doxorubicin, cyclophosphamide, methotrexate, cytarabine</p>

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Guides for managing anaemia, neutropenia and thrombocytopenia.

<p>Anaemia (Haemoglobin <10 gm/dL)</p>	<p>Monitor CBC for decreased haemoglobin</p> <p>Assess for tachycardia, heart murmur, pallor, tachypnoea, dyspnoea, level of consciousness</p> <p>Monitor for associated symptoms; irritability, fatigue, shortness of breath, chest pain with exertion, headaches</p> <p>Provide medical interventions as ordered</p> <ul style="list-style-type: none"> - Transfuse with PRBCs 10 ml/kg prn when symptomatic - Provide oxygen during periods of respiratory distress <p>Patient and family education</p> <ul style="list-style-type: none"> - Quiet activities are more well tolerated during periods of anaemia - Signs and symptoms that signal anaemia: irritability, change in skin colour, increased heart rate and respirations, shortness of breath
<p>Neutropenia (ANC < 1000/mm³ for 2 wks. to 1 yr. of age) (ANC < 1500/mm³ for children > 1 yr.)</p>	<p>Monitor CBC for decreased WBC count and ANC</p> <p>Assess for fever, skin ulcerations, pain, cough, tachypnoea, rales, wheezing, stomatitis, perirectal fissures</p> <p>Provide antibiotic therapy as ordered for fever >38.4°C</p> <p>Monitor temperature</p> <p>NO rectal temperatures or exams</p> <p>Avoid intramuscular injections</p> <p>Avoid urinary catheterization</p> <p>Prep skin with povidone-iodine or alcohol prior to phlebotomy</p> <p>Patient and family education</p> <ul style="list-style-type: none"> - Avoid ill contacts - Wash hands frequently - Notify healthcare provider when fever is >38.4°C - Practice meticulous oral hygiene
<p>Thrombocytopenia (Platelet count < 100,000/mm³)</p>	<p>Monitor CBC for decreased platelet count</p> <p>Assess for bleeding, bruising, petechiae, purpura</p> <p>Provide medical interventions as ordered</p> <ul style="list-style-type: none"> - Transfuse platelets 6 units/m² prn for active bleeding that is not controlled <p>Avoid intramuscular injections or lumbar puncture if possible</p> <p>Use pressure dressings if bone marrow aspiration is necessary</p> <p>NO rectal temperatures or exams</p> <p>Patient and family education</p> <ul style="list-style-type: none"> - Quiet activities help prevent bleeding associated with injury - Encourage fluids to prevent constipation - Notify healthcare provider if bleeding occurs and cannot be controlled

PART II

Paediatric HIV care and Treatment with ART

Chapter 5: Introduction Section

Chapter 6: Diagnosis of HIV infection in infants and children

Chapter 7: Routine care for HIV-Exposed and infected children

Chapter 8: Antiretroviral Therapy

Chapter 9: Nutritional Support

Chapter 10: Pain Management

Chapter 11: Disclosure and Psychosocial Support

Chapter 5

Introduction: Infants, children and HIV-infection

5.1 Key differences between adults and children

- Young children have immature immune systems, and if HIV-infected, are particularly susceptible to common childhood and opportunistic infections. They may experience a rapid progression of HIV disease if treatment is delayed.
- Maternal HIV antibodies can be passed to the child and last for up to 18 months, so HIV antibody testing does not reliably indicate HIV infection in children under 18 months of age. Positive HIV antibody testing in this time period can indicate exposure to HIV or HIV infection in the child and, where possible, should be followed up with a viral test.
- Children are at risk of acquiring HIV by breastfeeding from HIV-infected mothers. Children of any age are at risk of acquiring HIV during the entire time they are breastfed.
- Negative HIV antibody testing in a child who stopped breastfeeding at least 6 weeks prior to the test usually indicates the child is not HIV-infected.
- In young children normal CD4 counts are higher, age-dependent, and more variable than in adults. For children under 5 years of age, it is best to use %CD4 rather than absolute count.
- ARV drugs are handled differently in children's bodies, affecting the doses that are needed.
- ARV medicine dosages must be adjusted as the child grows.
- It can be challenging to communicate effectively with children about their HIV status, about the care they need, and to support their adherence to ART. As children grow, the counselling they receive must evolve as well.

In a family where one child is HIV-infected, it is possible that siblings may also be infected. Make sure diagnostic counselling and testing is offered to all siblings and parents.

5.2 Epidemiology

- 2.1 million children under the age of 15 years were living with HIV in 2009.
- 1000 children are newly infected every day.
- 90% of children living with HIV are in sub-Saharan Africa.
- Children under 15 years of age account for 1 in 6 AIDS-related deaths and 1 in 7 new HIV infections worldwide.

5.3 Modes of Transmission

- The three principal modes of transmission of HIV are vertical, parenteral, and sexual.
- 90% of children with HIV are infected through vertical (perinatal) transmission.
- The overall risk of vertical HIV transmission in the absence of any intervention is between 20% and 45%. The breakdown of risk of maternal-to-child-transmission (MTCT) by periods of transmission is:
 - 5-10% is in-utero

- 10-20% is intrapartum
- 5-20% is through breastfeeding

5.4 Immunology

As children acquire HIV when the immune system is immature, the immunology is different from adults. This results in:

- High rates of viral replication
- Very high HIV-1 viral load which takes 1-2 years to reach the viral set-point after primary infection
- High rates of CD4 positive cell destruction ~ 5% of total per day
- Very high rates of viral mutation (e.g. Amino acid substitution due to reverse transcription errors when there are high levels of replication)
- Faster rate of disease progression
- Good immunologic response to ART
- CD4 cell counts are high and variable in young uninfected children. CD4% is less variable, and as a result CD4% is used instead of CD4 cell count as an immunological marker in young children (<5-6 years)
- High mortality rate in perinatally infected children: >60% die by the age of 3 years in resource-poor settings

5.5 Natural History and Progression

There is limited data on the natural history of perinatally-acquired HIV in low-resource settings in general, and sub-Saharan Africa in particular. Higher mortality rates may be a result of several factors, including inter-current infections, malnutrition, and lack of access to early diagnosis and basic health care. Clinical experience indicates that perinatally HIV-infected children fit into one of 3 categories:

- Rapid progressors (about 25-30%), most of whom die before their first birthday and are thought to acquire infection in-utero or during the early postnatal period
- Children who develop symptoms early in life, then follow a downhill course and die by 3-5years (50-60%)
- Long-term survivors who live beyond 8 years (5-25%). These tend to have LIP, and are stunted with low weight and height for age.

References for further reading

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Chapter 6

Diagnosis of HIV infection in infants and children

6.1 Early identification of HIV infected infant or child

Saving children's lives depends on **early** identification of those who are HIV-infected. In 2007, the average age of children starting ART was 4.9 years, but recent research demonstrates that early ART initiation in infants and children prevents death.

The term "infant" refers specifically to a child under the age of 12 months

6.1.1 Infants (<12 months of age):

Available research confirms that, for infants acquiring HIV before or around delivery, disease progression occurs rapidly in the first few months of life and often leads to death. Over 80% of HIV-infected infants who are well at 6 weeks progress to become eligible to start ART before 6 months of age. *Early determination of HIV exposure and definitive diagnosis is thus critical. Therefore,*

- All infants and children should have their *HIV exposure status* established at their first contact with the health system, ideally before 6 weeks of age. To facilitate this, all Maternal, Neonatal and Child service delivery points in health facilities should offer HIV serological testing to mothers and their infants and children. In most cases the HIV status is established by:
 - asking about maternal HIV testing in pregnancy, labour or postpartum period
 - checking the child's and/or mother's health card,
 - offering a rapid antibody test to all infants and or mothers whose HIV status is unknown, especially where the national HIV prevalence is >1% .
- Viral testing (e.g. PCR) should be conducted at 4-6 weeks of age for infants known to be HIV-exposed, or at the earliest possible opportunity for those seen after 4-6 weeks of age.

Urgent HIV antibody testing should be carried out for any infant or child presenting with signs, symptoms, or medical conditions that indicate HIV.

Infants with detectable HIV antibodies should go on for a viral test.

6.1.2 Children over 12 months of age:

18 months of age and older: HIV antibody tests can provide definitive diagnosis in children ≥ 18 months of age, with known or unknown exposure to HIV.

HIV antibody testing should be carried out for children of this age group who present with signs, symptoms or medical conditions that indicate HIV (see section 2.1.3).

12-18 months of age: Viral testing for diagnostic purposes is recommended since HIV antibody tests may not accurately reflect infection of the child as a result of the possible persistence of maternal HIV antibodies. However this group of children should be offered antibody test, and only those who are positive subjected to viral test. Those who are negative on antibody test and have not breastfed for more than six weeks are not infected.

6.2 Diagnosis of HIV-infection in children

6.2.1 Signs or conditions that may indicate possible HIV infection:

HIV's clinical expression in children is highly variable. Many HIV-infected children develop severe HIV-related signs and symptoms in the first year of life. Other HIV-infected children remain asymptomatic or mildly symptomatic for more than a year and may survive for several years.

Suspect HIV if any of the following symptoms, signs, and/or clinical events are present, as they are not common in children without HIV:

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*: erythema and white-beige pseudomembranous plaques on the palate, gums and buccal mucosa. After the neonatal period the presence of oral thrush is highly suggestive of HIV infection when it is: occurring when there has been no antibiotic treatment, lasting over 30 days despite treatment, recurring, extending beyond the tongue, or presenting as oesophageal candidiasis.
- *Chronic parotitis*: unilateral or bilateral parotid swelling for ≥ 14 days, with or without associated pain or fever.
- *Generalized lymphadenopathy*: enlarged lymph nodes in two or more extra-inguinal regions without any apparent underlying cause.
- *Hepatomegaly with no apparent cause*: in the absence of concurrent viral infections such as cytomegalovirus (CMV).
- *Persistent and/or recurrent fever*: fever ($\geq 38^{\circ}\text{C}$) lasting ≥ 7 days, or occurring more than once over a period of 7 days.
- *Neurological dysfunction*: progressive neurological impairment, microcephaly, delay in achieving developmental milestones, hypertonia, or mental confusion.
- *Herpes zoster (shingles)*: painful rash with blisters confined to one dermatome on one side.
- *HIV dermatitis*: erythematous purpurular rash. Typical skin rashes include extensive fungal infections of the skin, nails and scalp, and extensive molluscum contagiosum.
- *Chronic suppurative lung disease*.

Signs or conditions very specific to HIV-infected children:

- Strongly suspect HIV-infection if the following conditions, which are very specific to HIV, are present: pneumocystis pneumonia (PCP), oesophageal candidiasis, lymphoid interstitial pneumonia (LIP), or Kaposi's sarcoma, and in girls, acquired recto-vaginal fistula.

Signs common in HIV-infected children, but also common in sick non-HIV-infected children:

- *Chronic otitis media*: ear discharge lasting more ≥ 14 days.
- *Persistent diarrhoea*: diarrhoea lasting ≥ 14 days.
- *Moderate or severe malnutrition*: weight loss or a gradual but steady deterioration in weight gain from expected growth, as indicated on the child's growth card. Suspect HIV particularly in breastfed infants < 6 months old who fail to thrive.

6.2.2 WHO Paediatric Clinical Staging for HIV

In a child with diagnosed or highly suspected HIV infection, the clinical staging system helps to assess the degree of damage to the immune system, and to plan treatment and care options. The stages determine the likely prognosis of HIV and are a guide when to start, stop, or switch ARV therapy.

The clinical stages identify a progression sequence from least to most severe (number 1 through 4)—the higher clinical stage, the poorer the prognosis. For classification purposes, once a stage 3 clinical condition has occurred, the child's prognosis will likely remain in stage 3 and will not improve to stage 2, even once the original condition is resolved, or a new stage 2 clinical condition appears. Antiretroviral treatment with good adherence dramatically improves prognosis.

The clinical staging events can also be used to identify the response to ARV treatment if there is no easy or affordable access to viral load or CD4 testing.

WHO Paediatric HIV Clinical Staging

WHO Paediatric Clinical Staging for HIV

Stage 1

Asymptomatic
Persistent generalized lymphadenopathy (PGL)

Stage 2

Hepatomegally
Papular pruritic eruptions
Seborrhoeic dermatitis
Extensive human papilloma virus infection
Extensive molluscum contagiosum
Fungal nail infections
Recurrent oral ulcerations
Lineal gingival erythema
Angular cheilitis
Parotid enlargement
Herpes zoster
Recurrent or chronic URTIs (otitis media, otorrhoea, sinusitis)

Stage 3	Stage 4
Moderate unexplained malnutrition, not adequately responding to standard therapy	Unexplained severe wasting or malnutrition not responding to standard therapy
Unexplained persistent diarrhoea (14 days or more)	Pneumocystis pneumonia
Unexplained persistent fever (intermittent or constant for longer than one month)	Recurrent severe bacterial infections (empyema, pyomyositis, bone or joint infections, meningitis, excluding pneumonia)
Oral candidiasis (outside the neonatal period)	Chronic herpes simplex infection (orolabial or cutaneous of more than one month's duration or visceral at any site)
Oral hairy leukoplakia (OHL)	Extrapulmonary Tuberculosis
Pulmonary Tuberculosis	Kaposi Sarcoma
Severe recurrent presumed bacterial pneumonia (2 or more episodes in 6 months)	Oesophageal candidiasis (or candida of the trachea, bronchi or the lungs)
Acute necrotizing ulcerative gingivitis/ periodontitis	Cytomegalovirus infection: retinitis or cytomegalovirus infection affecting another organ, with onset at age over one month
Lymphoid interstitial pneumonia (LIP)	Central nervous system toxoplasmosis (after the neonatal period)
Unexplained anaemia (<8gm/dl), neutropaenia (<500/mm ³) or thrombocytopaenia (<30000/mm ³)	Extrapulmonary cryptococcosis , including meningitis
	HIV encephalopathy
	Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidioidomycosis)
	Chronic cryptosporidiosis
	Chronic isosporiasis
	Disseminated non-tuberculous mycobacteria infection
	Cerebral or B cell non-Hodgkin lymphoma
	Progressive multifocal leucoencephalopathy
	HIV-associated cardiomyopathy or nephropathy.

6.2.3 Antibody test (ELISA or Rapid Test)

This is the most common test available for diagnosing HIV infection in health facilities within resource-limited settings.

Rapid test is available in most health facility outpatient clinics. Its benefits include: it is easy to carry out, it does not require a laboratory set up, most health workers (including nurses) can be trained to carry out the test, and the results can be given to the patient within 30 minutes, so all patients tested should go home aware of their HIV status. There is a need to make sure that the diagnostic kits for rapid test are made constantly available to all health facility service delivery points—including maternal and child health clinics, all outpatient clinics, and inpatient wards.

ELISA test requires laboratory equipment, a regular supply of reagents, and laboratory-trained health personnel to determine the test result.

Both rapid test and ELISA test are useful for diagnosing HIV infection in children aged 18 months and above. These tests should be performed according to the standard diagnostic HIV serological

testing algorithm used in adults. All infants and children, especially in countries with HIV prevalence > 1%, should be offered an HIV test at first contact with a health facility.

Maternal antibodies may persist until 18 months of age, so antibody tests are not reliable for diagnosing children less than 18 months of age. However, it is used in this age group for screening if a child has been exposed to HIV.

It is strongly recommended that HIV serological assays used for the purpose of clinical diagnostic testing have a minimum sensitivity of 99% and specificity of 98% under quality-assured, standardized, and validated laboratory conditions.

6.2.4 Virological Test (WHO 2010 recommendation)

This is the most reliable method for diagnosing HIV infection in infants and children less than 18 months of age. However it is expensive, and requires a sophisticated laboratory set up with trained staff to carry out the test. While such laboratories are situated in central hospitals away from most of the population, the use of the Dried Blood Spots (DBS) system should enable all health facilities in a country to access virological testing services.

It is strongly recommended that all HIV-exposed infants, and all infants with unknown or uncertain HIV status, should have an HIV virological test performed at 4–6 weeks of age or at the earliest opportunity thereafter. For infants and children with a positive result, a confirmatory test should be done. In infants and children undergoing virological testing, the following assays can be used,

- HIV DNA on whole blood specimen or DBS
- HIV RNA on plasma or DBS,
- Up24 Ag on plasma or DBS.

These assays should have a sensitivity of at least 95% — and ideally greater than 98% — and specificity of 98% or more under quality-assured, standardized and validated laboratory conditions.

All infants with an initial positive virological test result should be started on ART without delay and, at the same time, a second specimen be collected to confirm the initial positive virological test result. Do not delay ART. Immediate initiation of ART saves lives and it should not be delayed while waiting for the results of the confirmatory test. A positive virological test result should reach the mother/infant pair within A MAXIMUM OF FOUR weeks (of the result being established) to ensure early onset of treatment.

To reduce the cost of virological testing, a serological test should be done for HIV-exposed infants and children age 9 to 18 months. Only those with reactive serological assays should have a virological test to confirm HIV infection and determine who needs ART.

If access to viral tests is limited, it is recommended that the first viral testing should be conducted at 4–6 weeks following birth. However, a positive viral test at any age confirms HIV infection, and a repeat viral test on a separate specimen should be done to confirm the initial positive test. In children diagnosed with HIV infection on the basis of only one positive viral test, HIV antibody testing should preferably be performed once the child has reached 18 months of age in order to definitively confirm HIV infection.

Table 6.2.4. Summary of testing methods for infant and children

Testing Method/ Assay	Specimen Type/ Modality	Purpose	Paediatric population for testing	Comments
HIV serological	Whole blood	Screening test for HIV exposure	Infants <12 months	<p>Infants of unknown or uncertain HIV exposure whose mother is unavailable or does not consent to maternal testing.</p> <p>Confirm reactive result with virological test.</p> <p>Little data exists on performance of oral HIV serological assays for paediatric populations.</p>
			Well and/ or previously untested, HIV-exposed infants, or infants of unknown HIV exposure, at ~9 months	<p>Identifies potentially uninfected child if non-reactive result & not breastfed for at least 6 weeks prior to test.</p> <p>Conduct maternal or infant HIV serological test for infants whose HIV exposure status is unknown.</p> <p>Confirm reactive result with virological test</p> <p>If non-reactive serological test for HIV exposed, breastfeeding infant, repeat test 6 weeks after complete cessation of breastfeeding.</p>
			Infants or children with signs or symptoms suggestive of HIV infection	<p>If reactive result, start ART and HIV care for infant or child who qualifies, and confirm with virological test for those <18 months of age.</p> <p>Where virological testing is not available, for sick children with a reactive serological test, use the clinical algorithm for presumptive clinical diagnosis of HIV infection.</p>
			Infants/children >9-<18 months	<p>Confirm reactive result with virological test</p> <p>For breastfeeding infant/child who is HIV-exposed with non-reactive test result, repeat test 6 weeks after complete cessation of breastfeeding.</p>
		Diagnostic	Children >18 months	The nationally defined serial 2 or 3 test algorithm should be followed.
HIV DNA	Whole blood/ liquid	Diagnostic	Infants and children	Confirm positive result with a second virological test
HIV DNA	Whole blood/ DBS	Diagnostic	Infants and children	Confirm positive result with a second virological test
HIV RNA	Plasma/ liquid	Diagnostic	Infants and children	<p>Exercise caution in interpreting negative results if infant is established on ART.</p> <p>Confirm positive result with a second virological test</p>

Testing Method/ Assay	Specimen Type/ Modality	Purpose	Paediatric population for testing	Comments
HIV RNA	Whole blood/ DBS	Diagnostic	Infants and children	Exercise caution in interpreting negative results if infant is established on ART. Confirm positive result with a second virological test
Up24 antigen	Plasma/ liquid	Diagnostic	Infants and children	Use other virological test in regions where sub-type D is common or for infants already on ART. Confirm reactive result with second virological test
Up24 antigen	Whole blood/ DBS	Diagnostic	Infants and children	Use other virological test in regions where sub-type D is common or for infants already on ART. Confirm reactive result with second virological test

- a In children younger than 18 months, HIV infection is diagnosed based on:
- positive virological test for HIV or its components (HIV-RNA or HIV-DNA or ultrasensitive HIV p24 antigen)
 - confirmed by a second virological test obtained from a separate determination taken more than four weeks after birth.
- b Virological testing for infants require that test results are returned to the clinic and the child/mother/caregiver as soon as possible, and at the latest within 4 weeks of specimen collection. Positive results should be fast tracked to the mother/baby pair as soon as possible to enable prompt initiation of ART.

6.3 Counselling

If there are reasons to suspect HIV infection and the child's HIV status is not known, the health worker should counsel the family and offer diagnostic testing for HIV.

Pre-test counselling includes providing the reasons why the testing is being recommended and obtaining informed consent before any test is conducted.

Since the majority of children are infected through vertical transmission from the mother, this implies that the mother, and often the father, is also infected. They may not know this. Even in high-prevalence countries, HIV remains an extremely stigmatized condition and the parents may feel reluctant to undergo testing.

HIV counselling should account for the child as part of a family. This should include the psychological implications of HIV for the child, mother, father and other family members. Counselling should stress that, while a cure for HIV is currently not possible, there is much that can be done to improve the quality of life of the child and any HIV-infected parents. Counselling should make it clear that the hospital staff want to help, and that the mother should not be frightened of going to a health facility early in an illness—even if she only wants to ask questions.

Counselling requires time and has to be done by trained staff. If staff at the first referral level have not been trained, assistance should be sought from other sources, such as local community AIDS support organizations.

HIV testing should be **voluntary** and **free of coercion**, and informed consent is required before HIV testing is performed. All diagnostic HIV testing of children must be:

- **confidential**
- accompanied by **counselling**
- only conducted with **informed consent** so that it is both informed and voluntary.

For children this usually means parental or guardian consent. For the older minor, parental consent to testing and treatment is not generally required; however it is obviously preferable for young people to have their parents' support, and consent may be required by law. Accepting or refusing HIV testing should not lead to detrimental consequences to the quality of care offered to the individual.

6.3.1 Provider Initiated Testing and Counselling

Provider initiated testing and counselling (PITC) means that health care providers should recommend HIV testing and counselling to all children (and their family) presenting to a health facility, for whatever reason. The purpose of PITC is to make sure that the medical and other care interventions that would improve HIV-infected individuals' quality of life are provided in a timely manner. However,

- All HIV testing must be voluntary, confidential, and undertaken with the patient's and/or their family's consent.
- Informed consent from a child's parent or guardian is required, and every effort should be made to explain to the child what is happening and obtain her/his assent, according to their level of development.
- Patients have the right to decline the test. They should not be tested for HIV against their will, without their knowledge, without adequate information, or without receiving their test results.

HIV testing and counselling should be recommended to:

- All HIV-exposed infants
- Any infant or child presenting with signs, symptoms or medical conditions that could indicate HIV. Symptomatic infants require urgent testing.
- All Infants and children in generalized epidemic settings.^a
- All newborns, infants and children and the mothers of unknown HIV status in settings where local or national antenatal HIV seroprevalence is greater than 1%.^b
- All pregnant women.

^a Defined as: where HIV is firmly established in the general population. Although sub-populations at high risk may contribute disproportionately to the spread of HIV, sexual networking in the general population is sufficient to sustain an epidemic independent of sub-populations at higher risk of infection. Numerical proxy: HIV prevalence consistently over 1% in pregnant women.

^b Countries should determine prevalence thresholds and other circumstances where this recommendation should be followed.

6.4 Diagnosis of HIV under special conditions

6.4.1 Presumptive diagnosis of severe HIV disease in infants and children aged under 18 months where viral testing is not available

No single clinical diagnostic algorithm has proved to be consistently and highly sensitive or specific for diagnosing HIV infection, and in particular, they are less reliable in infants. However, there are situations where the use of a clinical algorithm may be required to initiate treatment of a seriously ill child.

Criteria for presumptive diagnosis of severe HIV disease:

- | | |
|----------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|
| 1. The child is confirmed as being HIV antibody-positive | 2a. The infant is symptomatic with two or more of the following:
oral thrush
severe pneumonia
severe sepsis |
| AND | OR |
| | 2b. Diagnosis of any AIDS-indicator condition(s) ^a can be made |

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

Recent HIV-related maternal death or advanced HIV disease

Child's %CD4+ < 20%

Confirmation the diagnosis of HIV infection as soon as possible.

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

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.

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, e.g. fast breathing, chest indrawing, bulging fontanelle, lethargy, reduced movement, not feeding or sucking breast milk, convulsions.

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

For infants and children less than 18 months of age, where access to viral testing is not available, but when they have symptoms suggestive of HIV infection and positive HIV antibody testing, a presumptive clinical diagnosis of severe HIV-infection may be necessary in order to permit the initiation of potentially life-saving ART. Criteria for diagnosis are shown in the table below. HIV serological test should be repeated at 18 months of age to confirm HIV infection. Note that WHO clinical staging of HIV disease can only be employed where HIV infection has been established.

6.4.2 Diagnosing HIV infection in breastfeeding infants

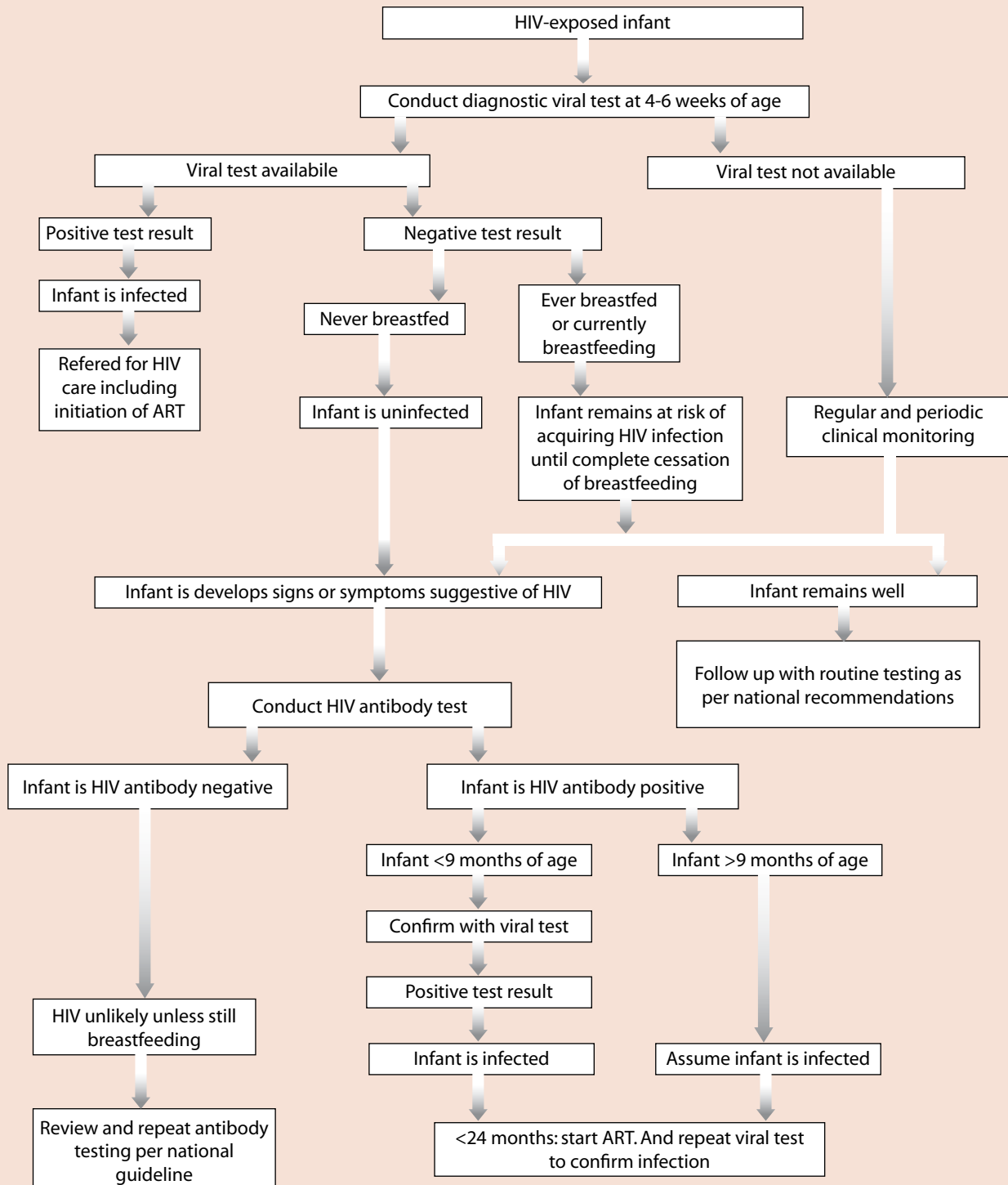
A breastfeeding infant is at risk of acquiring HIV infection throughout the breastfeeding period. Breastfeeding should not be stopped in order to perform diagnostic HIV viral testing. Positive test results should be considered to reflect HIV infection, with the usual confirmatory algorithms followed. However, interpreting negative results is difficult. A six-week window period after the complete cessation of breastfeeding is required before negative viral test results can be assumed to reliably indicate HIV infection status. For children over 12 months of age, the six week window is also required before HIV antibody testing.

6.4.3 Diagnosing HIV infection when mother or infant has received ARVs for PMTCT

HIV DNA assays are reliable for diagnosis when the mother or infant has been given ARV drugs for PMTCT. HIV-1 DNA remains detectable in the peripheral blood mononuclear cells and lymphoid tissue of HIV-infected children who have received ART and have undetectable viral replication as measured by HIV-RNA assays. DNA detection in the infant is not affected by maternal ART when the mother is breastfeeding.

It is not known whether maternal ART during breastfeeding affects HIV-RNA or Up24Ag detection in infants. Research indicates that all types of viral testing can be used from 6 weeks of age, even if the mother is breastfeeding and on ART--despite theoretical concerns about the sensitivity of HIV -RNA and Up24Ag assays in infants exposed to ARVs. Mothers should not discontinue the use of ART and should not discontinue breastfeeding for the purposes of testing for HIV.

Figure 3. Testing sequence for initial and subsequent visits of HIV-exposed infant



^a The risk of HIV transmission remains as long as the breastfeeding continues

^b Usually HIV antibodies testing from 9-18 months of age

Figure 4. Diagnostic HIV testing for sick infants where viral testing is available

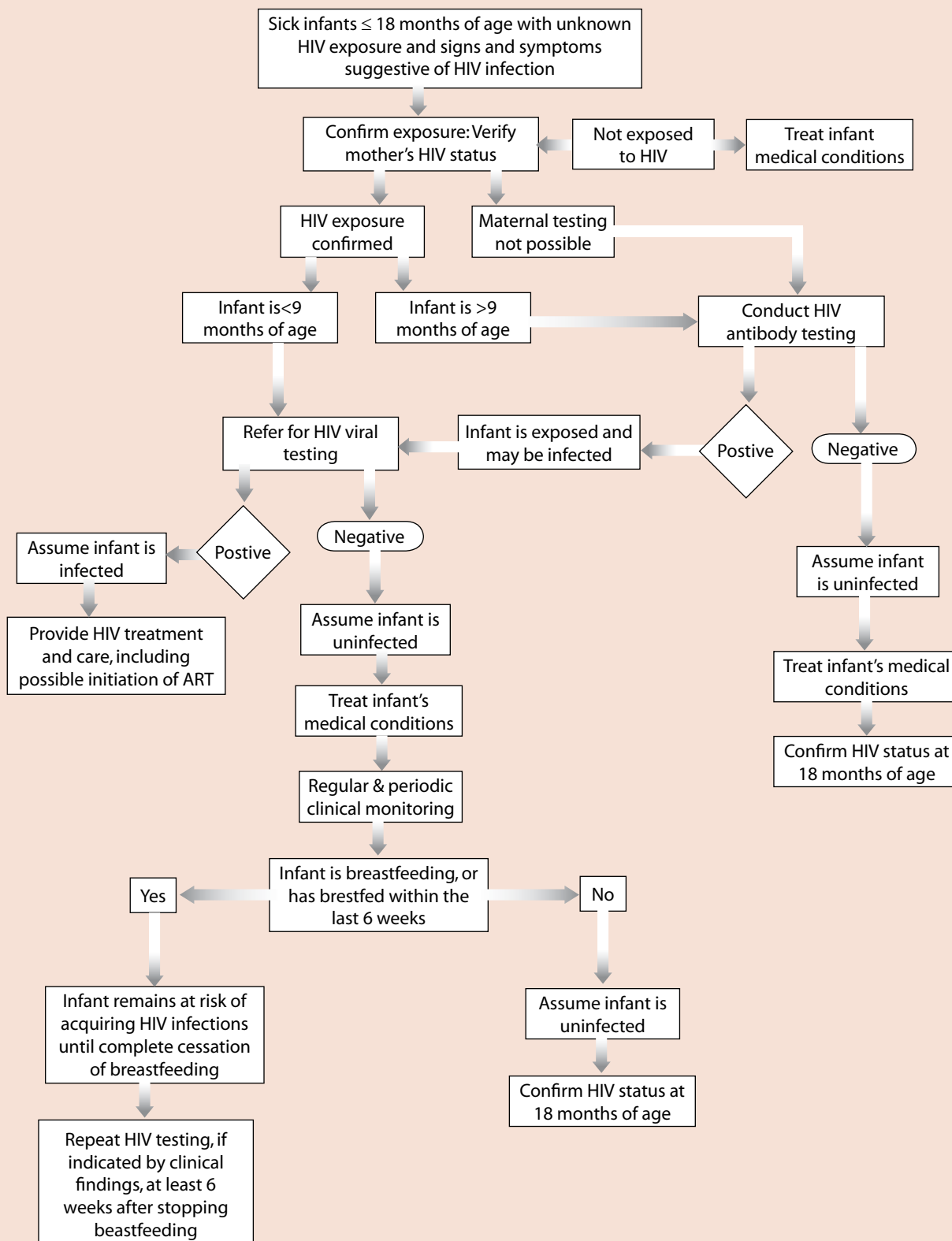
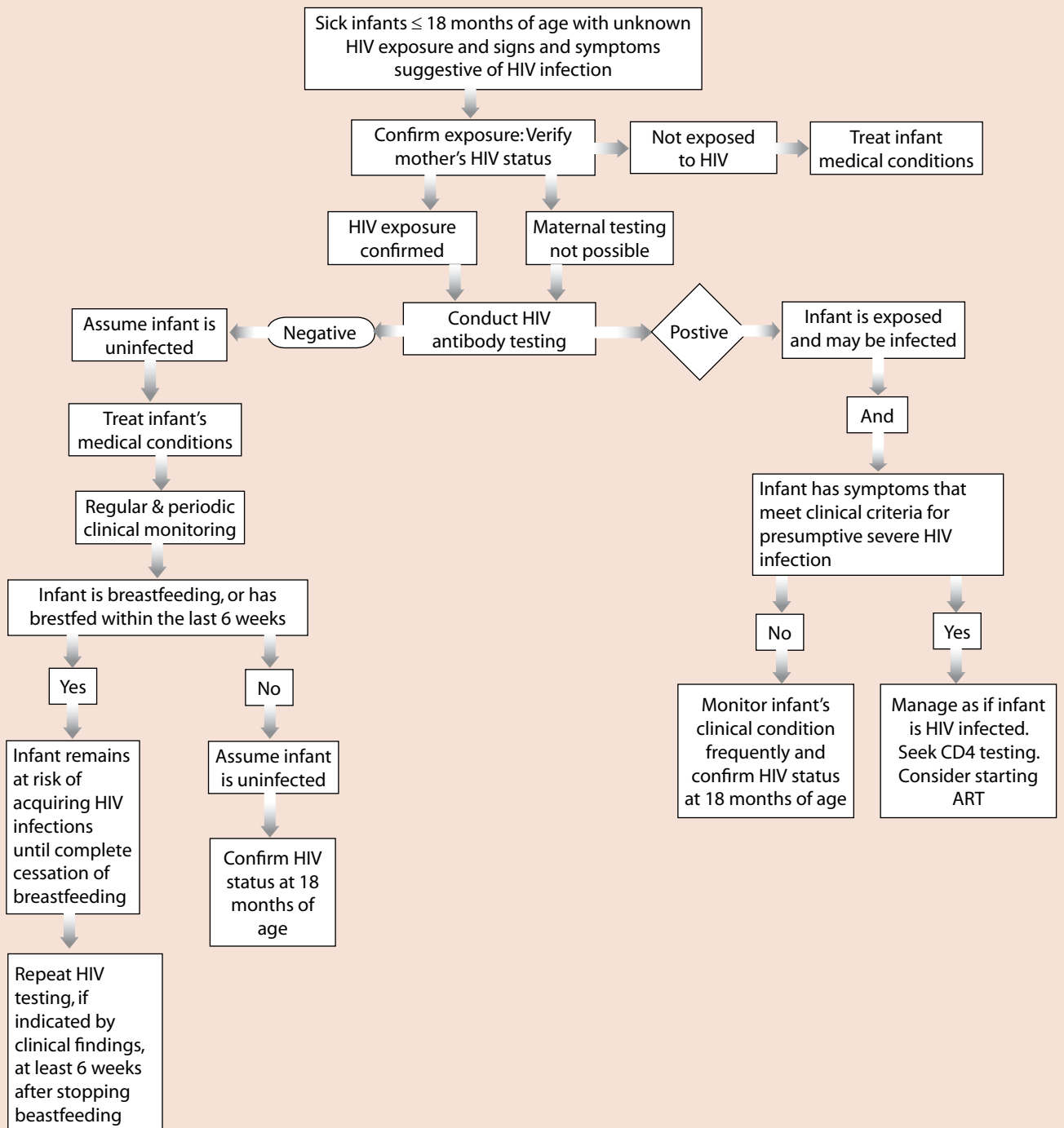


Figure 5. Diagnostic HIV testing for sick infants where viral testing is not available



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Chapter 7

Routine care for HIV-exposed and infected infants and children

Facts to consider in the care of HIV-exposed infants:

Exposed infants who are HIV-infected may not immediately present with signs and symptoms suggestive of HIV infection, but once they get sick they can rapidly deteriorate, even with normal CD4 levels.

- So all HIV infected infants and children <24 months must be immediately started on ART regardless of the clinical or immunological stage
- Clinical care providers should include HIV infection in their differential diagnosis of all infants at risk of, or known to be exposed to, HIV.
- If a mother has died of AIDS, the child's risk of dying is increased 3-4 times, even for children who are not HIV-infected. Therefore, special vigilance and accurate counseling of caregivers is very important at every visit.

HIV-exposed or infected infants and children should be provided with comprehensive care in the broader context of child health strategies. In addition to routine well-baby and under-5's clinic services, the following should be provided to HIV-exposed infants and children:

7.1 Immunizations

As early in life as possible, HIV-exposed infants and children should receive all vaccines under the Expanded Programme for Immunization (EPI), including *Haemophilus influenzae* type B and pneumococcal vaccine.

This should be done according to recommended national immunization schedules.

Modification to EPI schedules may be required for infants and children who are HIV-infected:

- Measles: Because of the increased risk of early and severe measles infection, infants with HIV should receive a dose of standard measles vaccine at six months of age, with a second dose as soon as possible after nine months of age, unless they are severely immuno-compromised at that time.
- Pneumococcal vaccine: Immunization with pneumococcal conjugate vaccine should be delayed if the child is severely immuno-compromised.
- *Haemophilus influenzae*: *Haemophilus influenzae* type B conjugate vaccine should be delayed if the child is severely immuno-compromised (until when?).
- BCG: New findings indicate a high risk of disseminated bacille Calmette-Guérin (BCG) disease developing in infants who have HIV, and therefore BCG vaccine should not be given to children known to be HIV-infected. However, infants cannot always be identified as HIV-infected at birth, so in areas with high prevalence of TB and of HIV, BCG vaccination should generally be given to all infants at birth.

7.2 Prophylaxis

7.2.1 Co-trimoxazole preventive therapy starting at 4-6 weeks of age

Co-trimoxazole prophylaxis prevents pneumocystis pneumonia (PCP) in infants and reduces morbidity and mortality among infants and children living with, or exposed, to HIV. Co-trimoxazole protects against common bacterial infections, toxoplasmosis, and malaria.

- All children born to HIV-infected mothers should receive co-trimoxazole prophylaxis starting at 4-6 weeks after birth, or at first encounter with the health care system. They should continue until HIV infection has been excluded and the infant is no longer at risk of acquiring HIV through breastmilk.
- In the infected child, co-trimoxazole should be continued until the child is 5 years of age AND ON ART WITH SUSTAINED CD4 ABOVE 25%. Adherence should be discussed at initiation and monitored at each visit.
- Dapsone can be provided for children who cannot tolerate co-trimoxazole.
- Severe adverse reactions to co-trimoxazole in children are uncommon.
- Co-trimoxazole is contraindicated for infants and children with glucose-6-phosphate dehydrogenase deficiency and those with a history of severe adverse reaction to co-trimoxazole or other sulpha drugs.

Table 7.2.1a: Who needs co-trimoxazole prophylaxis?

HIV-exposed infants and children	Situation		
	Infants and children confirmed to be living with HIV infection		
	< 1 year	1 – 4 years	≥ 5 years
Co-trimoxazole prophylaxis is universally indicated, starting at 4-6 weeks after birth and maintained until cessation of risk of HIV transmission and exclusion of HIV infection.	Co-trimoxazole prophylaxis is indicated regardless of CD4 percentage or clinical status	WHO clinical stages 2, 3 and 4 regardless of CD4 percentage OR Any WHO stage and CD4 <25%	Follow adult recommendations
Once a child with HIV infection is started on co-trimoxazole, prophylaxis should continue until five years of age regardless of clinical symptoms or CD4 percentage.			

Adapted from: WHO, 2006. Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults in resource-limited settings. Recommendations for a public health approach.

Table 7.2.1b: Co-trimoxazole dosage and formulations for infants and children

RECOMMENDED DAILY DOSAGE		SUSPENSION	CHILD TABLET	SINGLE-STRENGTH ADULT TABLET	DOUBLE-STRENGTH ADULT TABLET
		(5 ml syrup 200mg/ 40 mg)	(100 mg/ 20 mg)	(400 mg/ 80 mg)	(800 mg/ 160 mg)
<6 months	100 mg sulfamethoxazole/ 20 mg trimethoprim	2.5 ml	One tablet	¼ tablet, possibly mixed with feeding ^a	--
6 months – 5 years	200 mg sulfamethoxazole/ 40 mg trimethoprim	5 ml ^b	Two tablets	Half tablet	--
6 – 14 years	400 mg sulfamethoxazole/ 80 mg trimethoprim	10 ml ^b	Four tablets	One tablet	Half tablet
>=15 years	800 mg sulfamethoxazole/ 160 mg trimethoprim	--	--	Two tablets	One tablet

a Splitting tablets into quarters is not considered best practice and should be done only if syrup is not available.

b Children of these ages (6 months -14 years) may swallow crushed tablets.

Adapted from: WHO, 2006. Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults in resource-limited settings. Recommendations for a public health approach.

Circumstances when co-trimoxazole should be discontinued in infants and children

- Co-trimoxazole prophylaxis can be discontinued when HIV infection has been excluded and the infant or child is no longer at risk of acquiring HIV through breastmilk.
- Co-trimoxazole prophylaxis may need to be discontinued in the event of an adverse drug reaction. Although severe reactions to co-trimoxazole are uncommon, these may include:
 - Severe cutaneous reaction such as Stevens-Johnson syndrome
 - Severe anaemia
 - Pancytopenia
 - Renal and/or hepatic insufficiency
 - Severe haematological toxicity

As with all long-term medication, everyone starting co-trimoxazole should be provided verbal or written information on the potential adverse effects, and advised to stop the drug and report to the nearest health facility if co-trimoxazole-related adverse events are suspected.

There is insufficient data on co-trimoxazole desensitization among children to make any recommendations on its use in resource-limited settings.

7.2.2 Isoniazid (INH)

TB screening is **strongly recommended** for all infants, children and adults with HIV.

In addition to early ART the WHO recommends the *Three I's for HIV/TB* to reduce TB morbidity and mortality in people, including children living with HIV.

Decrease the burden of TB in people living with HIV with the Three I's for HIV/TB

1. Establish Intensified TB case-finding.
2. Introduce Isoniazid prevention therapy (IPT).
3. Ensure TB Infection control in health care and congregate settings.

TB screening, infection control for TB, and IPT should be core functions of HIV prevention, treatment and care services for infants, children and adults living with HIV.

The TB status of HIV-infected patients should be monitored at all visits to health providers. Those with symptoms or signs suggestive of TB should undergo further clinical investigation. Screening is essential in order to treat TB, and to determine whether patients are eligible for isoniazid (INH) preventive therapy (WHO 2010 recommendation).

Intensified tuberculosis case finding and prevention in children living with HIV

WHO recommends (refer to the guidelines for intensified tuberculosis case finding and isoniazid preventive therapy for people living with HIV in resource constrained settings):

Strong recommendation

- Children living with HIV who do not have poor weight gain, fever or current cough are unlikely to have active TB.
- Children living with HIV who have any one of poor weight gain, fever, current cough, or contact history with a TB case may have TB and should be evaluated for TB and other conditions. If the evaluation shows no TB, they should be offered IPT regardless of their age.
- Children over 12 months of age who are living with HIV and who are unlikely to have active TB on symptom-based screening, and have no contact with a TB case, should receive 6 months of INH preventive therapy (10mg/kg) as part of a comprehensive package of care.
- Children less than 12 months of age, only those children who have contact with a TB case and who are evaluated for TB (using investigations) should receive 6 months IPT if the evaluation shows no TB disease.

Conditional recommendation

- All children living with HIV after successful completion of treatment for TB disease should receive INH for an additional 6 months.

According to WHO, a tuberculin skin test (TST) may provide important additional information in assessing a child with suspected TB, especially if there is no positive contact history—but it is not required to initiate IPT in children, and should not be routinely used as part of the process to determine eligibility to initiate IPT.

Similarly IGRA (Interferon Gamma Release Assay) cannot discriminate between *M. tuberculosis* infection and active TB disease. Encouraging data shows that IGRAs are more sensitive than TST in HIV infected children, including those with a low CD4 count and/or malnutrition. In addition, excellent specificity for *M. tuberculosis* infection has been reported and unlike TST, IGRAs are unaffected by prior BCG vaccination or exposure to environmental mycobacteria. However more

evidence is needed and implementation issues affecting most HIV/TB endemic settings have to be solved. Therefore the use of IGRAs remains *not recommended* outside of research settings with lab validation procedures.

WHO recommends the use of a simplified screening algorithm that relies on four clinical symptoms to identify those eligible for either IPT or further diagnostic work-up for TB and other conditions (see page 11).

TB information provided to all patients with HIV, and to caregivers of infants and children with HIV, should include:

- the importance of knowing your HIV and TB status
- the importance of being regularly screened for TB
- risks of acquiring TB
- ways of reducing risks
- clinical manifestations of TB
- the risks of transmitting TB to others
- TB preventive therapy, where appropriate
- the importance of raising awareness in respective communities and community advocacy on paediatric HIV and TB prevention, treatment and care.
- the importance of setting up patient groups and networks to disseminate information on paediatric HIV and TB prevention, treatment and care.

INH should be provided as TB preventive therapy to all people with HIV *once active TB disease has been excluded*. Criteria are being developed for INH prophylaxis for HIV-exposed or HIV-infected infants and children <5 years of age. However for the time being, existing IMAI recommendations should be considered within the context of national guidelines, and include:

- Specialist advice should be sought for preventive therapy for those with multidrug-resistant or extensively drug-resistant TB.
- Previous TB is not a contraindication to TB-preventive therapy. WHO conditionally recommends that all children who have been successfully treated for TB and living in settings with high TB prevalence and transmission should receive IPT for an additional 6 months, and that IPT can be started immediately following the last doses of anti-TB treatment.
- Intensified TB case finding in people living with HIV is essential since TB is a curable disease. Intensified HIV case finding in people with TB is also essential because cotrimoxazole prophylaxis can prevent complications.

Isoniazid preventive therapy for TB contacts aged less than 5 years

- Children aged less than 5 years are at special risk for TB.
 - If a child aged less than 5 years has cough, fever, or weight loss, refer to clinician for assessment of TB
 - If child does not have TB, give Isoniazid daily for 6 months to prevent TB.
- Give preventive therapy with Isoniazid ONLY to children who do not have TB or possible TB and are well and thriving. Give 10 mg/kg Isoniazid daily for at least 6 months.
- See child monthly. Give one month supply of Isoniazid at each visit.

7.2.3 Other prophylaxis

Cryptococcus is a significant cause of illness and death in children (and adults) with HIV. Other fungal infections may be important depending on local epidemiological patterns.

In areas where cryptococcal disease is common, antifungal prophylaxis with azoles may be provided for HIV-infected adults if their condition satisfies specific clinical and immunological criteria. Further research is required before azole prophylaxis for HIV-infected children can be recommended.

7.3 Nutrition

A child has increased energy needs associated with HIV infection, which requires a proactive approach to nutritional support:

- From the time of first infection, energy needs increase by about 10%
- In HIV-infected children with chronic conditions such as LIP, persistent diarrhoea, HIV-related malignancies, and during infections such as TB, energy needs can increase by about 25-30%
- During and following periods of severe malnutrition, energy requirements may increase by 50-100% in order to recover weight
- These increased requirements are over and above normal energy and protein requirements that are needed by all children to support normal growth and development (see Chapter 10, sections 1, 2 and 5 in the Pocketbook of Hospital Care for children).

Nutritional assessment should be conducted for HIV-exposed and infected infants and children, covering:

- current nutritional status (weight and weight change, height, Body Mass Index or mid-upper arm circumference, symptoms)
- diet (access to food, care-giving practices, protein and micronutrient intake, possible drug-food interactions)

Children experiencing growth failure (i.e. failure to gain weight, or weight loss between regular measurements) or feeding difficulties require targeted support, including:

- counselling and education about locally available food choices, how to feed and manage anorexia and, where indicated, referral to food programmes
- Diagnose and treat any underlying illness
- Evaluate child for the need for, or switch of, ART.
- For conditions that interfere with normal ingestion or digestion (e.g. mouth ulcers, oral thrush, diarrhoea), counsel caregivers on how to alleviate symptoms and provide foods that can help ensure sufficient energy intake.

7.3.1 Infant feeding counselling and support

Breastfeeding reduces child mortality and has health benefits that extend into adulthood. For children born to HIV-negative mothers, the WHO recommends exclusive breastfeeding for the first six months of life, followed by continued breastfeeding with appropriate complementary foods for two years or beyond.

For mothers known to be HIV-infected, the WHO recommends that national (or sub-national) health authorities should decide whether health services will principally counsel and support mothers to:

- breastfeed and receive ARV interventions, **or**
- avoid all breastfeeding, as the strategy that will most likely give infants the greatest chance of HIV-free survival.

This decision should be based on international recommendations and should consider: the socio-economic and cultural contexts of the populations served by Maternal and Child Health services, the availability and quality of health services, and the local epidemiology, including HIV prevalence among pregnant women, the main causes of infant and child mortality, and the status of maternal and child under-nutrition.

Of infants born to HIV-positive women, an estimated 5% to 20% of infants will become infected through breastfeeding if HIV-related interventions are not provided. The risk of HIV transmission through breastfeeding increases with advanced maternal disease, low CD4 cell count, high viral load, mixed feeding, and prolonged duration of breastfeeding.

In resource-limited settings, breastfeeding is still the single most important intervention to prevent deaths in infants with HIV-positive mothers. Additionally, ARV interventions for infants and mothers significantly reduce HIV transmission through breastfeeding. Even when antiretroviral drugs are not (immediately) available, breastfeeding may still provide infants born to HIV-infected mothers with the greatest chance of HIV-free survival.

In countries where breastfeeding is the policy for HIV positive mothers:

- Women who are taking antiretroviral therapy for their health should exclusively breastfeed the infant for 6 months and continue breastfeeding as complementary feeds are added after six months. The baby should be given NVP from birth to 6 weeks of life.
- Women who were given AZT for prophylaxis during pregnancy should continue with AZT through the breastfeeding period. The baby is also given NVP during breastfeeding until one week after all exposure to breast milk has ended.

References for further reading

1. WHO. (2010). *Priority interventions: HIV/AIDS prevention, treatment and care in the health sector*. Geneva, World Health Organization. Available at: <http://www.who.int/hiv/data/en/>.
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Chapter 8

Antiretroviral Therapy (ART)

Antiretroviral (ARV) drugs continue to become more widely available, and it is now clear that the initiation of antiretroviral therapy (ART) at the earliest appropriate time is crucial to reducing mortality and morbidity for infants and children.

The focus for infants and children on ART has shifted from a response to an acute condition, to beginning a treatment program that they will be on for the rest of their lives. Recommendations for the care of those who are HIV-infected will change over time, but the challenges of providing this care are becoming the challenges of managing both acute and chronic conditions. ART is life-long therapy, and HIV-infected infants and children are surviving to adolescence and adulthood.

8.1 When to start ART for infants and children

WHO recommendations for when to start infants on ART changed in 2008. All HIV-infected infants under 24 months of age should begin ARVs, regardless of clinical or immunological status. Children 24 months and older should begin ARVs according to clinical and/or immunological criteria.

8.2 When to initiate ART in HIV-infected Infants AND CHILDREN UNDER 24 MONTHS (WHO 2010 recommendation)

- All CHILDREN <24 months of age with confirmed HIV infection should be started on ART, irrespective of clinical or immunological stage.
- Where viral testing is not available, infants <18 months of age with clinically diagnosed presumptive severe HIV should start ART. Confirmation of HIV infection should be obtained as soon as possible.

8.3 When to initiate ART in HIV-infected children 24 months of age and older

The decision of when to start ART in children is based on a combination of clinical and immunological criteria.

- For children ≥ 24 months of age, clinical and immunological thresholds should be used to identify those who need to start ART.
- For children ages 24-59 months, initiate ART for all children with:
 - Clinical Stage 3 and Stage 4 disease
 - CD4 <25% or CD4 count <750
- For children aged ≥ 60 months, initiate ART for all children with
 - Clinical Stage 3 and Stage 4 disease
 - CD4 count <350
- ART should generally be deferred until after acute infections have been treated.
- In the case of confirmed or presumptive TB disease, initiating TB treatment is the priority. Any child with active TB disease should begin TB treatment immediately and start ART as soon as tolerated within the first 8 weeks of TB therapy, irrespective of the CD4 count and clinical stage
- Deciding when to start ART one should also consider the child's social environment, including identification of a clearly defined caregiver who understands the prognosis of HIV and the requirements of ART.

8.3.1 Clinical criteria for eligibility for ART

- Clinical stages are a guide of when to start ARV therapy in HIV-infected children, especially in children aged less than or equal to 24 months. However it is less useful in children <24 months.
- Clinical staging system helps to recognize the degree of damage to the immune system and is used to plan treatment and care options.
- The clinical stages identify a progressive sequence from least to most severe, with each higher clinical stage having a poorer prognosis.
- Children in Clinical Stage 1 and 2 should be considered for ART when the CD4 value falls close to the threshold values set for each age group. A drop below the threshold value should be avoided as it is associated with higher mortality.
- However, relying only on clinical criteria may recognize the need to start ART too late. Therefore, countries are urged to ensure increased and optimal access to CD4 measurement technologies.

Baseline clinical and laboratory assessment

Following confirmation of HIV infection status the baseline, *clinical assessment* for children should include:

- clinical staging of HIV disease;
- identification of concomitant medical conditions (e.g. TB, pregnancy in adolescent girls);
- detailing of concomitant medications, including co-trimoxazole and traditional or herbal therapies;
- weight, height, head circumference and other measures of growth;
- developmental status;
- nutritional status, including assessment of quality and quantity of intake;

laboratory assessment should include:

- haemoglobin
- white blood cell count
- pregnancy test for sexually active adolescent girls;
- screening for TB and malaria (and diagnostic testing where clinically indicated), and for other major treatable HIV co-infections and HIV-related opportunistic diseases as clinically indicated.
- (CD4 monitoring and VL is desirable but not essential).

8.3.2 Immunologic criteria for eligibility for ART

- CD4 levels in children not infected with HIV are considerably higher than observed in uninfected adults, but then the CD4 levels slowly decline to match adult values by the age of about 6 years.
- Compared to absolute CD4 counts, the CD4 percentage values in young children vary less with age.
- In children <5 years of age, the absolute CD4 count is naturally more variable and age-dependent than %CD4.
- Serial CD4 measurements are more informative than individual values, as they reflect trends over time. Where possible, these assessments should compare the same parameter.
- The predictive value of total lymphocyte count (TLC) for mortality is not reliable, especially for younger infants. Therefore it is not recommended to use TLC to guide decisions on starting ART.

Tables 8.1 and 8.2 below summarize immunological criteria and combined clinical and immunological criteria for initiating ART.

Table 8.3.2a Immunological Criteria for initiating ART in infants and children; (2010)

Immunological Criteria for starting ART			
Age	Infants and Children <24 months	24 months through to 59 months	Five years and above
% CD4+	All regardless of CD4 levels	< 25%	Not Applicable
Absolute DC4+		< 750	<350 as in adults

Table 8.3.2b Recommendations for initiating ART in HIV-infected infants and children according to clinical stage and immunological markers

	Clinical stage	Immunological
<24 months	<i>Treat all</i>	
≥24 months	Stage 4 ^a	<i>Treat all</i> ^b
	Stage 3 ^c	<i>Treat all</i>
	Stage 2	No CD4 available: <i>Don't treat</i>
	Stage 1	or CD4 below age-adjusted threshold: <i>Treat</i>

^a Stabilize any opportunistic infection before initiation of ART.

^b Baseline CD4 is useful for monitoring ART even if it is not required to initiate ART.

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

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

In a child under 18 months, using a presumptive clinical diagnosis for initiating ART should be accompanied by immediate efforts to establish the HIV diagnosis with the best nationally or locally available test for age, and at the latest with an HIV antibody test at 18 months of age. Once the results are received, decisions on further treatment should be adjusted in accordance. The details of the clinical parameters used in presumptive diagnosis are summarised in Table 8.3 below.

Table 8.3.3 Criteria for presumptive diagnosis of severe HIV disease in infants and children aged under 18 months where viral testing is not available

A presumptive diagnosis of severe HIV disease should be made if:	
1. The infant is confirmed as being HIV antibody-positive	2a. The infant is symptomatic with two or more of the following:
AND	<ul style="list-style-type: none"> ◦ oral thrush ◦ severe pneumonia ◦ severe sepsis
	OR
	2b. Diagnosis of any AIDS-indicator condition(s) ^a can be made

Other things that support the diagnosis of severe HIV disease in an HIV-seropositive infant include:
Recent HIV-related maternal death or advanced HIV disease
Child's %CD4+ < 20%

Confirmation the diagnosis of HIV infection as soon as possible.

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

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.

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, e.g. fast breathing, chest indrawing, bulging fontanelle, lethargy, reduced movement, not feeding or sucking breast milk, convulsions.

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

8.3.4 Assessing the family's psycho-social readiness for ART

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

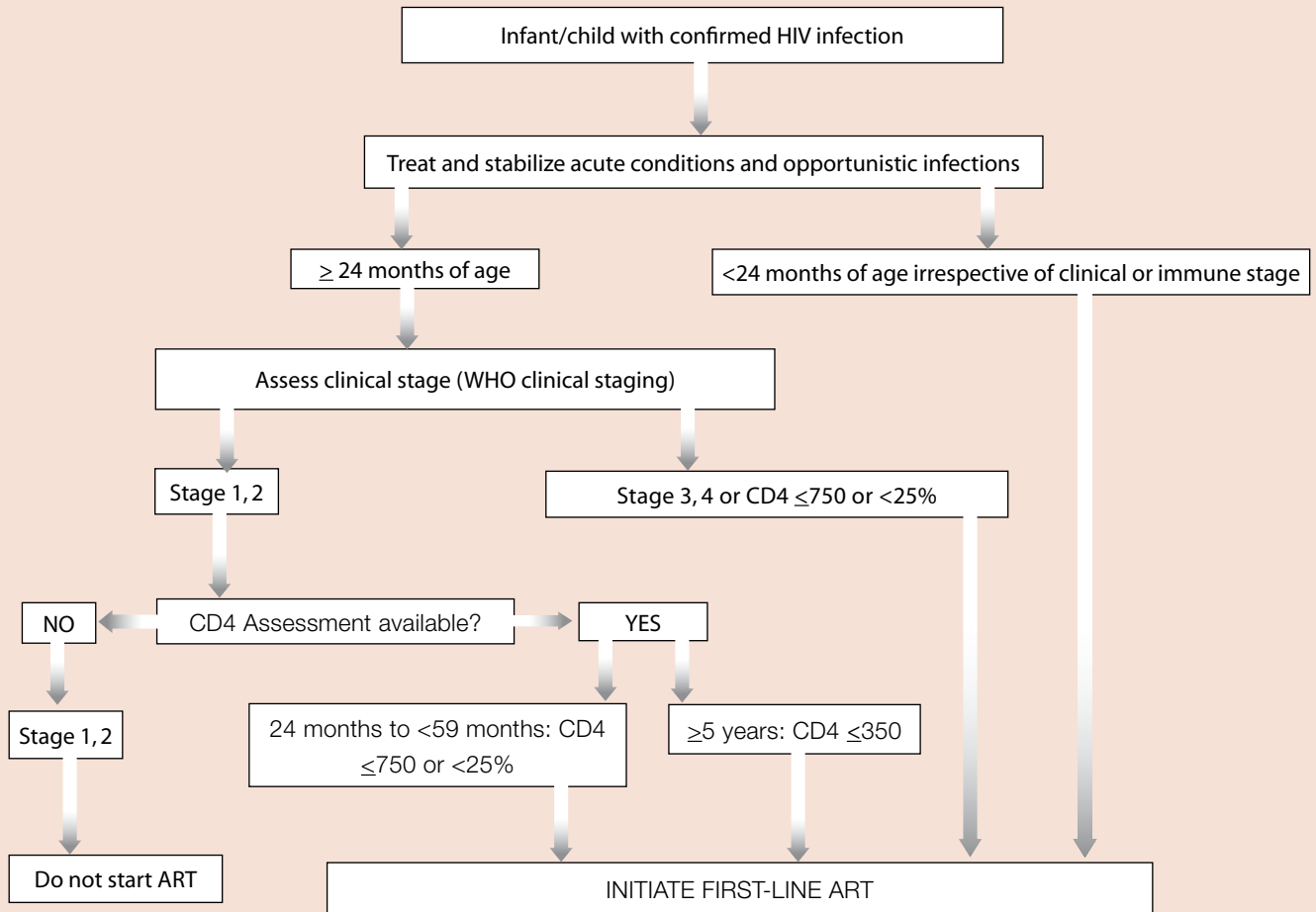
8.3.5 Routine clinical assessment of children who are not yet eligible for ART

The clinical evaluation of children who are not yet eligible for ART should be performed every 3-6 months and should include the same parameters used in baseline assessment. Together with the results of CD4 measurement, they are useful for updating the child's WHO paediatric clinical and immunological stage at each visit, and for determining if the child has become eligible for treatment.

As the child approaches the clinical or immunological threshold for initiating ART, clinical evaluation and CD4 measurements should be obtained more frequently. Additionally, due to the rapid rate of disease progression in young children, more frequent clinical and laboratory monitoring is critical.

Figure 6: Initiating ART for Infants and Children

Confirmation: serologic or virologic depending on age



8.3.6 Recommended first-line ARV regimens for infants and children

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

8.3.7 Drug formulations and doses for infants and children

Important considerations for ART regimens for infants and children include: the availability of a suitable formulation that can be taken in appropriate doses; simplicity of the dosage schedule; and the taste and palatability, and thus the potential for compliance in young children. Fixed-dose combinations (FDCs) are increasingly available for younger children, and are preferred to syrups and single drugs because they promote and support treatment adherence and reduce the cost of treatment. Adult tablets that require cutting up can result in underdosing or overdosing when given to children, and this may lead to an increased risk of resistance or toxicity. However, while the splitting of adult-dose solid formulation ARVs is suboptimal, it may be the only available option for treating children, and may be considered when no alternatives are available. The use of tablet cutters is beneficial, but it is preferable not to cut tablets to fractions below a half.

Dosing in children is usually based on either body surface area, or weight, OR MORE CONVENIENTLY BY WEIGHT BAND. As these change with growth, drug doses must be adjusted in order to avoid the risk of underdosage. ARV drug doses are provided in Annex A and B

8.4 ART drugs

Antiretrovirals comprise three main classes of drugs:

1. Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTIs)

Zidovudine	ZDV (AZT)
Lamivudine	3TC
Stavudine	D4T
Didanosine	Ddl
Abacavir	ABC
Emtricitabine	FTC

2. Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Nevirapine	NVP
Efavirenz	EFV

3. Protease Inhibitors (Pis)

Nelfinavir	NFV
Lopinavir/ritonavir	LPV/r
Atazanavir	ATZ

8.4.1 Paediatric ART regimens

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

NRTI's include:	
<i>a thymidine analogue</i>	zidovudine [AZT] or stavudine [d4T] (STAVUDINE IS NO LONGER PREFERRED)
Or	
<i>a guanosine analogue</i>	abacavir [ABC]
combined with	
<i>a cytidine analogue</i>	lamivudine [3TC] or emtricitabine [FTC]
NNRTI's include:	
	Efavirenz* [EFV] or nevirapine [NVP]

*Efavirenz should only be used in children over 3 years of age

8.4.2 Choice of a first-line regimen for infants

8.4.2.1 Infants with no exposure to NNRTIs

Standard nevirapine-containing triple therapy is the preferred option when choosing a first-line regimen for infants (<12 months) without exposure to maternal or infant NNRTIs, or whose exposure to maternal or infant ART is unknown.

Standard nevirapine-containing infant regimen

2 NRTIs + 1 NVP

8.4.2.2 Infants exposed to nevirapine

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

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

Infant protease inhibitor-based regimen

Lopinavir/ritonavir + 2 NRTIs

8.4.2.3 Choice of a first-line regimen for children

The recommended first line regimen for HIV-infected children >12 months of age is two NRTIs plus one NNRTI. Exceptions to this regimen:

- Efavirenz (EFV) *should not be used* in:
 - adolescent girls due to the teratogenic potential of EFV in the first trimester of pregnancy
 - in children <3 years of age due to lack of appropriate dosing information in this age group.

- Nevirapine (NVP) should not be used in adolescent girls with CD4 counts >250 cells/mm³ due to the risk of hepatotoxicity.

Infant protease inhibitor-based regimen

2 NRTIs + 1 NNRTI

8.4.3 Alternative regimen restricted to special circumstances

The use of a triple NRTI regimen (Box X4) can be considered as an option for simplifying initial therapy in special circumstances. Its use is currently restricted to special circumstances:

- Infants and children receiving TB treatment, where NVP may not be an optimal choice because of drug interactions with rifampicin.
- Treatment of pregnant adolescent girls with CD4 absolute cell counts >250/mm³.
- Adolescents with anticipated or documented poor adherence.

Regimen of triple NRTI

AZT/d4Ta + 3TCb + ABC

Of concern is the somewhat lower virological potency of this regimen compared to a two-class triple drug combination in adult studies.

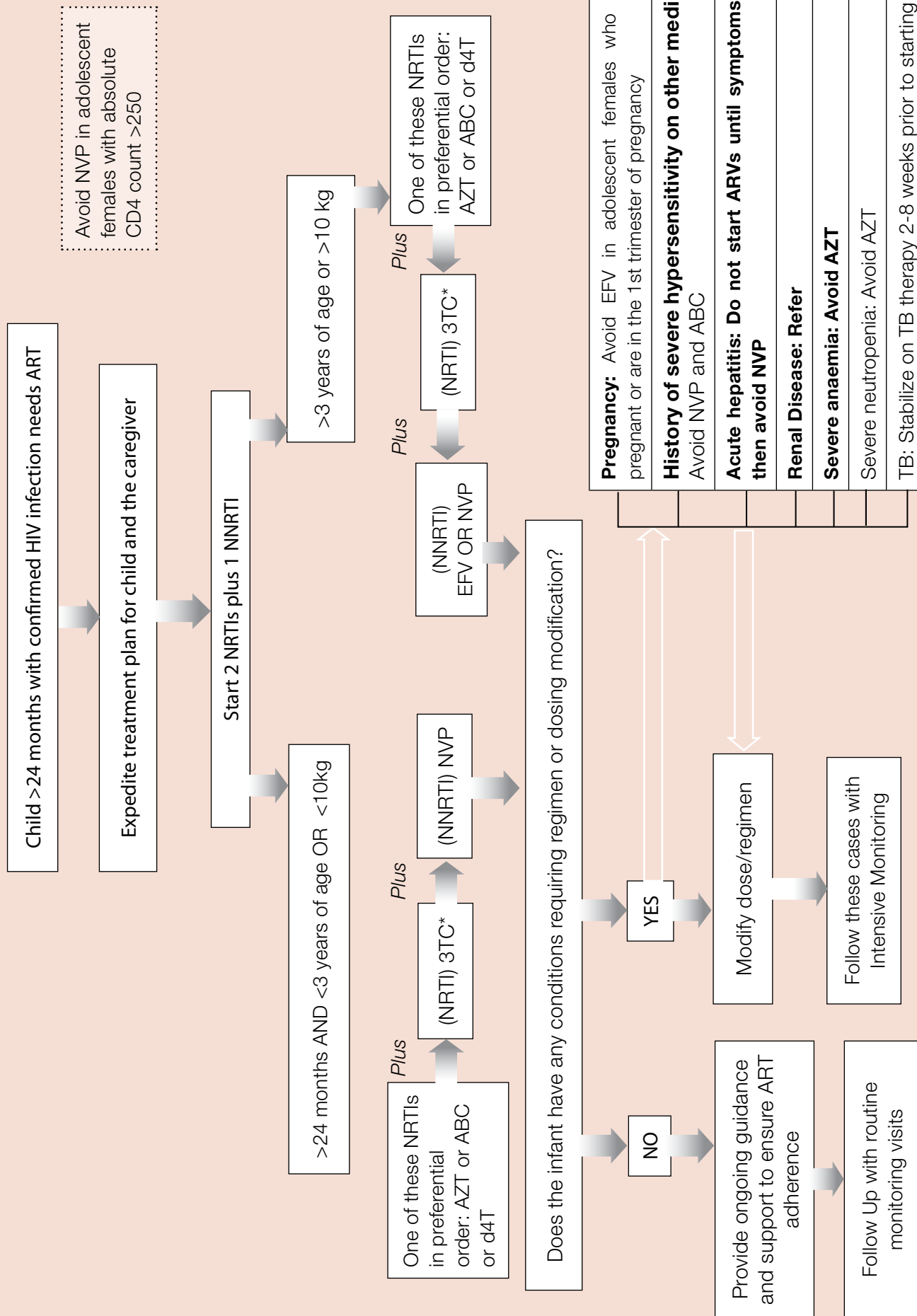
8.4.4 Second-line regimens

- In the event of treatment failure, the entire regimen should be changed from a first-line to a second-line combination.
- The new second-line regimen should include at least three new drugs, one or more of them from a new class.

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

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

Figure 8: First Line ART for Children >24 months



8.5 Clinical and Laboratory Monitoring

Clinical and laboratory assessments are generally required: at the time an infant or a child becomes known as HIV-exposed, during the time when they are not yet eligible for ART, at the time when they begin ART, and then ongoing throughout their lives.

8.5.1 Routine clinical monitoring of children on ART

Once an infant or child is on ART, in addition to the laboratory parameters, a clinical assessment should address the child's and/or caregiver's understanding of therapy adherence and their need for additional support.

Observation of the child's responses to therapy (i.e. reassessment of clinical stage) should be vigilant for symptoms of potential drug toxicities or treatment failure. Particularly important signs of infants' and children's responses to ART include:

- improvement in growth in children who have been failing to grow;
- improvement in neurological symptoms and development in children with encephalopathy or who have been demonstrating delay in the achievement of developmental milestones; and/or
- decreased frequency of infections (bacterial infections, oral thrush and/or other opportunistic infections).

The frequency of clinical monitoring depends on the response to ART. At a minimum, after starting ART, follow up visits should occur:

- For infants, at weeks 2, 4, 8, and then every 4 weeks for the first year.
- For children, at weeks 2, 4, 8, 12, and then every 2-3 months once the child has stabilized on therapy.

8.5.2 Routine laboratory monitoring of children on ART

Laboratory assessment of CD4 values is desirable every six months, or more frequently if clinically indicated.

- In infants and children initiating first-line regimens containing AZT, haemoglobin measurement should be performed during the first few months of treatment (at weeks 4, 8 and 12 after initiation of ART) or in a symptom-directed approach.
- Tests of liver function (i.e. liver enzymes) are recommended for infants or children receiving nevirapine during the first few months of treatment, or who have co-infection with hepatitis viruses, or who are on hepatotoxic medications.

When choosing other laboratory parameters, also consider clinical symptoms for assessing the response to therapy. Some routine monitoring tests may be advisable in accordance with the specific drugs used, but laboratory monitoring of adverse events should largely be directed by clinical symptoms.

It should be noted that an inability to perform laboratory monitoring should not prevent children from receiving ART.

VL should be assessed 6 months after ART initiation for infants on NVP-based regimens who were exposed to NVP intrapartum or during breastfeeding. Failure to suppress the VL to below 5000 copies/ml in an adherent child at this time indicates the need to switch NVP for LPV/r.

Table 8.5.2: Laboratory parameters for monitoring infants and children at baseline, before and during ART

Diagnosis and monitoring laboratory tests	Baseline (at entry into care)	At initiation of first-line or second-line ARV regimen	Every six months	As required or symptom-directed
HIV diagnostic testing: viral and Ab testing	✓	-	-	-
Haemoglobin ^a	✓	✓	-	✓
WBC and differential ^b	✓	✓	-	✓
%CD4+ or absolute CD4 cell count ^c	✓	✓	✓	✓
Pregnancy testing in adolescent girls	✓ ^d	✓	-	✓
Full chemistry (including, but not restricted to, ALT, ^e liver enzymes, renal function, glucose, lipids, amylase, lipase and serum electrolytes) ^f	-	-	-	✓
HIV viral load measurement ^g	-	-	-	✓

^aHaemoglobin monitoring at weeks 4, 8 and 12 after initiation of ART is recommended by some experts if AZT is used.

^bMonitoring at weeks 4, 8 and 12 after initiation of ART is optional.

^cChildren not yet eligible for ART should be monitored with CD4 every six months. For infants and children who develop new or recurrent WHO stage 2 or 3 events or whose CD4 approach threshold values the frequency of CD4 measurement can be increased. %CD4+ is preferred in children <5 years of age.

^dPregnancy testing may be needed for adolescent girls prior to initiating a regimen containing EFV.

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

^fRegular monitoring (every six months) of full chemistry, particularly lipid levels, liver enzymes and renal function, should be considered for infants and children on second-line drugs.

^gAt present, viral load measurement is not recommended for decision-making on the initiation or regular monitoring of ART in resource-limited settings. Tests for assessment of HIV RNA viral load can also be used to diagnose HIV infection [17], and to assess discordant clinical and CD4 findings in children suspected of failing ART.

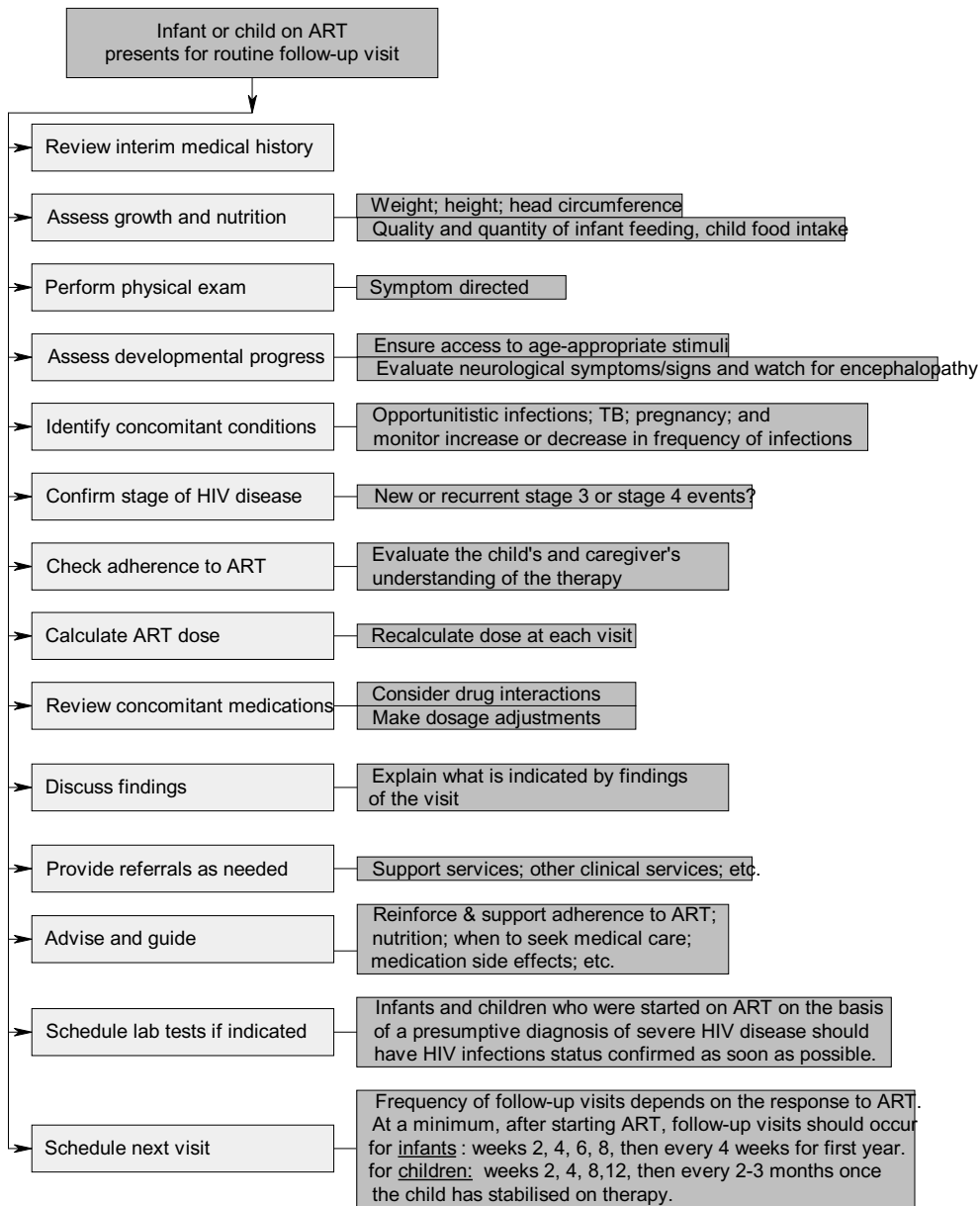
8.6 Adherence

Adherence to at least 90% of doses is necessary to maximize the long-term benefits of ART. However, there are special challenges to long-term adherence in children, some of which are listed below.

1 Drug Issues:

- Limited choice of formulations and drugs
- Poor palatability
- Large liquid volume
- Complex measurements and dosing requirements leading to inaccurate dosing
- Side-effects

Routine Follow Up Visit



Laboratory testing	Baseline	At Start of ART	Every 6 Months	As Indicated
HIV diagnostic testing: virological and Ab testing	X			
Haemoglobin	X	X		X
WBC and differential	X	X		X
%CD4 or absolute CD4 cell count	X	X	X	X
Pregnancy testing in adolescent girls	X	X		X
Full chemistry				X
HIV viral load measurement				X

2-Caregiver Issues:

- Family unit is often disrupted as a consequence of adverse health or economic conditions.
- Mothers of HIV-infected children are frequently HIV-infected themselves and the care of the children may be less than optimal because of the mothers' compromised health.
- May be difficult to find committed responsible caregivers

3-Disclosure:

- Fear of disclosure of status to family, friends or schools, restricts the child's access to essential support.

4-Developmental stages of childhood

- Development influences the extent to which the child will cooperate with regular administration of medicine and needs to be considered

5-Maximizing Adherence

- Efforts to support and maximize adherence should begin before treatment is initiated. Developing an adherence plan is essential. Elements of that plan include:
 - Education
 - Basic information about HIV, natural history, benefits and risks of ART
 - Taking the medications properly—for example, if medications are mixed with food, consuming all food is important in order to ensure full administration
 - How to manage severe and non-severe adverse effects
 - Special Approaches for children
 - Caregivers practising measuring liquids
 - Training in pill swallowing.
 - Identifying a back-up informed caregiver to be involved in providing care
 - Fitting the ARVs into the child's (or caregiver's) lifestyle
 - Match drug regimens for children to those for adult caregivers

6-Special Care with NNRTI based regimens:

Adherence during the first days and weeks of treatment is critical to the long-term success of a regimen—particularly for NNRTI drugs, which have been associated with rapid resistance development. NNRTI components have half-lives that are several days longer than the half-lives of NRTI components, therefore a sudden or periodic interruption of NRTIs results in sub-therapeutic drug levels, and may lead to developing NNRTI resistance. Therefore with an NNRTI regimen, emphasizing the need to consistently take the ARV drugs is therefore particularly important.

7- Measuring adherence

- Continuously assessing adherence is vital to a comprehensive and sustainable approach to ART delivery. Adherence monitoring should be a duty of every health care provider participating in the care of HIV-infected children. It should be performed whenever there is a visit to a health centre in order to identify children in need of the greatest support for adherence. Methods to measure adherence include:
 - Ask child or caregiver how many doses of medication have been missed during the past 3, 7 or 30 days
 - Leftover pill counts if child is on tablets or capsules
 - Comparing weights of returned bottles with bottles with known quantities of syrup

- Viral load measurements to assess adherence
- MCV measurements in patients on ZDV or D4T - USUALLY ELEVATED
- Reviews of pharmacy records
- Obtaining descriptions of impediments to adherence or problems encountered.

8- Supporting Adherence

- In addition to assessing adherence, ongoing adherence support is a vital component of successful treatment. Practical aids can be helpful, including:
 - Use of calendars or other visual AIDS to illustrate dosing
 - Pillboxes, blister packs and labelled syringes
 - Directly observed therapy
 - Treatment supporters have been successful in some settings, especially in families where the caregiver is also HIV-infected and may be unwell
 - Community and psychological support can be critical to caregivers as well as to children
 - Peer support groups may be particularly beneficial for mothers with young children on ART
- Note that adherence may vary with time: families may have periods when adherence is excellent and other periods when it fails, often because of changing life circumstances
- Adherence may also suffer as the child responds to therapy, health improves, and the motivation to take daily medication decreases.

8.7 ARV drug toxicity

One factor that affects adherence is toxicity from the ARV medicines. The content of the box below and Flow chart 10.4X capture the principles for management of such toxicities when they occur

Box 8.7 Guiding principles in the management of ARV drug toxicity

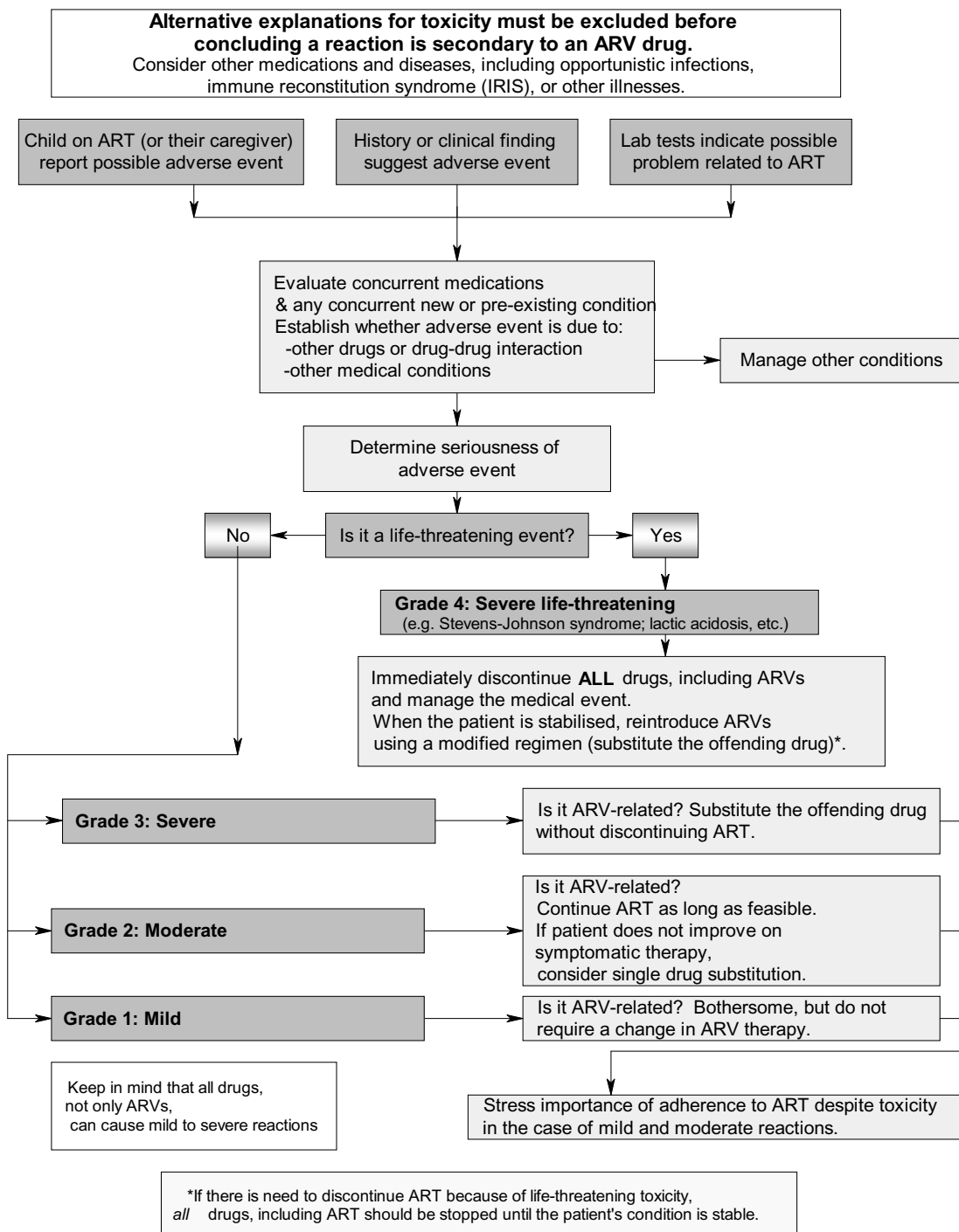
1. Determine the seriousness of the toxicity.
2. Evaluate concurrent medications and establish whether the toxicity is attributable to an ARV drug (or drugs), or to a non-ARV medication taken at the same time.
3. Consider other disease processes (e.g. concurrent infectious process / common childhood illnesses). Not all problems during treatment are caused by ARV drugs.
4. Manage the adverse event according to severity. In general:
 - Severe life-threatening reactions: Immediately discontinue all ARV drugs, manage the medical event (i.e. symptomatic and supportive therapy) and reintroduce ARV drugs using a modified regimen (i.e. with an ARV substitution for the offending drug) when the patient is stabilized.^a
 - Severe reactions: Substitute the offending drug without stopping ART.
 - Moderate reactions: Consider continuing ART as long as feasible. If the patient does not improve on symptomatic therapy, consider single-drug substitutions.^a For a few moderate toxicities (e.g. peripheral neuropathy or lipodystrophy) single drug substitution needs to be considered earlier.
 - Mild reactions are bothersome but do not require changes in therapy.
5. Stress the maintenance of 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.

- Before concluding that ARV drugs are the primary cause for toxicity, alternative explanations for toxicity must be excluded.
- Adverse reactions that have a non-ARV drug aetiology do not require changing the ARV drug.

Drug-related adverse events may be:

- Acute occurring soon after a drug has been administered;
 - subacute, occurring within 1 to 2 days of administration
 - late, occurring after prolonged drug administration
 - varying in severity, from mild to severe and life-threatening
- Adverse events may affect adherence to therapy. Proactively manage toxicity:
 - Discuss potential ART regimen side-effects with the child and caregivers before starting the regimen, and continue discussions during the early stages of treatment.
 - Increase the likelihood of adherence by offering support during minor and moderate adverse events.
 - Some acute ARV drug toxicities are time-limited; symptoms can resolve while continuing ART.
 - Ensure child/caregivers are familiar with signs of serious and life-threatening toxicities that require immediate contact with the provider; especially Stevens-Johnson syndrome, symptomatic hepatitis, and ABC-associated hypersensitivity reaction.

Figure 9 Management of ARV toxicity



1. For grading of severity, see Chapter 15 and Annex's F and G in *Management of HIV Infection and Antiretroviral Therapy in Infants and Children; A Clinical Manual*, WHO and UNICEF, 2006.

8.8 IRIS: Inflammatory immune reconstitution syndrome

IRIS has been observed in patients on ART who are also receiving anti-TB therapy. IRIS occurs most often during the first 3 months of ART.

IRIS is characterized by:

- worsening of disease after initial clinical improvement
- with new onset of systemic symptoms, especially fever
- worsening of pulmonary infiltrates
- development of peripheral and mediastinal adenopathy
- expanding CNS lesions in patients with tuberculomas
- SHINGLES

Clinical disease progression should be differentiated from the IRIS, as symptoms can be similar to those seen in opportunistic infections. Immunological reconstitution may lead to the development of atypical presentations of some opportunistic infections.

- A thorough evaluation is necessary to exclude other causes (e.g. TB treatment failure), before diagnosing IRIS.
- IRIS is generally self-limiting and last 10–40 days.
- Some cases of IRIS may be severe and require a short course of treatment with a glucocorticoid.

8.9 Substituting drugs because of toxicity in infants and children

If toxicity is related to an identifiable drug in a regimen, the offending drug can be replaced with another drug from the same class that does not have the same adverse effect.

Given the limited number of ARV drug options available, drug substitutions should be limited to situations where toxicity is severe or life-threatening.

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 (efavirenz) because of the potential for class-specific toxicity; this would require a change to either a triple NRTI regimen or to a protease inhibitor, thereby introducing a drug class usually reserved for second-line regimens.

Figure 10: Severe toxicities of first-line ARVs in infants and children, and potential drug substitutions

Severe toxicities in infants and children associated with specific first-line ARV drugs and potential first-line drug substitutions

Toxicity Event	Most Usual ARV Cause	Suggested first-line ARV drug substitution
Acute symptomatic hepatitis ^a	NVP	EFV ^b
Hypersensitivity reaction		Preferred substitution of NVP to: - a third NRTI (disadvantage: may be less potent) <i>or</i> -PI (disadvantage: premature start of class usually reserved for second-line) ^d
Severe or life-threatening rash (Stevens-Johnson syndrome) ^c		
Lactic acidosis	d4T	ABC ^e
Peripheral neuropathy		AZT or ABC ^f
Pancreatitis		
Lipoatrophy/metabolic syndrome ^g		ABC
Severe anaemia ^h or neutropenia ⁱ	AZT	d4T or ABC
Lactic acidosis		ABC ^e
Severe gastrointestinal intolerance ^j		d4T or ABC
Persistent and severe central nervous system toxicity ^k	EFV	NVP
Potential teratogenicity (adolescent girl in first trimester of pregnancy, or of childbearing potential and not receiving adequate contraception)		
Hypersensitivity reaction	ABC	AZT
Lipoatrophy/metabolic syndrome	LPV/r ^l	NNRTI

Note: 3TC/FTC-associated pancreatitis has been described in adults but is considered very rare in children.

a Symptomatic NVP-associated hepatotoxicity is very rare in HIV-infected children before adolescence.

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

c Severe rash is defined as extensive rash with desquamation, angioedema, or a reaction resembling serum sickness; 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 because of the potential for NNRTI-class specific toxicity.

d The introduction of the PI class of drugs in the first-line regimens leads to limitations in the choice of drugs in the event of treatment failure (i.e. second-line regimens).

e Reinitiation of ART should not include d4T or AZT if possible, therefore ABC is preferred.

f In children, ABC or AZT can be considered as an alternative.

g Substitution of d4T typically may not reverse lipoatrophy.

h Exclude malaria in areas of stable malaria; severe anaemia is defined as Hb < 7.5 g/dl

i Defined as neutrophil count <500/mm³

j Defined as severe, refractory gastrointestinal intolerance that prevents ingestion of ARV drug regimen (e.g. persistent nausea and vomiting).

k e.g. persistent hallucinations or psychosis.

l. LPV/r is the only PI recommended as a first-line drug for NVP-exposed infants.

8.9.1 First-line Regimen Treatment Failure; when to switch regimens

ARV treatment failure may be due to:

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

A reasonable trial on the therapy is required before an ARV regimen is determined to be failing, based on clinical criteria alone:

1. The child should have received the regimen for at least 24 weeks
2. Adherence to therapy should be assessed and considered optimal
3. Any opportunistic infections should be treated and resolved
4. Immune reconstitution inflammatory syndrome (IRIS) must be excluded.
5. Before considering a switch of treatment because of growth failure, ensure the child is receiving adequate nutrition

Treatment failure is identified using

1. clinical criteria
2. CD4 criteria, where possible
3. Virological criteria, where possible

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

8.9.2 Defining treatment failure

8.9.2.1 Clinical definition of treatment failure

The detection of new or recurrent clinical events classified within the WHO clinical staging may reflect progression of disease when a child is on ART. Treatment failure should be considered when either new or recurrent clinical stage 3 or 4 events develop in a child who has been on therapy for at least 24 weeks and is proven to be adherent on treatment.

A new or recurrent stage 4 event may be sufficient criterion to consider switching. Similarly switch may be considered with a new or recurrent stage 3 event, in the absence of CD4 measurements—except in a child with pulmonary or lymph node TB, or with severe recurrent bacterial pneumonia (all considered clinical stage 3 events). Such child should receive appropriate TB or antibacterial therapy and re-evaluated before switching regimens (see table below).

Table 8.9.2a Using the WHO Paediatric Clinical Staging events to guide decision-making on switching to second-line therapy for treatment failure

New or recurrent event on ART ^{a, b}	Management options ^{c, d}
No new events or PGL (T1)	<ul style="list-style-type: none"> ○ Do not switch to new regimen ○ Maintain regular follow up
Stage 2 events (T2)	<ul style="list-style-type: none"> ○ Treat and manage staging event ○ Do not switch to new regimen ○ Assess and offer adherence support ○ Assess nutritional status and offer support ○ Schedule earlier visit for clinical review and consider CD4
Stage 3 events (T3)	<ul style="list-style-type: none"> ○ Treat and manage staging event and monitor response^e ○ Check if on treatment 24 weeks or more ○ Assess and offer adherence support ○ Assess nutritional status and offer support ○ Check CD4^f – where available ○ Institute more frequent follow-up ○ Consider switching regimen
Stage 4 (T4)	<ul style="list-style-type: none"> ○ Treat and manage staging event ○ Check if on treatment 24 weeks or more ○ Assess and offer adherence support ○ Assess nutritional status and offer support ○ Check CD4^f – where available ○ Switch regimen

^a A clinical event refers to a new or recurrent condition as classified in the WHO clinical staging at the time of evaluating the infant or child on ART.

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

^c Differentiation of opportunistic infections from IRIS is important.

^d In considering changing treatment because of growth failure, it should be ensured that the child has adequate nutrition and that any intercurrent infections have been treated and resolved.

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

^f CD4 is best performed once acute phase of presenting illness is resolved.

8.9.2.2 Immunological definition of treatment failure

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

Comparing with previous CD4 values is required to recognize treatment failure on the basis of immunological values. Treatment failure is characterized by a drop in the CD4, after the initial immune recovery following ART initiation, to values at or below the age-related CD4 threshold for treatment initiation (see table below).

Box 8.9.2b CD4 criteria suggesting immunological failure^{a, b, c}

- Development of age-related severe immunodeficiency after initial immune recovery.
- New progressive age-related severe immunodeficiency, confirmed with at least one subsequent CD4 measurement.
- Rapid rate of decline to below threshold of age-related severe immunodeficiency.
- Failure to rise from initiation value to above threshold.

In a fully adherent child who has been on ART for at least 24 weeks, ART Failure is considered if, in :

- 2 to 4 years old, CD4 count is <200cells/mm³ml or %<10
 - 5 years and older, CD4 <100 cells/mm³
-

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

^b Preferably at least two CD4 measurements should be available.

^c use of %CD4+ in children aged under 5 years and absolute CD4 counts after 5 years of age is preferred; if serial CD4 values are available the rate of decline should be taken into consideration.

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

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

Table 8.9.2c Decision-making on switching to second-line therapy for treatment failure based on availability of CD4 measurement

New or recurrent clinical event on ART ^a	Availability of CD4 measurement ^b	Management options ^c
T1 or T2 event(s)	No CD4	<ul style="list-style-type: none"> ○ Do not switch regimen
	CD4	<ul style="list-style-type: none"> ○ Consider switching regimen only if two or more values below the age-related threshold for severe immunodeficiency^d are available ○ Increase clinical and CD4 follow-up if CD4 approaches the age-related threshold for severe immunodeficiency^e
T3 event	No CD4	<ul style="list-style-type: none"> ○ Consider switching regimen^{e,f}
	CD4	<ul style="list-style-type: none"> ○ Switching regimen is recommended if CD4 is below the age-related threshold for severe immunodeficiency^d and particularly if the child initially had a good immune response to ART ○ Increase clinical and CD4 follow-up if CD4 approaches age related threshold for severe immunodeficiency
T4 event	No CD4	<ul style="list-style-type: none"> ○ Recommend switching regimen
	CD4	<ul style="list-style-type: none"> ○ Switching is generally recommended but it may not be necessary where CD4 is above age related threshold for severe immunodeficiency

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

^b Consideration of previous CD4 is useful.

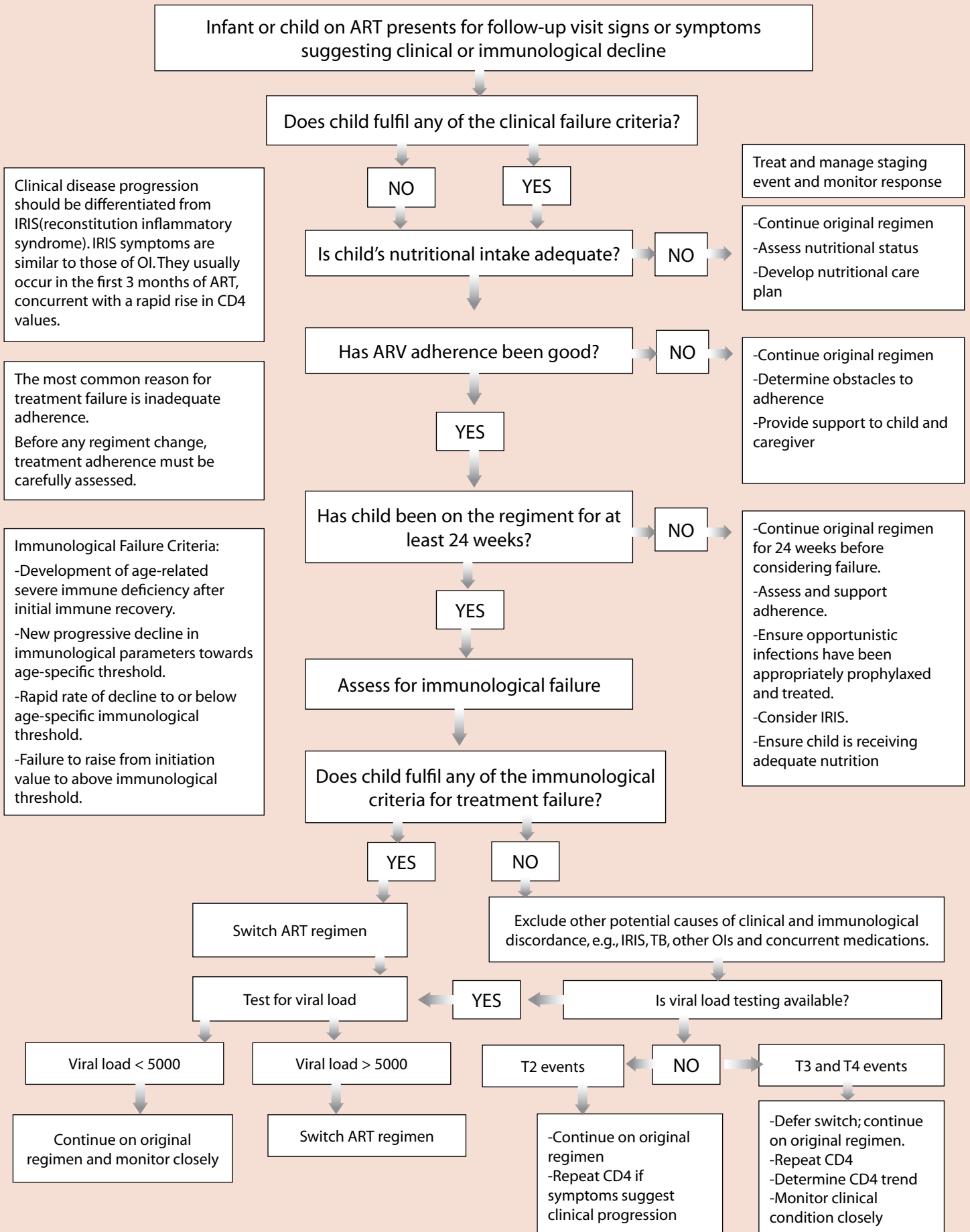
^c Any intercurrent infections should be treated according to national treatment guidelines and it is necessary to ensure that the child had at least 24 weeks of ART, adherence to therapy has been assessed and considered adequate before considering switching to a second-line regimen. Additionally, in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

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

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

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

Figure 11 Management of ARV treatment failure when CD4 testing is available



8.10 Choice of second-line regimens in the event of treatment failure

- In the event of treatment failure, the entire regimen should be changed from a first-line to a second-line combination.
- The new second-line regimen should include at least three new drugs, one or more of them from a new class.

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

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

SITUATION	Preferred first line regimen	Preferred second line regimen
INFANTS		
Infant not exposed to ARV	NVP + 2 NRTI	LPV/r + 2 NRTI
Infant exposed to NVP	LPV/r + 2NRTI	NNRTI + 2NRTI
Infant with unknown ARV exposure	NVP + 2 NRTI	LPV/r + 2 NRTI
CHILDREN		
Children 12 months or over	NNRTI + 2NRTI	Boosted PI + 2 NRTI
CONCOMITANT CONDITIONS		
Child or adolescent with severe anaemia	NVP + 2NRTI no AZT	Boosted PI + 2 NRTI
Child, adolescent or adult with TB	EFV + 2NRTI or 3NRTI	Boosted PI + 2 NRTI
Adolescent with Hepatitis B	TDF + 3TC + NNRTI	Boosted PI + 2 NRTI
Adolescent with Hepatitis C	EFV + 2NRTI	Boosted PI + 2 NRTI

References for further reading

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4. WHO. (2010). *Guidelines for intensified tuberculosis case finding and isoniazid preventive therapy for people living with HIV in resource constrained settings*. Geneva, World Health Organization. Available at: <http://www.who.int/hiv/pub/tb/9789241500708/en/index.html>

Chapter 9

Nutritional Support

Anorexia and wasting (low weight-for-height) are characteristic of HIV-infection. Anorexia can prevent infants and children from achieving optimum growth or from maintaining proper nutritional status. Furthermore, HIV infection increases energy requirements, and the side-effects of medications for treating HIV can intensify anorexia. In situations where undernutrition already is common, these problems may become even more acute.

Key Practices for Infant and Young Child Nutrition

The principles of infant and young child nutrition apply to all children, regardless of whether or not they are infected with HIV. **However, special considerations and adjustments to these principles are necessary in the context of HIV.**

The key practices of Essential Nutrition Actions (to all infants and children)

- Infants should be **exclusively** breastfed from immediately after birth through six months of age. Breastfeeding should be frequent and on-demand, day and night.
- Infants should be fed solid food from six months of age as a complement to breast milk (**which should continue on demand until at least 24 months**). The type and quantity of food, and the frequency of feeding should be appropriate for the infant/child's age (refer to feeding and nutrition in IMCI guidelines).
- Sick infants and children should continue to feed, and additional feeding is necessary to recover nutritional status during and after illness.
- Infants and children require adequate micronutrient intake, particularly in the case of vitamin A, iron, iodine and zinc

9.1 Special Considerations for HIV Infection

There are three main considerations in the context of HIV infection that affect these key practices.

Baseline clinical and laboratory assessment

- Improve chances of survival for children of mothers known to be HIV-infected,
- Prevent of mother-to-child-transmission (MTCT) of HIV via breast feeding,
- Increase energy requirements of HIV infection,
- Prevent and respond to HIV-related wasting.

9.2 Prevention of mother-to-child-transmission (MTCT) of HIV via breast feeding

HIV can be transmitted through breast milk, and the risk of transmission remains as long as infants and children breastfeed. While avoiding breastfeeding might seem to be an obvious way to prevent this risk, using breast milk substitutes (BMS) denies an infant the immune protection that breast milk provides, and exposes him/her to pathogens. In countries with high infant mortality, children are more likely to die from formula feeding than from HIV (Kuhn, Stein and Susser, 2004).

For these reasons WHO recommends that national (or sub-national) health authorities should decide whether health services will principally counsel and support mothers known to be HIV-infected to:

- breastfeed and receive ARV interventions, or
- avoid all breastfeeding, as the strategy that will most likely give infants the greatest chance of HIV-free survival.

This decision should be based on international recommendations and should consider: the socio-economic and cultural contexts of the populations served by Maternal and Child Health services, the availability and quality of health services, and the local epidemiology, including HIV prevalence among pregnant women, the main causes of infant and child mortality, and the status of maternal and child under-nutrition.

In settings where national authorities decide to promote and support breastfeeding and ARVs to reduce HIV transmission to infants:

- **Mothers known to be HIV-infected (and whose infants are HIV uninfected or of unknown HIV status)** should exclusively breastfeed their infants for the first 6 months of life, introducing appropriate complementary foods thereafter, and continue breastfeeding for the first 12 months of life.
- Breastfeeding should then only stop once a nutritionally adequate and safe diet without breast milk can be provided.
- When HIV-infected mothers decide to stop breastfeeding (at any time) they should do it so gradually within one month.
- Mothers known to be HIV-infected should also be provided with lifelong antiretroviral therapy or antiretroviral prophylaxis interventions to reduce HIV transmission through breastfeeding according to WHO recommendations

Up to 6 months of age

- **Breastfeed exclusively** as often as the child wants, day and night.
- Feed at least 8 times in 24 hours
- Do not give other foods or fluids (mixed feeding may increase the risk of HIV transmission from mother to child when compared with exclusive breastfeeding).

6 months to 12 months

- Give 3 adequate servings of nutritious complementary foods plus one snack per day (to include protein, mashed fruit and vegetables). Each meal should be 3/4 cup.
- If possible, give an additional animal source food, such as liver or meat

Please note that HIV exposed infants energy intake should be increased by 10% even in the absence of symptoms.

In countries where the policy is formula feeding:

Formula feed exclusively (no breast milk at all)

- Give formula or modified cow's milk. Other foods or fluids are not necessary.
- Prepare correct strength and amount just before use.
- Use milk within an hour and discard any left over (a fridge can store formula for 24 hours)
- Cup feeding is safer than bottle feeding
- Clean the cup and utensils with soap and water
- Give the formula 6 to 8 times per day

Up to 6 Months of Age

- Give formula
- Other foods or fluids are not necessary
- Prepare correct strength and amount just before use. Use milk within two hours and discard any left over (a fridge can store formula for 24 hours)
- Cup feeding is safer than bottle feeding
- Clean the cup and utensils with hot soapy water
- Give these amounts of formula 6 to 8 times per day

* Exception: heat-treated breast milk can be given

Age mos	Average amount and times/ day
0 up to 1	60 ml x 8
1 up to 2	90 ml x 7
2 up to 3	120 ml x 6
3 up to 4	120 ml x 6
4 up to 5	150 ml x 6
5 up to 6	150 ml x 6

6 months up to 12 months

- Give about 1-2 cups (500 ml) of full cream milk or infant formula per day
- Give milk with a cup, not a bottle
- If no milk is available, give 4-5 feeds per day
- Give 3 adequate servings of nutritious complementary foods plus one snack per day (to include protein, mashed fruit and vegetables). Each meal should be 3/4 cup*.
- If possible, give an additional animal-source food such as liver or meat.

12 month up to 2 years

- Give 3 adequate nutritious feeds plus 2 snacks per day (each meal should be 1 cup).
- If possible, give an additional animal-source food, such as liver or meat.
- Give fruit or vegetables twice every day
- Give about 2 cups (250 x 2=500 ml) of full cream milk or infant formula per day. If no milk is available, give 4-5 feeds per day.
- Feed actively with own plate and spoon

9.2.1 Stopping breastfeeding

Changing from all breast milk to no breast milk (gradually within 1 month).

Plan in advance to have a safe transition.

Stop breastfeeding as soon as this is AFASS

Help mother prepare for stopping breastfeeding:

- Mother should discuss stopping breastfeeding with her family if possible
- Express milk and give by cup

- Find a regular supply of formula or other milk, e.g. full cream cows milk
- Learn how to prepare and store milk safely at home

Help mother make the transition:

- Teach mother to cup feed her baby
- Clean all utensils with soap and water
- Start giving only formula or cows milk

Stop breastfeeding completely

Counsel the mother about stopping breastfeeding:

- While you are breastfeeding teach your infant to drink expressed breast milk from a cup. This milk may be heat-treated to destroy HIV.
- Once the infant is drinking comfortably, replace one breastfeed with one cup feed using expressed breast milk.
- Increase the number of cup-feeds every few days and reduce the number of breastfeeds. Ask an adult family member to help with cup feeding.
- Stop putting your infant to your breast completely as soon as your baby is accustomed to frequent cup feeding. From this point on it is best to give your child heat treated expressed breast milk.
- If your infant is receiving milk only check that your baby has at least 6 wet nappies in a 24 hour period. This means he is getting enough milk.
- Gradually replace the expressed breast milk with commercial infant formula or home-modified animal milk.
- If your infant needs to suck, give him/her one of your clean fingers instead of the breast.
- To avoid breast engorgement (swelling) express a little milk whenever your breasts feel full. This will help you feel more comfortable.
- Use cold compresses to reduce inflammation.
- Wear a firm bra to prevent discomfort.
- Do not begin breastfeeding again once you have stopped. If you do you can increase the chances of passing HIV to your infant.
- If your breasts become engorged express breast milk by hand.
- Begin using a family planning method of your choice, if you have not already done so, as soon as you start reducing breastfeeds.

9.3 Increased energy requirements of HIV-infected children.

Breastfeeding is recommended for HIV-positive children following the same guidelines for the general population of children (HIV-negative and unexposed children). However the daily energy requirements for HIV-infected infants and children are higher, even if they are asymptomatic. Table 9.3a outlines these additional requirements according to the child's status.

Table 9.3 Additional energy requirements for HIV-infected infants/children (to be modified according to ongoing review).

Infant/Child Status	Additional energy requirement*
Asymptomatic or mild symptoms, or stable after > 6 months ART	10%
Chronic illness or opportunistic infection	25-30%
Severely malnourished child	50-100%
Recent weight loss, or recently started on ART and recovering weight	100-150%

*Balanced with no more than 10-15% of energy supplied from protein

Feeding advice for a mother of a child with confirmed HIV infection

- The child with confirmed HIV infection should be encouraged to breastfeed as s/he is already HIV infected but needs the benefits of breastfeeding.
- The child should be fed according to the feeding recommendations for his age
- For breastfeeding HIV-infected infants/children, daily energy intake from solid food (as a complement to on-demand breast feeding) should be roughly:
 - 220 kCal/day from 6-8 months (~450 kCal/day from breast milk);
 - 330 kCal/day from 9-11 months (~420 cKal/day from breast milk).
 - 605 kCal/day from 12-23 months (~380 kCal/day from breast milk) .
- For non-breastfeeding HIV-infected infants, total daily energy intake should be roughly:
 - 675 kCal/day from 6-8 months;
 - 750 kCal/day from 9-11 months.
 - 990 kCal/day from 12- 23 months.
- These children often suffer from poor appetite and mouth sores so give appropriate advice
- If the child is being fed with a bottle encourage the mother to use a cup as this is more hygienic and will reduce episodes of diarrhoea
- Ensure adequate vitamin A intake (e.g., ensure mass-dose vitamin A supplementation within the last six months).
- Ensure household consumption of iodized salt.
- Inform the mother about the importance of hygiene when preparing food because her child can easily get sick.
- She should wash her hands after going to the toilet and before preparing food.
- If the child is not gaining weight well, the child can be given an extra meal each day and the mother can encourage him to eat more by offering him snacks that he likes if these are available
- Advise her about her own nutrition and the importance of a well balanced diet to keep herself healthy.
- Encourage her to plant vegetables and keep chicken to feed her family.

The need to prevent and respond to HIV-related wasting.

Infant and child feeding is more difficult for caregivers of HIV-infected children. HIV infection increases energy intake requirements, HIV-related wasting requires aggressive feeding intervention to help the infant/child recover, and frequent opportunistic infections require caregivers to be especially vigilant to sustain the infant/child's weight and growth.

General principles of good chronic care for HIV-infected children

- Develop a treatment partnership with the mother and infant or child
- Focus on the mother and child's concerns and priorities
- Use the '5 As' : Assess, Advise, Agree, Assist, Arrange to guide you with the steps on chronic care consultation. Use the 5A's at every patient consultation
- Support the mother and child's self-management
- Organize proactive follow-up
- Involve "expert patients", peer educators and support staff in your health facility
- Link the mother and child to community-based resources and support
- Use written information – registers, Treatment Plan and treatment cards - to document, monitor and remind
- Work as a clinical team
- Assure continuity of care

9.4 Steps For Assessing Child Feeding And Counseling The Caregiver

- Weigh the infant/child
- Assess current nutritional status, or growth relative to the standard growth curve
- Assess child feeding

I. Normally Growing HIV-infected or exposed infants and children:

Follow the feeding recommendation described above for a child classified as HIV-exposed and for a child with confirmed HIV infection

II. Presence of Current infection or illness

All intercurrent infections reduce the appetite of a sick child.

- If the child is not feeding well during illness, counsel the mother to
 - Breastfeed more frequently and for longer if possible.
 - Use soft, varied, appetizing, favourite foods to encourage the child to eat as much as possible, and offer frequent small feedings.
 - Clear blocked nose if it interferes with feeding.
 - Expect that appetite will improve as child gets better.
- If the child has a poor appetite:
 - Plan small, frequent meals
 - Give milk rather than other fluids except where there is diarrhoea with some dehydration
 - Give snacks between meals
 - Give high energy foods
- If the child has sore mouth or ulcers:
 - Treat the oral lesions
 - Give soft foods that will not burn the mouth, such as eggs, mashed potatoes, pumpkin or avocado
 - Avoid spicy, salty, or acidic foods
 - Avoid rough, very hot, or sticky foods

- Make foods moist or dip food in liquids
- Chop or mash foods finely
- Give cold drinks or ice, if available
- Use a straw to drink
- In addition to the steps outlined above
 - Ensure that the mother does not withhold breast milk or breast milk substitutes during the illness.
 - If child is breastfed, breastfeed more frequently and for longer at each feed. If child is taking breast-milk substitutes, increase the amount of milk given
 - Increase other fluids. For example, give soup, rice water, yoghurt drinks or clean water.
 - Advise the mother to feed the infant frequently, in small amounts, for the duration of the illness, and discuss the need for patience and persistence in feeding during this time.
 - Recommend 25-30% increased daily feeding for the infant.

III. Failing growth or current malnutrition, no current illness

In addition to the steps outlined in the IMCI guideline and for the child with inter-current illness

- If the mother reports difficulty with breastfeeding:
 - Assess breastfeeding.
 - As needed, show the mother correct positioning and attachment for breastfeeding.
- If the child is less than 6 months old and is taking other milk or foods:
 - Build mother's confidence that she can produce all the breast milk that the child needs.
 - Suggest giving more frequent, longer breastfeeds day or night, and gradually reducing other milk or foods.
 - If the child is HIV exposed, counsel the mother about the importance of not mixing breastfeeding with replacement.
- If other milk needs to be continued, counsel the mother to:
 - Breastfeed as much as possible, including at night.
 - Make sure that other milk is a locally appropriate breast milk substitute.
 - Make sure other milk is correctly and hygienically prepared and given in adequate amounts.
 - Finish prepared milk within an hour.
- If the mother is using a bottle to feed the child:
 - Recommend substituting a cup for bottle.
 - Show the mother how to feed the child with a cup.
- In addition
 - Take the child's history to assess whether infections are contributing to growth failure. Promote positive care-seeking practices that may lead to earlier initiation of care, and discuss feeding practices for sick children (see above).
 - Ask the caregiver about the child's appetite, and assess whether poor appetite could be due to sores in her/his mouth or throat, vomiting or nausea. Manage each of these appropriately.

- If the child has lost weight, advise the mother to increase daily feeding by 100 to 150% to re-establish lost weight.
- If the child is on ART, ask about administration of the medicine— weight loss or failure to gain weight may be an indication that the child is not receiving ART correctly or that a different ARV should be introduced.
- If the child has lost weight, advise the mother to increase daily feeding by 100 to 150% to re-establish lost weight. Provide sample diets and give suggestions on enhancing the diet's energy content.
- Schedule a follow-up visit with the caregiver within one month to assess progress on feeding recommendations.
- If edema is present in both the child's feet, if weight-for-height is less than 70% of (or -3 SD below) the reference, or if visible severe wasting is present, manage severe malnutrition according to established protocols.

9.5 Management of a severely malnourished child with HIV infection

Severe wasting is a common clinical presentation of HIV infection in children. All children with severe malnutrition are at risk for a number of life-threatening problems and require urgent and appropriate nutritional rehabilitation. HIV-infected children with severe malnutrition have a higher risk of mortality than uninfected children due to the frequency and severity of opportunistic infections including TB. Early diagnosis and treatment of such infections will avoid unnecessary deaths in these children. HIV infected children with severe malnutrition who fail to adequately respond to standard nutrition therapy and treatment of complicating infections (a Clinical Stage 4 event), should be offered ART regardless of the CD4 values.

The optimal time at which to start ART in severely malnourished children is not presently known (Heikens 2008). It is however recommended that HIV-infected children with severe malnutrition, should be stabilised from the acute phase of malnutrition while simultaneously preparing for initiation of ART, which should be started as soon as clinically possible following stabilisation.

Successful viral suppression and immune restitution with ART can reverse losses in weight and linear growth. Children who gain weight rapidly with ART and adequate nutrition should be reassessed frequently and ARV dosages revised as needed (see Annex E of WHO recommendations on paediatric ART).

References for further reading

1. WHO. (2009). *Guidelines for an Integrated Approach to the Nutritional care of HIV-infected children, (6 months – 14 years)*. Geneva, World Health Organization. Available at: <http://www.who.int/nutrition/publications/hiv/aids/en/index.html>
2. WHO. (2007). *WHO HIV and infant feeding technical consultation. Held on behalf of the Inter-agency Task Team (IATT) on Prevention of HIV infections in pregnant women, mothers and their infants*. Consensus Statement. Geneva, World Health Organization.
3. PAHO/WHO. (2003). *Guiding principles for complementary feeding of the breastfed child*. Washington: PAHO,.
4. WHO. (1999). *Management of Severe Malnutrition: a manual for physicians and other senior health workers*. Geneva: World Health Organization.
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Chapter 10

Pain Management in HIV-infected children

Pain is a common symptom that is commonly unrecognized, poorly assessed, inadequately treated, and not prioritized—especially in HIV-infected children. Pain may be localized or generalized, but in both cases it decreases the quality of life and is a multi-factorial problem to manage. Localized pain in the HIV-infected child is usually caused by inflammation, infections, neoplasms, psychiatric disorders, drug adverse events, and iatrogenic interventions, among other non-HIV related causes. Unless the cause is identified and treated, and symptomatic pain is managed, the symptom will likely persist.

10.1 Recognition and assessment of Pain in children

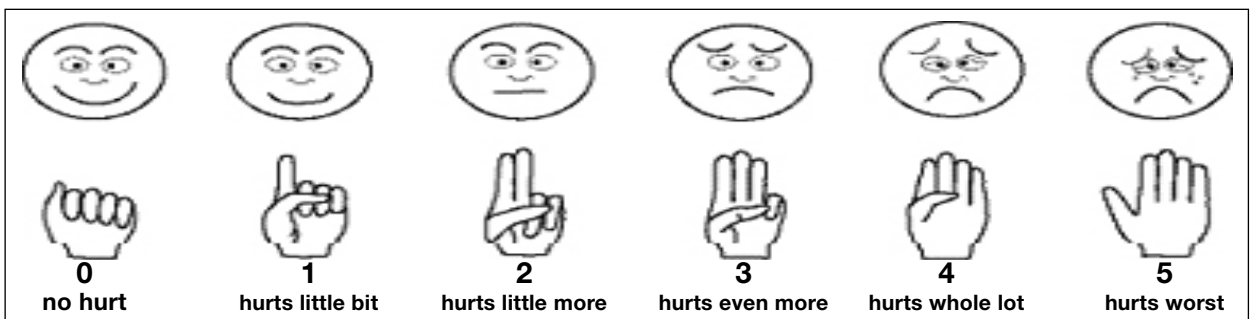
Older children complain of pain, but some may not (for example, because they usually experience and understand pain as a punishment for wrongdoing). Such children and those younger usually need adults to recognize and respond to their pain. These children in pain may present with

- Crying and distressed facial expression (Acute brief pain)
- Behavioral changes (irritability, restlessness, lack of interest, reduced concentration)
- Sleep disturbances
- Changes in gait/movement
- Increased breathing or heart rates

10.1.1 Assessing pain in children

An older child's activities and functions may be restricted accordingly by the severity of pain. Documenting this loss of function indicates the severity of the symptom. Additional quantification of pain can be accomplished using standard paediatric visual analogue pain scales and rating systems modified to account for age, developmental status, severity of illness, and cultural factors. An older child can grade pain by number of fingers, or pointing on a ruler or faces (smiling or frowning). This is illustrated below:

Figure 15: Assessing pain using facial expressions



In these assessments, it is essential to differentiate pain from anxiety, and to recognize that guardians may inadequately estimate pain in their child. The child's subjective judgment of pain control should direct needs wherever possible. Anticipating and preventing the need for analgesia, especially during potentially painful interventions, needs to be considered to help cope with pain.

10.2 Managing pain in children

Successful pain management in HIV-infected children begins with efforts to diagnose and treat the underlying conditions causing pain.

Non-pharmacological measures: Appropriate pain management in children begins with recognizing pain and its severity. Various cognitive methods help relieve pain:

- Age-appropriate active distraction
- Older children can be encouraged to concentrate on a game, a conversation or special story
- Other non-drug methods: Swaddling or carrying an infant, providing warmth, breastfeeding or feeding, stroking, rocking, massage.
- Relaxation techniques and behaviour modifications.
- Environmental management, including play opportunities, music, scheduled (rather than random) medical and nursing interventions, and structured opportunities for sleep and rest.
- Gentle handling and supportive positioning.
- Nutritional support, adequate hydration, and electrolyte replacement.

Pharmacological measures: Analgesia should be initiated after assessing the patient, and concurrently with efforts to diagnose and treat the underlying pathological conditions causing pain. Analgesia should be given by the following principles:

- By mouth (preferable to injectable).
- By the clock (regularly, periodically to minimize the recurrence of severe pain)
- By 2 steps (analgesia in increasing doses; start with mild analgesics and progress to strong analgesics as the requirement for pain relief rises or tolerance develops)
- By the child (preferably patient driven need, doses/frequencies individualized)

10.2.1 Levels of analgesia

Local anaesthetics: For painful lesions in the skin or mucosa or during painful procedures.

- Lidocaine: apply on gauze to painful mouth ulcers before feeds (apply with gloves, unless the family member or health worker is HIV-positive and does not need protection from infection); it acts in 2– 5 minutes.
- TAC (tetracaine, adrenaline, cocaine): apply to a gauze pad and place over open wounds; it is particularly useful when suturing.

Analgesia: For mild-moderate pain (such as headaches, post-traumatic pain, and pain from spasticity), Acetaminophen and NSAIDs remain the mainstay. For moderate-severe persisting pain, poorly responsive to the above, opiates should be used.

When treating chronic severe pain, give regular doses of pain relief. There are two steps in the analgesic ladder

Step 1:

- use
 - Acetaminophen (Paracetamol)
 - Non-steroidal anti-inflammatory drugs (e.g. Ibuprofen)

Step 2:

- use
 - opiates eg morphine (po or IV q4–6h or continuous IV infusion)

Table 10.2.1 Dosages of paracetamol and oral morphine.

	STEP 1	STEP 2
Age or weight	Paracetamol q4-6h (100mg tablet) OR Ibuprofen*	Oral morphine (5mg/5ml)
2 mo up to 4 mo (4-<6kg)	-	0.5ml (dose reduced in infants <6 mo)
4 mo up to 12 mo (6-<10kg)	1	2ml
12 mo up to 2 yr (10-<12kg)	1 1/2	3ml
2 yr up to 3 yr (12-<14 kg)	2	4ml
3 yr up to 5 yr (14-19kg)	2	5ml

*Recommended dosages for ibuprofen: 5-10 mg/kg orally, q6-8h to a maximum of 500 mg per day i.e. ¼ of a 200 mg tablet below 15 kg , ½ tablet for 15 up to 20 kg of body weight.

References for further reading

1. WHO. (2011). Guidelines for pharmacological treatment of persisting pain in children with medical illnesses. In preparation for publication.

Chapter 11

Disclosure and psychosocial support for children

HIV/AIDS has profound effects on an individual's physical, emotional, social, and economic wellbeing, and addressing these dimensions of life is an integral part of HIV care. Effective HIV/AIDS treatment programs provide far more to patients than medication, and take into account a broad range of issues, including: psychological, spiritual, and psychosocial support, as well as the need for community mobilization around HIV/AIDS and good health. This collection of services – ranging from counselling to practical assistance – is loosely titled “psychosocial support,” and may include:

- Individual, family, and/or group counselling
- Disclosure support
- Identification, assessment, and treatment of mental health problems related to HIV
- Respite for caregivers
- Community and recreational activities for children and families
- Referral for practical assistance (community food banks, vocational counselling, employment opportunities, microfinance projects, etc.)
- Referral for spiritual / religious support
- Referral for legal advice

11.1 Disclosure

Parents and caretakers of HIV-exposed infants are understandably anxious about the health of their children. Most are worried that their child has or will have HIV infection. Given the complexity of the subject, it can be very difficult to explain the issues around infant diagnosis to parents and caretakers. However, a number of steps can be taken to help them better understand the situation.

1. Begin talking about infant diagnosis as early as possible, preferably during the antenatal period or the first paediatric appointment.
2. Inform parents that it can take many months, often as long as 18 months, to be sure that the child does not have HIV infection.
3. Prepare them for early diagnostic testing by telling them that the child will have a blood test during the first months of life (6-12 weeks) that will aim to diagnose HIV infection in the baby.
 - If the early diagnostic test is negative, parents can be reassured that the evidence of virus cannot be found so far. It may still be there, but this is a good sign. As long as s/he stays healthy, the baby will be tested again when s/he is older (>12 months).
 - If the early diagnostic test is positive, parents will need to be told that the child is likely to have HIV infection. The test will be repeated to make sure it is correct and other tests will be done to evaluate the baby's health status. It can be reassuring for parents to learn that care and treatment will be available to the child now and in the future.
4. Speaking openly with parents at each visit can be very helpful. Asking them for their questions, and addressing all questions and concerns can lessen their anxiety. Telling them about the baby's progress and highlighting positive findings (good growth, normal examination) can also be reassuring.
5. Inform parents of infants with initial negative virologic testing that a subsequent test for HIV antibody will be conducted at >12 months. However, if the child is symptomatic, then virologic testing may be to be repeated at an earlier date.

Sharing a diagnosis of HIV may be difficult under the best of circumstances, and discussing HIV/AIDS with children poses additional challenges. Adults always struggle with the questions of whether, when, and how to tell children that they have HIV. It is important for a child to know his/her HIV status and/or that of a family member. Open communication about the infection or illness will allow the child to express his/her fears, obtain support, understand the infection, and participate in finding ways of taking treatment regularly. Of course, disclosure should take family and community issues into consideration, should occur when age-appropriate, and should be conveyed with appropriate language and terms.

11.1.1 Issues to be considered

It is important to assess each caregiver's awareness of the child's right to understand what is happening to him/her or to someone in the family, and be involved in planning for the future.

- Protecting the child from painful topics leaves him/her to cope with fears alone: fantasies may be worse than reality.
- Children become frightened when they sense fear in adults: talk naturally to the child about the infection and illness, and let her/him understand that the caregiver feels comfortable with this. Be attentive to a child's ways of expressing anxiety (withdrawal, anger, acting out, regression, craving attention, difficulty sleeping) and encourage him/her to talk about it.
- Start disclosing HIV status as soon as possible in an age-appropriate way
- Ideally the caregiver should be the one to disclose to the child, with a trusted relative/family friend if possible, and should provide consistent ongoing support and loving empathy throughout the process
- Disclosure to children should be done little by little, and includes encouraging questions, providing truthful answers and making the child understand s/he can come back with more questions at any time, providing a loving context, and using child-friendly language
- Listen to the child and encourage him/her to express fears and emotions
- Always be truthful to gain the child's trust
- Involve the child in decisions concerning his/her future
- Reassure the child that it is not his/her fault if s/he or a family member is sick
- Tell the child whom s/he can talk to about the illness, not that it is a secret
- Link caregiver with peer support group for caregivers of a child infected by HIV

11.1.2 Disclosure of HIV status to a child according to his/her age

Up to 2 years

- Talk to the child simply and naturally about his/her health.
- Avoid transmitting anxiety to the baby through body language or voice tone.

2 - 3 years

- Be aware of children's sensitivity to adult's feelings through body language.
- Talk openly and naturally about child's health without transmitting anxiety.
- If the child is sick talk gently about his/her illness, and provide constant loving care.

3 - 5 years

- Use stimulating questions such as asking the child what s/he understands about having to go to the clinic, taking medicine, being often sick, and what s/he fears.
- Listen carefully and answer truthfully and naturally, giving little information at a time, as the child seems ready to take it in.

- Use simple language, such as “a virus (or germ) inside you that can make you sick”, “medicine will make the body stronger to fight against the virus”, “the same virus your mother has and sometimes make her sick”.
- Answer questions about dying: “everyone will die one day, no one knows when, meanwhile all children need to look forward to playing, learning new skills, making friends and growing up”.
- Provide ongoing loving reassurance and support.
- Tell the child that s/he can play with, hug and hold hands with other children without giving them the virus, and that if some adults seem afraid it is because they don’t know enough about this.

6 - 9 years

- Start disclosure process as soon as possible, paying attention to nonverbal expressions of anxiety and denial.
- Encourage and stimulate questions from the child. If the child does not ask questions, ask him about his fears.
- Talk about the illness openly and simply, giving information a little at a time, as the child seems ready to take it in.
- Provide information about the infection/ illness, its name, its causes and whether it will lead to death (see 3-5yrs).
- Explain that medicine will fight against the infection and make him/her feel better, but that it needs to be taken very regularly.
- Reassure the child that s/he must lead a life like all children, and can go to school, play games, hold hands and hug other children without transmitting the infection.

11.2 Adherence to treatment

Adherence to antiretroviral treatment is essential for treatment success. For sustained suppression of viral replication, the adherence has to be more than 95%.

Children’s adherence depends largely on the understanding, perseverance, and creativity of the parent or **other** caregiver. An older HIV-infected child who understands about his/her infection **should** be actively involved in adherence to ARV treatment, but will need constant support to maintain it.

While preparing for counselling for adherence, it is important to assess:

- HIV-positive parent’s own adherence to treatment if s/he is the caregiver
- caregiver’s awareness of risks to the child deriving from incorrect adherence
- whether the caregiver is anxious that the medication could harm the child
- caregiver’s cognitive capacity to understand the nature of the treatment and importance of adherence
- older child’s awareness of importance of adherence to treatment
- presence of depression or “giving up” in the caregiver or older child

The caregivers have to be informed that

- child’s health depends on strict regularity of pill-taking
- ART has possible transitory side-effects that vary in duration and severity

Thereafter, the treating team should

- identify strategies to facilitate correct adherence (taste, association of pill-taking with regular daily occurrences or game, respect for confidentiality)
- let the child take part in choosing the best way to take medicine regularly

Based on the above assessment the treating team should develop a treatment plan which respects the child's privacy and allows him/her to carry on with regular activities.

The treating team should arrange next follow-up visit and facilitate linkages/home visits.

11.3 Psychosocial support for HIV-infected children

Support for families

Caregivers may not know how to provide essential care and attention to the child. Helping caregiver to strengthen their coping skills will allow them to better support the children.

Support for HIV infected children

HIV-infected children have the same basic needs as all children. They should be encouraged and assisted to lead the life of any other child and helped to develop healthily.

In addition, an infected child has further serious needs:

- to face her/his own infection and learn to live with HIV
- to look after his/her health
- to grow and develop without transmitting HIV to others
- to overcome discrimination/ignorance/fear in others in a positive way

The recommendations for supporting a children living with an HIV-infected family member should also be applied to the infected children who themselves are likely to be living with an infected or sick family member.

The process of providing psychosocial support to children and their families includes assessment of:

- Family needs
 - psychological and social needs with special attention to stigma,
 - financial needs linked to lack of income due to illness and death,
 - practical needs particularly concerning child-care,
 - legal needs
- Child's needs:
 - quality of care and support;
 - exposure to developmental stimuli such as communication, play, school, learning **new skills**, recreational activities;
 - psychological condition linked to fear and understanding of **own** and other family member's HIV status;
 - understanding of HIV/AIDS and **of** the importance of taking treatment regularly;
 - possible risks **of discrimination, linked to stigma**

- **Caregiver's** own support and guidance needs, in relation to issues such as disclosure, adherence, support for a sick or dying child, coping with stigma, accessing available services
- Availability of further adult **support** in the family or community to ensure respite care and support to a sick child

The family could be assisted to

- identify ways of generating further income
- identify potential support figure or service in family circle and/or community
- encourage caregiver to meet own support needs
- access legal services for coping with stigma, inheritance issues, child abuse or exploitation

The treating team should then

- develop a plan addressing these needs
- involve the child in planning for his/her future

Support could be obtained from

- peer support groups for caregivers/older children
- community volunteer support
- organizations of PLWHAs

It is also important to arrange follow-up meetings or visits to review the plan's progress and to modify it if necessary

11.3.1 Support development in HIV-infected children

- Assess caregiver's awareness of the child's need to lead a normal life of any child, and the need for stimulation for healthy child development
- Advise the caregivers:
 - not to overprotect the child
 - to make sure that the child leads a full life, including play, educational and recreational activities with other children
 - to show appreciation for the child's achievements and encourage further improvement
 - to provide guidance, trust and respect for older children

Counsel caregiver on age-specific needs to ensure healthy development, as follows:

Up to 4 Months of age	4 months up to 6 months	6 months up to 12 months	12 months up to 2 years	2 years and older
<i>Play:</i> Provide ways for your child to see, hear, feel and move.	<i>Play:</i> Have large colourful things for your child to reach for, and new things to see.	<i>Play:</i> Give your child clean safe household things to handle, bang and drop.	<i>Play:</i> Give your child things to stack up, and to put into containers and take out.	<i>Play:</i> Help your child count, name, and compare things. Make simple toys for your child. Encourage playing with other children
<i>Communicate:</i> Look into your child's eyes and smile at him or her. When you are breastfeeding is a good time.	<i>Communicate:</i> Talk to your child and get a conversation going with sounds or gestures.	<i>Communicate:</i> Respond to your child's sounds and interests. Teach your child the names of things and people.	<i>Communicate:</i> Ask you child simple questions. Respond to your child's attempts to talk. Play games like "bye"	<i>Communicate:</i> Encourage your child to talk. Answer your child's questions. Teach you child stories, songs and games

11.3.2 Support for special circumstances

11.3.2.1 For children with HIV-infected parents and siblings

Caring for sick parents and siblings has a huge emotional impact on children. Witnessing illness and death of close family members, and discrimination and stigma, can result in severe depression. Children often are not able to talk about their fears and difficulties. Adequate care, protection, guidance, and support are often lacking. This can inhibit the children's health. The family often needs assistance to understand children's needs, how to communicate with and support them, and how to plan ahead for them. Children whose parent(s) or other family members are HIV-infected need to: (advice appropriate to their age)

- know who is responsible for them
- **understand** what is happening (they often know more than they are told)
- be supported in their fears and their emotions
- be able to continue to attend school and play with friends
- **understand** that they are not expected to take over from their parents
- **be helped to cope with illness, dying and bereavement**
- **get health care when they need it**
- get legal protection for rights
- **be protected from sexual abuse and exploitation**
- **be helped to demand and access** social services

Caregivers of children living in families where one or more members are infected by HIV may find it difficult to provide essential care and attention to the children. Helping caregivers to strengthen their own coping skills and capacities will allow them to better support the children.

11.3.2.2 Support when an HIV-infected parent or sibling is sick or dying

In such a situation assess:

- Availability of adult support in the family or community that can provide provisional and/or long-term loving care for the child/children
- Need to protect the child's inheritance rights

The following steps may be taken:

- gradual transition to a loving caregiver; siblings are better off together in their own environment than broken up into different families or other structures
- talk to the child about the illness and answer possible questions about death truthfully taking care to always leave space for hope
- allow the child to spend time with the sick parent or sibling
- help the child identify small tasks "to help"
- tell the child it is not his/her fault that the parent or sibling is sick or dying
- encourage and assist the child to carry on with habitual everyday activities such as school, sports, recreational activities, and to keep up friendships and relationships
- encourage child to talk about his/her feelings. Listen and provide loving support
- start a memory-box containing happy memories and loved objects

Guidance and information on relevant services available in the community may be provided, such as:

- home care
- community volunteer support
- part or full-time foster care
- support groups for older children
- child counseling
- schools day-care centers
- sports and other play activities
- services providing school fees
- meals for children
- legal services

11.3.2.3 Additional assistance when a parent or sibling has died:

- be patient with a grieving child, encourage him/her to express grief
- **encourage the child to talk about the person who has died**
- listen to the child, provide loving care and empathy
- allow the child to participate in the dying process and burial activities and to share in adults' expression of grief, so as not to feel alone in his/her bereavement
- **make sure that the child's routine changes as little as possible, tell the child that normal everyday life will go on as before (school, day care, playing with friends, sports), and encourage him/her to go on continue participating in all activities**
- make sure the children's inheritance rights are respected
- assist the caregiver to draw up a plan for the children, bearing in mind the points listed above.

Annexes

Paediatric ART drug formulations and dosages

(modified from Annex E of ART for HIV infections in infants and children 2010 WHO revision page 101 to 155)

1. NRTIs

1.1 Lamivudine (3TC)

LAMIVUDINE (3TC)			
FORMULATIONS			
Tablets	Capsules	Liquid	FDC
150 mg	None	10 mg/ml	Baby 30 mg 3TC Adult 150 mg 3TC <ul style="list-style-type: none"> ◦ 3TC+d4T+NVP ◦ TC+d4T ◦ 3TC+AZT+NVP ◦ 3TC+AZT+ABC ◦ 3TC+AZT ◦ 3TC+ABC ◦ Junior 60 mg 3TC ◦ 3TC+d4T+NVP ◦ 3TC+d4T

DOSE AND DOSE FREQUENCY

Target doses

- Age less than 30 days of life: 2 mg/kg/dose twice daily (this dose should be used for infant prophylaxis during the first 30 days of life)
- Age more than 30 days of life: 4 mg/kg/dose twice daily
- Weight greater than 50 kg: 150 mg twice daily

Note: Once-daily dosing is not yet approved for children but encouraging pharmacokinetic data are available for children switching to once daily dosing once virally suppressed on ART

Administration – adult tablets

- Can be crushed and contents mixed with a small amount of water or food and taken immediately

Storage

- Store tablets/capsules at room temperature (25°C; range 15° to 30°C)
- Store liquid at room temperature (25°C; range 15° to 30°C)
- Use within one month of opening

OTHER COMMENTS

<u>General</u>	<u>Pharmacokinetic data</u>
<ul style="list-style-type: none"> ◦ Well tolerated ◦ No food restrictions ◦ Also active against hepatitis B 	<ul style="list-style-type: none"> ◦ Available for all ages
	<u>Major drug interactions</u>
	<ul style="list-style-type: none"> ◦ None

1.2 Stavudine (d4T)

STAVUDINE (d4T)

FORMULATIONS

Tablets	Capsules	Liquid	FDC
None	15 mg 20 mg 30 mg	1 mg/ml	Baby 6 mg d4T Junior 12 mg d4T Adult 30 mg d4T <ul style="list-style-type: none"> ◦ d4T+3TC+ NVP ◦ d4T+3TC

DOSE AND DOSE FREQUENCY

- Target doses
- Weight less than 30 kg 1 mg/kg/dose twice daily
- Weight more than 30 kg 30 mg/dose twice daily

Note: Once-daily dosing is not yet approved for children but encouraging pharmacokinetic data are now available for children switching to once daily dosing once virally suppressed on ART

- Adults 30 mg/dose twice daily

Administration – capsules

- Can be opened and mixed with small amount of food or water and taken immediately (stable in solution for 24 hours if kept refrigerated)

Administration – liquid

Liquid must be well shaken prior to each use

Storage

- Store capsules at room temperature (25°C; range 15° to 30°C) in a tightly closed container
- Store powder for solution at room temperature (25°C; range 15° to 30°C) in a tightly closed container (to protected from excessive moisture)
- After constitution, solution needs refrigeration (2°C to 8°C) and storage in original container
- Discard any unused solution after 30 days

OTHER COMMENTS

General

- Well tolerated in short term, but significant long term toxicities
- No food restrictions

Pharmacokinetic data

- Available for all ages

Major drug interactions

Do not use stavudine with zidovudine (AZT) due to an antagonistic effect

ZIDOVUDINE (AZT or ZDV)

FORMULATIONS

Tablets	Capsules	Liquid	FDC
60 mg 300 mg	100 mg 250 mg	10 mg/ml	Baby 60 mg AZT Adult 300 mg AZT <ul style="list-style-type: none"> ◦ AZT+3TC+NVP ◦ AZT+3TC ◦ AZT+3TC+ABC

DOSE AND DOSE FREQUENCY

- Maximum dose 300 mg twice daily

Target dose

- Liquid (oral dosing) 180-240 mg/m² per dose given twice daily (total daily dose 360-480 mg/m²).
- For children with suspected nervous system involvement, it may be beneficial to use a dose at the higher end of the range.

Maximum dose

- 300 mg twice daily

MTCT prevention dose

- Oral target dose 4 mg/kg every 12 hours starting within 12 hours after birth and continuing up to 6 weeks of age, depending on national recommendations
- Intravenous target dose of 1.5 mg/kg infused over 30 minutes every 6 hours until oral dosing is possible
- For prophylaxis against MTCT, liquid (oral dosing) is preferred in infants since accurate dosing with paediatric tablets is not possible

Administration – capsules

- Can be opened and dispersed in water or on to a small amount of food and immediately ingested

Administration – tablets

- 60 mg tablets are scored and can be split.
- 300 mg tablets are often not scored - may be cut in half with a tablet cutter in a pharmacy
- Tablets may be crushed and combined with a small amount of food or water and immediately ingested
- Some paediatric FDC formulations of this drug are dispersible

Storage

- Store capsules at room temperature (25°C; range 15° to 30°C) in a tightly closed container (to protected from moisture)
- Store tablets at room temperature (25°C; range 15° to 30°C)
- Liquid is stable at room temperature but needs storage in glass jars and is light-sensitive

1.4 Abacavir (ABC)

Abacavir (ABC)

FORMULATIONS

Tablets	Capsules	Liquid	FDC
60 mg 300 mg	None	20 mg/ml	Baby 60 mg ABC ABC+AZT+3TC ABC+3TC Adult 300 mg ABC ABC+AZT+3TC ABC+3TC

DOSE AND DOSE FREQUENCY

Target dose

- Age less than 16 years or weight less than 37.5 kg: 8 mg/kg/dose twice daily
- Note: Once-daily dosing is not yet approved for children but encouraging pharmacokinetic data are now available

Maximum dose

- Age less than 16 years or weight less than 37.5 kg: 300 mg/dose twice daily

Administration – tablets

- 60 mg tablets are scored and can be split.
- Tablets may be crushed and mixed with small amount water or food and immediately ingested

Storage

- Store tablets at controlled room temperature of 20°C to 25°C
- Store liquid at controlled room temperature of 20°C to 25°C
- Liquid may be refrigerated but do not freeze

OTHER COMMENTS

General

- Parents must be warned about potential hypersensitivity reaction
- Screening for HLA-B*5701 may identify those most likely to have hypersensitivity
- ABC should be stopped permanently if hypersensitivity reaction occurs
- No food restrictions

Pharmacokinetic data

- Available for children over the age of 3 months

Major drug interactions

- None reported

1.5 Didanosine (DDL)

Didanosine (DDL)

FORMULATIONS

Chewable tablets (buffered)	Enteric-coated beadlets in capsules	Liquid	FDC
25 mg	125 mg	10 mg/ml	None
50 mg	200 mg		
100 mg	250 mg		
200 mg	400 mg		

DOSE AND DOSE FREQUENCY

Target dose

- Age less than 3 months: 50 mg/m²/dose twice daily
- Age 3 months to 13 years: 90-120 mg/m²/dose twice daily

Maximum dose

- Age 13 years or older, or weight greater than 60 kg: 200 mg/dose twice daily or 400 mg once daily

Administration – chewable (buffered) tablets

- At least two tablets of appropriate strength must be used at any one time for adequate buffering (e.g. if the child's dose is 50 mg, administer two 25 mg tablets instead of one 50 mg tablet)
- ddl tablets should be chewed, crushed or dispersed in water or clear juice before they are taken
- ddl tablets should not be swallowed whole

Administration – enteric-coated beadlets in capsules (EC)

- EC capsules should be swallowed whole. If there is no other therapeutic option and the child is too small to swallow capsules, they should be opened and taken with a small quantity of food or liquid, not with a meal
- The beadlets inside the capsule should not be crushed or chewed, and if the capsules are opened, the beadlets should be sprinkled on a soft food that does not require chewing
- Opened capsules should be taken immediately after mixing

Administration – liquid

- Is not easy to use and should be avoided if possible
- Prior to dispensing, the pharmacist must constitute dry powder with purified water to an initial strength of 20 mg/ml and immediately mix the resulting solution with antacid to a final strength of 10 mg/ml

Storage

- Keep liquid refrigerated (2°C to 8°C).
- Liquid remains stable for 30 days (shake well before using).
- Discard any unused liquid after 30 days.

Didanosine (DDL)**OTHER COMMENTS**General

- ddl is degraded rapidly unless given as an enteric formulation or combined with buffering agents or antacids
- In children this effect may be less marked and ddl may not have to be administered on an empty stomach

Pharmacokinetic data

- PK data are available for all ages. However, pharmacokinetic data at less than 2 weeks of age are variable.

Major drug interactions

- Tenofovir and ribavirin are not recommended to be taken with ddl

1.6 Emtricitabine (FTC)**EMTRICITABINE (FTC)****FORMULATIONS****Tablets****Capsules****Liquid****FDC**

None

200 mg

10 mg/ml

None

DOSE AND DOSE FREQUENCYTarget dose

- Liquid 6 mg/kg
- Capsules 200 mg capsule once daily (weight more than 33 kg)

Storage

- Store capsules at 25°C (range 15°C to 30°C)
- Liquid should be stored refrigerated (2°C to 8°C)
- Liquid should be used within 3 months if not refrigerated

OTHER COMMENTSPharmacokinetic data

- Available for children aged 3 months to 18 years

Major drug interactions

- None reported

1.7 Tenofovir (TDF)

Tenofovir (TDF)

FORMULATIONS

Tablets	Capsules	Liquid	FDC
300 mg	None	None	Adult 300 mg TDF TDF+FTC+EFV TDF+FTC TDF+3TC TDF+3TC+EFV

DOSE AND DOSE FREQUENCY

Target dose

- 300 mg/day for children from 12 years of age

Storage

- Store tablets at 25°C (range 15°C to 30°C)

OTHER COMMENTS

General

- TDF is the preferred ARV in children with hepatitis B aged over 12 years

Pharmacokinetic data

- Available for 12 years and over

Major drug interactions

- None reported

2. NNRTIs

2.1 Efavirenz (EFV)

EFAVIRENZ (EFV)			
FORMULATIONS			
Tablets	Capsules	Liquid	FDC
200 mg	50 mg	30 mg/ml	Adult 600 mg EFV
600 mg	100 mg		◦ EFV+TDF+FTC
	200 mg		◦ EFV+TDF+3TC
DOSE AND DOSE FREQUENCY			
<u>Target dose</u>			
◦ Liquid		19.5 mg/kg/day or	
◦ Capsule/tablet		15 mg/kg/day once daily	
◦ Weight greater than 40 kg	600 mg	once daily	
<u>Administration –tablets</u>			
◦	200 mg tablet is double-scored and can be split		
<u>Administration –capsules</u>			
◦	Capsules may be opened and added to a small amount of food or liquid; they have a very peppery taste but can be mixed with sweet foods to disguise the taste		
<u>Storage</u>			
◦	Storage at 25°C (range 15°C to 30°C)		
OTHER COMMENTS			
<u>General</u>			
◦	EFV can be given with food but if taken with food, especially high-fat meals, absorption is increased by an average of 50%		
<u>Pharmacokinetic data</u>			
◦	Available for children over 3 years of age		
◦	Insufficient data on dosing for children younger than 3 years old or weighing less than 10 kg		
<u>Major drug interactions</u>			
◦	It is not recommended to take with amodiaquine with EFV		

2.2 Nevirapine (NVP)

Nevirapine (NVP)

FORMULATIONS

Tablets	Capsules	Liquid	FDC
50 mg 200 mg	None	10 mg/ml	Baby 50 mg NVP Adult 200 mg NVP <ul style="list-style-type: none"> ◦ NVP+d4T+3TC ◦ NVP+AZT+3TC Junior 100 mg NVP <ul style="list-style-type: none"> ◦ NVP+d4T+3TC

DOSE AND DOSE FREQUENCY

Target dose – maintenance therapy

- 160-200 mg/m² to maximum dose of 200 mg twice daily

Target dose – prophylaxis

- Aim for exposure of 100 ng/ml
- Birth to 6 weeks of age:

weight less than 2.5 kg	10 mg/daily;
weight greater than 2.5 kg	15 mg per day
- Age 6 weeks to 6 months 20 mg per day
- Age 6 months-9 months 30 mg per day
- Age 9 months to end of breast feeding 40 mg per day

Special considerations on MTCT prevention in infants

- Give first dose as early as possible after delivery, preferably within first 6 hours
- If infant weight is not available, administer 1 ml liquid and thereafter follow national MTCT dosing recommendations

Special considerations on maintenance therapy

- Induction dose: during the first 14 days omit the evening dose of NVP. If the morning and evening doses are unequal, give the higher morning dose and omit the lower evening dose
- Maintenance dose: target dose is 160–200 mg/m² given twice daily and adjusted for more aggressive dosing in the younger age group
- If a mild rash occurs during the first 14 days of induction dosing, continue once daily dosing and only escalate dose once the rash has subsided and the dose is well tolerated. If a severe rash occurs (especially if accompanied by fever, blistering or mucosal ulcerations), discontinue drug
- Administration – tablets
- Some manufacturers make 200 mg tablets that are scored and can be divided into two equal parts. Other preparations may not be scored and where possible should be divided with a pill cutter. Broken tablets can be crushed and combined with a small amount of water or food and taken immediately.
- 50 mg tablets are scored and can be split

Administration – liquid

- Use an oral dosing syringe or dosing cup
- Must be well shaken

Storage

- Storage of liquid at 25°C (range 15°C to 30°C)
- Bottle of liquid should be used within 6 months of opening

Nevirapine (NVP)**OTHER COMMENTS**General

- Parents must be warned about a potential severe, life-threatening rash during the 14-day lead-in period. The once-daily induction dose is used to reduce the frequency of rash.
- NVP should be permanently discontinued and not restarted in children who develop severe rash
- Can be given without regard to food

Pharmacokinetic data

- Available from birth

Major drug interactions

- Avoid NVP if rifampicin is co-administered; also interacts with ketoconazole

3. Protease inhibitors**3.1 Saquinavir (SQV)****Saquinavir (SQV) HGC****FORMULATIONS**

Tablets	Hard gel capsules	Liquid	FDC
500 mg	200 mg	None	None

DOSE AND DOSE FREQUENCYTarget dose – hard gel capsules (HGC)

- Studies have reported using 33 mg/kg three times a day

Administration – tablets

- Usually taken with RTV
- Should be taken with food as absorption is improved; it is suggested that it be taken within two hours after a meal

Storage

- Store capsules at room temperature (25°C; range 15° to 30°C) in a tightly closed container (to protected from moisture)
- SQV HGC do not need refrigeration

OTHER COMMENTSGeneral

- Not licensed for use in children under 16 years of age or less than 25 kg
- Safety and effectiveness not yet well established in younger children

Major drug interactions

- None reported

3.1 Saquinavir (SQV)

Lopinavir/ritonavir (LPV/r)

FORMULATIONS

Co-formulated heat-stable tablets	Capsules	Liquid	FDC
Paediatric LPV 100 mg/RTV 25 mg Adult LPV 200 mg/RTV 50 mg	None	LPV 80 mg/ml + RTV 20 mg/ml	None

DOSE AND DOSE FREQUENCY

LPV Target dose

- 230-350 mg/m² twice daily

Maximum dose

- LPV 400 mg + RTV 100 mg twice daily

Administration – tablets

- Must be administered intact and cannot be split or crushed

Administration – liquid

- Must be well shaken

Storage

- Liquid should be refrigerated
- Can be stored at room temperature (up to 25°C) for two months (at >25°C the drug degrades more rapidly).
- For tablets, exposure to high humidity is not recommended for more than 2 weeks.

OTHER COMMENTS

General

- Higher doses of LPV/r may be required when co-administered with enzyme-inducing drugs such as NVP, EFV; fosamprenavir, rifampicin
- Do not have food restrictions although bioavailability is reportedly increased when administered with food
- Should be taken with food
- In non-fasting state, absolute bioavailability of LPV/r liquid is decreased by 22% compared to LPV/r tablet
- Low volume but bitter taste
- Once daily dosing is not approved for infants or children
- LPV/r liquid has a high alcohol content

Pharmacokinetic data

- Available for 14 days and older

Major drug interactions

- Not recommended to be taken with rifampicin, omeprazole or simvastatin

3.3 Rotinavir (RTV)

Ritonavir (RTV)

FORMULATIONS

Co-formulated tablets	Heat-stable tablets	Liquid	FDC
Paediatric 100 mg LPV + 25 mg RTV	100 mg	80 mg/ml	None
Adult 200 mg LPV + 50 mg RTV			

DOSE AND DOSE FREQUENCY

Target dose

- RTV is used to boost other protease inhibitors

Administration – tablets

- Must be administered intact and cannot be split or crushed

Administration – liquid

- Liquid may be taken alone or mixed with milk or food but should not be mixed with water or other fluids
- Liquid is unpalatable and excipient contains 43% alcohol

Storage

- Store tablets at 20° to 25°C (range 15° to 30°C). Exposure of tablets to high humidity outside tight container for longer than 2 weeks is not recommended.
- Store liquid at room temperature (20°C to 25°C). Do not refrigerate. Shake well before each use. Use within 30 days from dispensing. Avoid exposure to excessive heat. Keep cap tightly closed.
- Liquid should be protected from light

OTHER COMMENTS

General

- Adverse event profile seen during clinical trials and post-marketing similar to that for adults
- Should be taken with food

Pharmacokinetic data

- Available for infants and children

Major drug interactions

- None reported

3.4 Darunavir (DRV)

Darunavir (DRV)

FORMULATIONS

Film-coated tablets	Capsules	Liquid	FDC
75 mg	None	None	None
150 mg			
300 mg			
400 mg			
600 mg			

DOSE AND DOSE FREQUENCY

Target dose

- 10-20 mg/kg twice daily

Maximum dose

- 600 mg DRV with 100 mg RTV twice daily

Administration – tablets

- Once daily dosing should not be used in paediatric patients
- Should be taken with food

Storage

- Storage at temperature of 25°C (range 15° to 30°C)

OTHER COMMENTS

General

- RTV increases metabolism and absorption, and should be given with every dose of DRV
- The preferred ratio of DRV to RTV is 8:1. Adding more RTV does not lead to further boosting of DRV levels
- Parents/carers should be warned about potential skin rash
- Darunavir rarely has been observed to cause liver problems

Pharmacokinetic data

- Available for children aged 6 years or older

Major drug interactions

- None reported

3.4 Atazanavir (ATV)

Atazanavir (ATV)

FORMULATIONS

Tablets	Capsules	Liquid	FDC
None	100 mg 150 mg 200 mg 300 mg	None	None

DOSE AND DOSE FREQUENCY

Target dose ATZ/RTV

Treatment-naïve

- Weight 15 kg to less than 25 kg: 150 mg ATV/80 mg RTV
- Weight 25 kg to less than 32 kg: 200 mg ATV/100 mg RTV
- Weight 32 kg to less than 39 kg: 250 mg ATV/100 mg RTV

Treatment-experienced

- Weight 25 kg to less than 32 kg: 200 mg ATV/100 mg RTV
- Weight 32 kg to less than 39 kg: 250 mg ATV/100 mg RTV

Maximum dose

- ATV 300 mg / RTV 100 mg once daily

Administration

- Should be taken with food

Storage

- Store capsules at 25°C (range 15°C to 30°C)

OTHER COMMENTS

General

- To be used in combination with RTV in paediatric patients
- Recommended for patients aged 6 to <18 years of age
- Not to be used in patients less than 3 months of age due to risk of kernicterus. There is insufficient data for patients less than 6 years of age
- Dosage is based on body weight (8.5 mg/kg for weights 15 kg to less than 20 kg and 7 mg/kg for weight 20 kg or greater)

Pharmacokinetic data

- Available for children aged 3 months to 21 years

Major drug interactions

- None reported

4.1 Zidovudine (AZT) plus lamivudine (3TC)

Zidovudine (AZT) plus lamivudine (3TC)

FORMULATION

FDC tablets

AZT 60 mg + 3TC 30 mg

AZT 300 mg + 3TC 150 mg

DOSE AND DOSE FREQUENCY

Target dose

- AZT 180-240 mg/m² twice daily
- 3TC 4 mg/kg twice daily

Maximum dose

- 1 adult tablet/dose twice daily

Administration

- Paediatric tablet is scored and can be split
- Can be crushed and contents mixed with a small amount of water or food and immediately taken

Storage

- Store tablets between 2°C and 30°C

OTHER COMMENTS

General

- See comments under individual drug components
- No food restrictions
- AZT/3TC FDC can be used for lead-in dosing when initiating AZT+3TC+NVP therapy

Pharmacokinetic data

- Available for adolescents and adults

4.2 Zidovudine (AZT) plus lamivudine (3TC) plus nevirapine (NVP)

Zidovudine (AZT) plus lamivudine (3TC) plus nevirapine (NVP)

FORMULATION

FDC tablets

AZT 60 mg + 3TC 30 mg + NVP 50 mg

AZT 300 mg + 3TC 150 mg + NVP 200 mg

DOSE AND DOSE FREQUENCY

Target dose

- AZT 180-240 mg/m² twice daily
- 3TC 4 mg/kg twice daily

Maximum dose

- 1 adult tablet/dose twice daily

Administration

- Paediatric tablet is dispersible and maybe split
- Can be dispersed into a small volume of water or crushed and mixed into a small amount of food and immediately taken

Storage

- Store tablets between 2°C and 30°C

OTHER COMMENTS

General

- See comments under individual drug components
- No food restrictions
- Pharmacokinetic data
- Available for adolescents and adults

4.3 Stavudine (d4T) plus lamivudine(3TC)

FORMULATION

FDC tablets

d4T 6 mg + 3TC 30 mg

d4T 12 mg + 3TC 60 mg

d4T 30 mg + 3TC 150 mg

DOSE AND DOSE FREQUENCY

Target dose

- d4T 1 mg/kg twice daily
- 3TC 4 mg/kg twice daily

Administration

- Paediatric tablet is dispersible and crushable, can be split

Storage

- Store tablets between 2°C and 30°C
-

OTHER COMMENTS

General

- See comments under individual drug components
- d4T and 3TC can be used in evening for lead-in dosing for d4T+3TC+NVP

Pharmacokinetic data

- Available for adolescents and adults
-

4.4 Stavudine (d4T) plus Lamivudine (3TC) plus Nevirapine (NVP)

Stavudine (d4T) plus lamivudine(3TC) plus nevirapine (NVP)

FORMULATION

FDC tablets

d4T 6 mg + 3TC 30 mg + NVP 50 mg

d4T 12 mg + 3TC 60 mg + NVP 100 mg

d4T 30 mg + 3TC 150 mg + NVP 200 mg

DOSE AND DOSE FREQUENCY

Target dose

- d4T 1 mg/kg twice daily
- 3TC 4 mg/kg twice daily
- NVP 160-200 mg/m² to maximum dose of 200 mg twice daily

Maximum dose

- One 30 mg d4T-based tablet twice daily

Administration

- Paediatric tablet is dispersible and crushable, can be split
- If unable to swallow, disperse 1 tablet in 2 teaspoons of water

Storage

- Store tablets below 25°C

OTHER COMMENTS

General

- See comments under individual drug components
- A lead-in dose of NVP, half of the normal daily dosage, is used for 2 weeks to decrease the likelihood of rash incidence.
- for lead-in dosing, d4T+3TC+NVP can be used in the morning and d4T+3TC in the evening
- If the child experiences a rash in the lead-in period, then remain on the half dosage until the rash resolves. Wait no longer than 28 days for the rash to resolve then seek an alternative regime.

Pharmacokinetic data

- Available for adolescents and adults

4.5 abacavir (ABC) plus zidovudine (AZT) plus lamivudine (3TC)

Abacavir (ABC) plus zidovudine (AZT) plus lamivudine (3TC)

FORMULATION

FDC tablets

Paediatric ABC 60 mg + AZT 60 mg + 3TC 30 mg

Adult ABC 300 mg + AZT 300 mg + 3TC 150 mg

DOSE AND DOSE FREQUENCY

Target dose

- ABC 8 mg/kg twice daily
- AZT 180-240 mg/m² twice daily
- 3TC 4 mg/kg twice daily

Maximum dose

- 1 adult tablet/dose twice daily

Administration

- Paediatric tablet is crushable and can be split

Storage

- Store tablets between 2°C and 30°C

OTHER COMMENTS

General

- See comments under individual drug components
- parents/carers must be warned about potential hypersensitivity reaction
- ABC should be stopped permanently if hypersensitivity reaction occurs

Pharmacokinetic data

- Available for adolescents and adults

4.6 Abacvir (ABC) plus zidovudine(AZT) plus lamivudine (3TC)

Abacvir (ABC) plus zidovudine(AZT) plus lamivudine (3TC)

FORMULATION

FDC tablets

Paediatric ABC 60 mg + 3TC 30 mg

Adult ABC 600 mg + 3TC 300 mg

DOSE AND DOSE FREQUENCY

Target dose

- Lamivudine: 4 mg/kg twice daily
- Abacavir: 8 mg/kg twice daily

Administration

- Paediatric tablet is scored and can be split
- Can be crushed and contents mixed with a small amount of water or food and immediately taken

Storage

- Store tablets between 2°C and 30°C

OTHER COMMENTS

General

- See comments under individual drug components
- No food restrictions

Pharmacokinetic data

- Available for adolescents and adults

Simplified Paediatric ART dosage tables

NEVIRAPINE (NVP)

Recommended maintenance dose based on weight-bands for children >6 weeks of age using liquid, adult tablets. Target dose 160-200mg/m² to max 200 mg twice daily

Weight range (Kg)		Formulations					
		10/mg/ml liquid		50 mg tablet		200 mg tablet	
Bottom	Top	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.
3	5.9	5ml	5ml	1	1		
6	9.9	8ml	8ml	1.5	1.5		
10	13.9	10ml	10ml	2	2		
14	19.9			2.5	2.5	1	½
20	24.9			3	3	1	½
25	34.9					1	1

EFAVIRENZ (EFV)

Recommended maintenance dosing based on weight-bands for children > 3 years old and > 10 kg. Target dose 15 mg/Kg/day Weight >40 Kg: 600 mg once daily

Weight range (Kg)		Dose (200 mg tablet)
Bottom	Top	Once daily
10	13.9	1
14	24.9	1.5
25	34.9	1

ZIDOVUDINE (AZT or ZDV)

Recommended dosing based on weight-bands for children >6 weeks of age using liquid, capsules, pediatric tablets and adult tablets. Target dose 180-240mg/m² twice daily

Weight (Kg)	range	Formulations							
		10/mg/ml liquid		100 mg capsule		60 mg tablet		300 mg tablet	
Bottom	Top	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.
3	5.9	6 ml	6 ml			1	1		
6	7.9	9 ml	9 ml			1.5	1.5		
8	9.9	9 ml	9 ml	1	1	1.5	1.5		
10	13.9	12 ml	12 ml	1	1	2	2		
14	19.9			2	1	2.5	2.5	½	½
20	24.9			2	2	3	3	1	½
25	29.9			2	2			1	1
30	34.9			3	3			1	1

LAMIVUDINE (3TC)

Recommended dosing based on weight-bands for children >6 weeks of age using liquid and adult tablets

Weight range (Kg)		Dose (ml or tablets)		Target dose 4mg/Kg twice daily to a maximum of 150 mg twice daily
Bottom	Top			Formulation
3	5.9	3ml	3ml	10 mg/ml liquid
6	9.9	4ml	4ml	
10	13.9	6ml	6ml	
14	19.9	½	½	150mg Tablets
20	24.9	1	½	
25	34.9	1	1	

STAVUDINE (d4T)

Recommended dosing based on weight-bands for children >6 weeks of age using liquid and adult capsules

Weight range (Kg)		Target dose 1mg/kg twice daily up to 30 mg twice daily	Dose (ml or capsules)	
Bottom	Top	Formulation	a.m.	p.m.
3	5.9	1mg/ml liquid	6ml	6ml
6	9.9		9ml	9ml
10	13.9	15 mg capsule	1	1
14	24.9	20 mg capsule	1	1
25	34.9	30 mg capsule	1	1

ABACAVIR (ABC)

Recommended maintenance dose based on weight-bands for children >6 weeks of age using liquid and adult tablets

Weight (Kg) range Dose (ml or tablets) Target dose <16 years or <37.5 Kg: 8mg/Kg/dose twice daily. Max dose children and adult: 300 mg/dose given twice daily

Bottom	Top	a.m.	p.m.	Formulation
3	5.9	3ml	3ml	20 mg/ml liquid
6	9.9	4ml	4ml	
10	13.9	6ml	6ml	
14	19.9	½	½	300 mg tablet
20	24.9	1	½	
25	34.9	1	1	

LOPINAVIR/RITONAVIR

Recommended dosing based on weight-bands for children >6 weeks of age using liquid, and pediatric tablets. Target dose 230-350mg/m² twice daily

Weight range (Kg)		Formulations					
		80 mg LPV/20 mg RTV ml liquid		60 mg tablet		300 mg tablet	
Bottom	Top	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.
3	3.9	1ml	6 ml	1	1		
4	9.9	9 ml	9 ml	1.5	1.5		
10	13.9	9 ml	9 ml	1.5	1.5		
14	19.9	12 ml	12 ml	2	2		
20	24.9			2.5	2.5	½	½
25	29.9			3	3	1	½
30	34.9					1	1

COMBINATION ARV

Recommended dosing based on weight-bands

Weight range (Kg)		AZT/3TC Tablet 60/30 mg		AZT/3TC/ NVP Tablet 60/30/50 mg		D4T/3TC Tablet 6/30 mg		D4T/3TC/ NVP Tablet 6/30/50 mg		ABC/ AZT/3TC Tablet 60/60/30mg		ABC/3TC 60/30 mg	
Bottom	Top	a.m	p.m	a.m	p.m	a.m	p.m	a.m	p.m	a.m	p.m	a.m	p.m
3	5.9	1	1	1	1	1	1	1	1	1	1	1	1
6	9.9	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
10	13.9	2	2	2	2	2	2	2	2	2	2	2	2
14	19.9	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
20	24.9	3	3	3	3	3	3	3	3	3	3	3	3
		AZT/3TC: Tablet 300/150 mg		AZT/3TC/ NVP: Tablet 300/150/200 mg		D4T/3TC: Tablet 30/150 mg		D4T/3TC/ NVP: Tablet 30/150/200 mg		ABC/ AZT/3TC: Tablet 300/300/150 mg		ABC/3TC: 600/300 mg	
25 kg	34.9 kg	1	1	1	1	1	1	1	1	1	1	1	1

AZT for PMTCT prophylaxis in newborns

Infant age	Daily dosing
Birth to 6 weeks:	
<ul style="list-style-type: none"> Birth weight 2000-2499 g Birth weight >2500 g 	10 mg once daily 15 mg once daily

NVP for PMTCT prophylaxis in newborns

Infant age	Daily dosing
Birth to 6 weeks:	
<ul style="list-style-type: none"> Birth weight 2000-2499 g Birth weight >2500 g 	10 mg once daily 15 mg once daily
>6 weeks to 6 months	20 mg once daily
>6 months to 9 months	30 mg once daily
>9 months to end of BF	40 mg once daily
Low birth weight infants should receive mg/kg dosing, suggested starting dose is 2 mg/kg once daily. Therapeutic drug monitoring is recommended	



**World Health
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