6.2 Viral infections

6.2.A Chickenpox

**BOX 6.2.A.1 Minimum standards**
- Antipyretics and antipruritus treatment (e.g. chlorpheniramine/promethazine).
- Antibiotics for secondary infection.
- Aciclovir in immunosuppressed, neonates and other at-risk groups.
- VZIG IM (if available) for immunocompromised patients.
- Live attenuated varicella vaccine (for susceptible groups when in remission).

Introduction
Chickenpox is caused by varicella zoster virus (VZV), a member of the herpesvirus family. It is spread by direct contact, droplet or airborne transmission, and is very contagious.

Chickenpox manifests as a generalised pruritic vesicular rash typically consisting of crops of lesions in varying stages of development and resolution (crusting), mild fever, and other systemic symptoms. Varicella tends to be more severe in adolescents and adults than in young children.

The peak age for infection is 5 to 9 years. In immunocompetent children it is usually a mild disease, and lifelong immunity follows an infection.

Groups at increased risk include those with immune deficiency (mainly those with HIV infection), those on chemotherapy or long-term steroids (defined as those who within the previous 3 months received prednisolone, or its equivalent, at a daily dose of 2 mg/kg/day or more than 40 mg/day for at least 1 week or 1 mg/kg/day for 1 month), and neonates whose mothers have had chickenpox just before or just after the birth. Patients on lower doses of steroids plus another immunosuppressant drug and patients with an additional medical problem (e.g. nephrotic syndrome) should be included, plus those on salicylate therapy or with chronic lung or skin problems, including eczema. Acyclovir should be used in these groups.

Children with chickenpox are at increased risk of developing Reye's syndrome if given aspirin and other non-steroidal anti-inflammatory drugs.

Clinical presentation
- The incubation period is 14–21 days. There is low-grade fever and headache, followed by the rash, which is mostly on the trunk and face. The rash develops into successive small single oval vesicles with an erythematous base which break within 2 days to develop into scabs and heal. It is very itchy, and scratching may result in secondary bacterial infection and scar formation.
- The course of the disease is about 1 week. Children are infectious from 1 to 2 days before the rash appears until 1 or 2 days after all of the lesions have formed scabs.
- Complications include septicaemia, bronchopneumonia, hepatitis, thrombocytopenia, purpura, pericarditis, myocarditis, endocarditis, arthritis, myositis, glomerulonephritis, ascending mediastinitis and post-infectious encephalitis, especially with cerebellar involvement. Any fever or other symptom occurring within a few days of apparently resolving chickenpox must be taken seriously.
- Guillain–Barré syndrome, facial nerve palsy, transverse myelitis, hypothalamic involvement, optic neuritis and transient loss of vision have been reported.
- Intrauterine infection, especially in the first two trimesters, may result in a congenital varicella syndrome (i.e. intrauterine growth retardation, scarred skin, limb atrophy, mental retardation, CNS and eye complications). Only 1–2% of infants with intrauterine exposure develop complications.
- In mothers, chickenpox but not shingles, occurring between 5 days before and 2 days after delivery, may result in a severe infection in the neonate. This is probably due to lack of formation of VZV IgG antibodies that would have crossed the placenta and would be protective for the newborn baby. The infant should be treated as soon as possible with varicella-zoster immunoglobulin (if available) and with IV aciclovir as well if infection manifests (see below and Section 2.8.1).

Management
- Keep the child clean, and cut and clean under their nails to discourage scratching and prevent secondary skin infection.
- Baking soda baths or calamine lotion may relieve the itching.
- Antihistamines, such as chlorpheniramine 1 mg twice daily (1 month to 2 years of age), 1 mg three to six times a day; maximum 6 mg daily (2–6 years), 2 mg three to four times a day; maximum 12 mg daily (6–12 years), or 4 mg three to six times a day; maximum 24 mg daily (over 12 years) may reduce scratching.
- Give paracetamol for fever.
- Appropriate antibiotics should be given for secondary bacterial infection, which is mostly due to Staphylococcus aureus or Streptococcus pyogenes.
- Aciclovir IV 10 mg/kg 8-hourly or 250 mg/m² 8-hourly for 7–10 days is recommended for immunocompromised children who develop chickenpox. Oral aciclovir (20 mg/ kg four times a day) is given for HIV-infected patients whose CD4+ counts are relatively normal. It should
be considered for HIV-infected children with a CD4+ T-lymphocyte percentage of 15% or greater. If available, IM varicella-zoster immunoglobulin (VZIG) should be given at the following doses: birth to 5 years, 250 mg (one vial); 6–10 years, 500 mg (two vials); 10–15 years, 750 mg (three vials) and 15–18 years, 1 gram. This may modify the disease if given shortly (not more than 4 days) after exposure. Indications include immunocompromised children, such as HIV-infected pregnant women and premature infants born at less than 28 weeks’ gestation, who have had intimate contact (face to face) with chickenpox or herpes zoster. Neonates whose mothers develop varicella between 7 days before and 28 days after delivery are offered VZIG 250 mg as a single IM injection. If VZIG is not available, oral or IV aciclovir (at the above doses) may be given. In addition to standard precautions, airborne and contact precautions are recommended for patients with varicella for a minimum of 5 days after the onset of rash and until all lesions are crusted, which in immunocompromised patients can be 1 week or longer.

Prevention
- Live attenuated varicella vaccine (monovalent varicella vaccine or measles, mumps, rubella, varicella: MMRV) given as two subcutaneous or intramuscular injections confers over 95% protection against severe disease. Both have been licensed for use in healthy children from 12 months to 12 years of age. Children in this age group should receive two 0.5-mL doses of varicella vaccine administered subcutaneously, separated by at least 3 months.
- Susceptible children aged 13 years or older without immunocompromise should receive two 0.5-mL doses of varicella vaccine separated by at least 28 days.
- Patients in whom vaccine is contraindicated include those who are immunocompromised children and those receiving aspirin.
- Patients who are receiving immunosuppressive treatment (including steroid therapy) are generally immunised when in complete remission. The total lymphocyte count should be > $1.2 \times 10^9$/litre and there should be no other evidence of a lack of cellular immune competence.
- The vaccine should not be given within 3 months of VZIG.

6.2.B Dengue

**Box 6.2.B.1 Minimum standards**
- Airway, Breathing and Circulation assessment and management.
- Recognition and treatment of shock.
- Blood transfusion and replacement of clotting factors and platelets.
- High-dependency/intensive care.
- Vector control.

**Introduction**
Dengue infection is caused by an RNA virus of the Flaviviridae family. The disease first appeared in an epidemic in the Philippines in 1957, subsequently in Thailand, and then in other South-East Asian countries. It is now an important health threat in most Asian and South American countries, with an estimated 50–100 million dengue infections worldwide every year and a fatality rate of about 2.5% in hospitalised cases, although this could be reduced by earlier detection and access to good medical care.

Epidemics occur every year during the rainy season, and the mosquitoes *Aedes aegypti* and *Aedes albopictus* are the main vectors.

The dengue virus comprises four serotypes (type 1, 2, 3 and 4) which cause lifelong specific antibody responses. Unusually, a second infection with a different serotype of the virus puts the sufferer at greater risk of more severe illness.

**Table 6.2.B.1 Increasing signs of severity in dengue**

<table>
<thead>
<tr>
<th>Dengue: diagnosis</th>
<th>Warning signs of severity</th>
<th>Severe dengue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable dengue</td>
<td>Require close observation and medical care</td>
<td>Any of the following:</td>
</tr>
<tr>
<td>Live in or travel to dengue endemic area</td>
<td>Persistent vomiting</td>
<td>Severe plasma leakage showing as shock or respiratory distress</td>
</tr>
<tr>
<td>Fever and two of the following: Nausea, vomiting</td>
<td>Mucosal bleed</td>
<td>Severe bleeding as evaluated by clinicians</td>
</tr>
<tr>
<td>Rash</td>
<td>Lethargy, restlessness</td>
<td>Liver enlargement &gt; 2 cm</td>
</tr>
<tr>
<td>Aches and pains</td>
<td>Laboratory: increase in haematocrit concurrent with rapid decrease in platelet count</td>
<td>Severe organ involvement:</td>
</tr>
<tr>
<td>Tourniquet test positive</td>
<td>and either</td>
<td>- liver (AST, ALT &gt; 1000)</td>
</tr>
<tr>
<td>Supportive serology</td>
<td>Abdominal pain and tenderness</td>
<td>CNS: impaired consciousness</td>
</tr>
<tr>
<td>or Occurrence at the same location and time as other confirmed dengue cases</td>
<td></td>
<td>- heart and other organ failure</td>
</tr>
</tbody>
</table>

AST, aspartate aminotransferase; ALT, alanine aminotransferase; CNS, central nervous system.
severe clinical illness, and involves plasma leakage, significant bleeding and shock with a significant fatality rate, especially where intensive-care facilities are lacking. There are no available vaccines for dengue and no specific antiviral treatment. Treatment is supportive. Control is currently by control of the vectors.

**Diagnosis**

In 2009, the WHO classification of dengue infection was revised to simplify diagnosis and management. Table 6.2.B.1 shows the warning signs that severe dengue may develop.

This new WHO guideline classifies the infection either as dengue or as severe dengue. The old definition of (non-severe) dengue is the same as that of dengue fever (A90 according to the ICD code) and severe dengue means dengue hemorrhagic fever (A91 according to the ICD code).

The alternative differential diagnosis of acute febrile illness with non-specific symptoms is as follows:
- septicaemia
- scrub typhus
- viral infection

**Pathogenesis of severe dengue or dengue haemorrhagic fever (DHF)**

Infection with one dengue serotype gives specific lifelong antibody with only partial protection against other serotypes. Therefore, unusually, severe dengue or DHF occurs predominantly in patients with second infections who have a different serotype in their second infection from their first (previous dengue fever). Antibody-dependent enhancement, immune enhancement and T-cell (T8) proliferation and apoptosis are important in the development of disease.

Hypotheses for severe dengue or DHF include the following:
- Non-neutralising antibodies to dengue virus enhance viral uptake and replication in target cells (monocytes).
- Enhanced viral replication in the presence of T-cell apoptosis, resulting in large antigen load in the face of massive T-cell activation, releasing cytokines that lead to tissue damage and vascular leakage.

**FIGURE 6.2.B.1** Pathophysiology of severe dengue or dengue haemorrhagic fever. AST, aspartate aminotransferase; ALT, alanine aminotransferase; PT, prothrombin time; PTT, partial thromboplastin time.
Antibodies against dengue virus bind to complement pathway, releasing mediators that lead to vascular leakage as well.

Figure 6.2.B.1 shows a proposed pathophysiological pathway for severe dengue.

**TABLE 6.2.B.2 Clinical course of severe dengue or DHF**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Symptoms</th>
<th>Signs</th>
<th>Laboratory test</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Febrile phase</td>
<td>High continuous fever (39–40°C), headache, anorexia, nausea, vomiting, myalgia, arthralgia, epigastric discomfort, right upper quadrant pain, fine rubelliform maculopapular rash, mucosal bleeding</td>
<td>Facial flushing, injected conjunctivae Tourniquet test positive (see Figure 6.2.B.2), tenderness at right upper quadrant, hepatomegaly, lymphadenopathy, dry lips and mucosa</td>
<td>Not significant</td>
</tr>
<tr>
<td>duration 3–5 days (days 1–5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Haemorrhagic shock or toxic phase</td>
<td>Fever declines, abdominal pain especially in the right upper quadrant, bleeding in skin and mucosa (nose, gums, gastrointestinal tract) About 30% of cases will develop shock (irritability, restlessness, severe abdominal pain, sweating) Shock is less common when IV fluids have been given early</td>
<td>Right upper quadrant tenderness, hepatomegaly, tourniquet test positive, bleeding of mucosa, signs of dehydration (dry lips and mucosa, dark yellowish urine) Cold clammy skin (prolonged capillary refill time &gt; 2 seconds) Thready pulse, tachycardia, narrow pulse pressure (&lt; 20 mmHg, e.g. 90/70, 100/80)</td>
<td>Blood count; rising haematocrit, decreased platelet count (&lt; 100 x 10^9/litre), leucopenia Abnormal liver function test (albumin, liver enzyme: AST, ALT), renal function, calcium, electrolyte, blood gas in severe dengue with intractable and prolonged shock</td>
</tr>
<tr>
<td>phase duration 1–2 days (days 4–6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Convalescence phase</td>
<td>No fever or low-grade biphasic fever Increased appetite Diuresis</td>
<td>Convalescence rash on extremities with itching Widespread petechial rash with scattered round pale areas Sinus bradycardia</td>
<td>Stable haematocrit (or slowly increasing is a good clinical sign due to diuresis in some cases) Rising platelet count</td>
</tr>
<tr>
<td>Duration 2–3 days</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dengue or dengue fever (non-severe dengue) has only phases 1 and 3.

- Antibodies against dengue virus bind to complement pathway, releasing mediators that lead to vascular leakage as well.

Management of dengue and severe dengue (dengue haemorrhagic fever, DHF)

The aim of management of dengue and severe dengue is supportive, aiming to maintain adequate intravascular volume to prevent shock and to use blood and blood products to combat severe bleeding.

**Management of severe dengue with shock and respiratory distress**

**Initial management of shock**

1. Give high-flow oxygen with a mask with reservoir or nasal cannulae.
2. Give a bolus of Ringer-lactate or Hartmann’s or 0.9% saline solution (20 mL/kg).
3. If the child shows improvement, give 10 mL/kg of Ringer-lactate or Hartmann’s solution or 0.9% saline with 5% dextrose over 1 hour (add 50 mL of 50% dextrose to each 500-mL bag).
4. Reduce IV fluids (Ringer-lactate or Hartmann’s solution or 0.9% saline plus 5% dextrose) to 7 mL/kg/hour for 6 hours if vital signs improve.
5. Check vital signs every 15 minutes until stable, then every hour for 4 hours, then every 2–4 hours.
6. Check haematocrit every 4 hours.
7. If vital signs are stable, haematocrit declines to 36–40% and no warning signs appear, then reduce IV fluid to 5 mL/kg/hour for 6 hours followed by maintenance fluids (2–3 mL/kg/hour).
8. Stop IV fluid when the child drinks more than half of the required intake or there is a diuresis.
**TABLE 6.2.B.3 Management of dengue and severe dengue without shock**

<table>
<thead>
<tr>
<th>Day of illness</th>
<th>Assessment</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 1–3 (febrile phase)</td>
<td>Monitor temperature, blood pressure and pulse rate at least every 4–6 hours</td>
<td>1 Tepid sponge, paracetamol (do not give salicylate or other non-steroidal anti-inflammatory drugs, as they may cause bleeding, acidosis, hepatotoxicity and Reye’s syndrome)</td>
</tr>
<tr>
<td></td>
<td>Do tourniquet test</td>
<td>2 Give ORS/fruit juice/water frequently and in small amounts</td>
</tr>
<tr>
<td></td>
<td>Look for signs of dehydration (dry lips and mucosae, low urine output)</td>
<td>3 If the child is vomiting, try domperidone 0.2 mg/kg 6- to 8-hourly</td>
</tr>
<tr>
<td></td>
<td>Look for warning signs (see Table 6.2.B.1)</td>
<td>4 Admit if the child has signs of dehydration, gastrointestinal bleeding or cannot drink</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 Give IV fluid: 5% dextrose in Ringer-lactate or Hartmann’s or 0.9% saline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 Stop IV fluid when the child can drink more than half of normal or there is a diuresis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 Measure fluid intake and output every 4–8 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8 If calculated total intake is maximum (&gt; 7 mL/kg/hour), haematocrit is &gt; 40%, and shock has been present for &gt; 24 hours, try furosemide 200–500 microgram/kg IV or 5–10 mg per dose for most children &gt; 1 year of age.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9 If total intake is maximum (&gt; 7 mL/kg/hour), haematocrit is &gt; 40% and duration since first shock is &lt; 24 hours consider giving sodium bicarbonate, give inotropic drugs and consider positive pressure ventilation with PEEP (if available).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 Blood and blood components should be given only in cases of suspected or severe bleeding or intractable shock.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11 Fluid management</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plasma expanders</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colloid solutions to expand the intravascular volume:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Dextran 40 (osmolarity = 600 mOsmlitre), maximum 30 mL/kg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 6% hydroxyethyl starch (osmolarity = 308 mOsmlitre)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 4.5% albumin in severe hypoalbuminaemia with moderate to massive effusion/ascites and respiratory distress.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood products to combat bleeding:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• fresh frozen plasma (FFP), 10 mL/kg/dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• packed red cells (PRC), 5–10 mL/kg/dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• platelet transfusion, 0.2 units/kg/dose.</td>
</tr>
</tbody>
</table>

**Shock that does not improve with the first 20 mL/kg bolus of Ringer-lactate or Hartmann’s or 0.9% saline solution**

1 Continue high-flow oxygen.
2 Give a bolus of Dextran 40 (especially if the haematocrit is very high (> 50%) or the child has a puffy face or distended abdomen), 10 mL/kg over 15–30 minutes.
3 If the haematocrit is < 42% or has decreased by more than 5% consider careful transfusion of packed red cells, 5–10 mL/kg over 30 minutes to 1 hour.
4 If the child improves, revert to Ringer-lactate or Hartmann’s solution or 0.9% saline plus 5% dextrose, 5–7 mL/kg/hour for 6 hours and follow management in steps (7) and (8) above, 5 mL/kg/hour for 6 hours.
5 Check vital signs every 15 minutes until the child is stable, then every hour.
6 Check haematocrit every 4 hours and aim to maintain it at 40–45%.
7 Measure fluid intake and output every 4–8 hours.

**Shock that does not improve with Dextran 40 bolus**

1 Consider giving 4.2% sodium bicarbonate, 1–2 mL/kg IV slowly over 10 minutes.
2 Continue giving Dextran 40 at 7 mL/kg/hour.
3 Consider using an inotropic drug, such as dopamine or dobutamine 5–15 micrograms/kg/minute, if the child is still shocked or not improving.
4 Consider transfusion with packed red cells if the child is shocked with haematocrit < 42% or haematocrit declines by more than 5% of previous value.

**Intractable shock with respiratory distress**

1 Continue high-flow oxygen.
2 If calculated total intake is maximum (> 7 mL/kg/hour), haematocrit is > 40%, and shock has been present for > 24 hours, try furosemide 200–500 microgram/kg IV or 5–10 mg per dose for most children > 1 year of age.
3 If total intake is maximum (> 7 mL/kg/hour), haematocrit is > 40% and duration since first shock is < 24 hours consider giving sodium bicarbonate, give inotropic drugs and consider positive pressure ventilation with PEEP (if available).

### Management of dengue and severe dengue without shock

**Blood products**

- fresh frozen plasma (FFP), 10 mL/kg/dose
- packed red cells (PRC), 5–10 mL/kg/dose
- platelet transfusion, 0.2 units/kg/dose.

**Fluid management**

**Plasma expanders**

- Dextran 40 (osmolarity = 600 mOsmlitre), maximum 30 mL/kg/day
- 6% hydroxyethyl starch (osmolarity = 308 mOsmlitre)
- 4.5% albumin in severe hypoalbuminaemia with moderate to massive effusion/ascites and respiratory distress.

*Haematocrit of normal child is usually 35–36%, so if a child has haematocrit > 42% this means that it has risen to 20% or more above normal level.*
### Crystalloids

Normal maintenance fluids are 5% dextrose in Ringer-lactate or Hartmann’s or 0.9% saline solution, about 2–3 mL/kg/hour or:

- Up to 10 kg = 100 mL/kg/day
- From 11–20 kg = 100 mL/kg/day \( \times \) 10 kg for the first 10 kg, PLUS 50 mL/kg/day \( \times \) body weight in kg above 10 kg
- > 20 kg = 1500 mL, PLUS 20 mL/kg/day \( \times \) body weight in kg > 20 kg

Example: body weight of 14 kg = 1000 mL + (4 \( \times \) 50) = 1200 mL.

Example body weight of 30 kg = 1500 mL + (10 \( \times \) 20) = 1700 mL.

In an obese child, use ideal body weight to calculate IV fluids. For example, for an obese 7-year-old girl with body weight 40 kg, IV fluids should be calculated from her age multiplied by 2 plus 8 (7 \( \times \) 2 + 8 = 22 kg).

In practice, based on the above we can calculate IV fluids easily and rapidly as follows:

- 5 mL/kg/hour is equal to a 5% deficit if body weight < 40 kg
- 4 mL/kg/hour is equal to a 5% deficit if body weight > 40 kg

The maximum fluid that should be given in 24 hours (maximum fluid = resuscitation [20 mL/kg] + 10% deficit + maintenance) is 7 mL/kg/hour.

### Inotropic drugs

- Dopamine will increase renal blood flow: dose is 5–15 micrograms/kg/minute.
- Dobutamine is usually used in patients with poor peripheral circulation: dose is 5–15 micrograms/kg/minute.

### Severe dengue with organ involvement

Vital organs are not primarily involved in severe dengue, but are affected secondarily to plasma leakage, shock, haemorrhage and hypoxia. Notably, hepatic dysfunction and renal failure may occur especially in cases with prolonged shock.

Central nervous system involvement may be manifested by convulsions, spasticity and/or change in consciousness. Some cases have reported dengue virus in cerebrospinal fluid as in encephalitis.

### Prevention and control

There is no vaccine to protect against dengue. Development of a vaccine against dengue infection has been challenging, although there has been recent progress.

At present, the only method for controlling or preventing the transmission of dengue virus is to combat vector mosquitoes by preventing them from accessing egg-laying habitats. This is achieved by environmental management and modification, with community participation and active monitoring.
6.2.C Acute hepatitis

BOX 6.2.C.1 Minimum standards
- Liver function tests.
- International normalised ratio (INR) or prothrombin time.
- Blood glucose measurement.
- Vitamin K.
- Immunisation against hepatitis B: population vaccination.

Introduction
- Acute hepatitis results in liver dysfunction of duration less than 6 months.
- Transaminases (AST and ALT) are abnormal, but patients are not necessarily jaundiced.
- Acute hepatitis may be cholestatic, and may be complicated by acute liver failure as described in Section 5.7.A.
- Hepatitis A is common and usually self-limiting, but other important diseases may occur at the same time or appear similar and be overlooked (see Table 6.2.C.1).

TABLE 6.2.C.1 Causes of acute hepatitis-like presentation

<table>
<thead>
<tr>
<th>Aetiological group</th>
<th>Examples</th>
<th>Possible cholestasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral</td>
<td>Hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis E virus, delta superinfection, cytomegalovirus, Epstein–Barr virus, herpes simplex, parovirus, measles, mumps, varicella, rubella, adenovirus, ECHO, coxsackie, flaviviruses (e.g. yellow fever, dengue, Lassa, Ebola, Rift Valley fever).</td>
<td>Hepatitis A virus, hepatitis B virus, hepatitis E virus</td>
</tr>
<tr>
<td>Bacterial/fungal</td>
<td>Salmonella, Leptospira, any septicaemia</td>
<td>Not usually</td>
</tr>
<tr>
<td>Protozoal + parasitic</td>
<td>See Section 6.3.A.d and 6.3.C</td>
<td>Not usually</td>
</tr>
<tr>
<td>Drugs and toxins</td>
<td>See Section 7.4</td>
<td>Drug cholestasis</td>
</tr>
<tr>
<td>Shock</td>
<td>Cardiac arrest, post surgery, heat stroke, radiation</td>
<td>Occurs 7–10 days after injury</td>
</tr>
<tr>
<td>Immune</td>
<td>Autoimmune, lupus, Kawasaki disease</td>
<td>Autoimmune, lupus, Kawasaki disease</td>
</tr>
<tr>
<td>Infiltrative</td>
<td>Leukaemias, haemophagocytic syndromes, Hodgkin's disease</td>
<td>Leukaemias, Hodgkin's disease</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Urea cycle disorders</td>
<td>Usually not</td>
</tr>
<tr>
<td></td>
<td>Wilson's disease</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Management of acute hepatitis
- Exclude hepatitis A with HAV IgM and attempt diagnosis with tests (if available).
- Monitor hepatic synthetic function for liver failure using prothrombin time or INR, having given IV vitamin K.
- Monitor for complications, including hypoglycaemia, encephalopathy, bone-marrow aplasia, secondary sepsis and pancreatitis (see Section 5.7.A).
- Treat complications when possible.
- Give vitamin K, 300 micrograms/kg.
- Give anti-emetics if there is severe nausea and vomiting.
- Give intravenous fluids only if oral or nasogastric rehydration is not possible.
- See Section 5.7.A for the management of acute liver failure if this develops.
- If available, immunise all family contacts for HAV and HBB (HAV A, two doses 2 weeks apart; HAV B, three doses, the first being given immediately, the second 1 month later, and the third 3–6 months later).

Hepatitis A
- Hepatitis A (HAV) is a picornavirus spread by the faecal–oral route.
- The incubation period from infection to raised transaminases is 10–20 days.
- Before jaundice is seen there may be anorexia, nausea, vomiting, fever and liver tenderness.
- Jaundice is related to age, with more than 90% of children under 2 years being asymptomatic, and only 76% of teenagers jaundiced.
- A minority of cholestatic cases have a relapsing course, and 0.1–0.2% develop acute liver failure. The prognosis for almost all is excellent with symptomatic treatment.
- Chronic liver disease does not develop, but occasional patients have a transient nodular regenerative phase with evidence of portal hypertension lasting up to 1 year. Aplastic anaemia is a rare complication.
- HAV vaccine is highly efficacious and without side effects.

Hepatitis B
Acute hepatitis B (see also section on chronic hepatitis)
- This is spread by blood and body fluid products, vertical transmission from mother to baby, and sexual contact. The risk of all such spread is much greater than for HIV infection.
- The incubation period is 60–90 days, but rarely up to 7 months.
- The risk of acute liver failure is less than 1%, and the risk of chronic liver disease depends on the patient’s age: it is approximately 90% at birth, 25% in childhood and less than 10% in adults.
- Hepatitis B vaccine is usually given by three injections over 6 months, but an accelerated course can be given
over 21 days, and post-exposure vaccination is usually given in combination with immunoglobulin in a different site. All healthcare workers should be immunised against HBV and their immunity status checked.

**Hepatitis C**
- The mechanisms of spread are the same as for hepatitis B, but vertical spread is rare (around 4%).
- The incubation period is 2–26 weeks, followed by acute hepatitis that is almost always asymptomatic.
- Chronic hepatitis ensues in 30–90% of cases.
- Symptomatic liver disease is almost never seen in childhood.
- Treatment with a combination of pegylated interferon and ribavirin is becoming progressively more successful (if available).

**Hepatitis E**
- Spread is by the faecal–oral route and is endemic in Southern Europe, the Middle East and Asia.

**6.2.D Human immunodeficiency virus (HIV) infection**

**BOX 6.2.D.1 Minimum standards**
- Preventive campaigns.
- Antenatal HIV screening.
- Antenatal and postnatal antiretroviral (ARV) drugs.
- Paediatric HIV testing.
- Antiretroviral drugs (triple drug regimes for all), including those to prevent vertical transmission guaranteed.
- Health system strengthening to provide a capacity to treat all with ARV and give supportive treatment.
- Correction of nutritional deficiencies.
- Antibacterial drugs, including anti-TB and antifungal drugs.
- Analgesia and palliative care.
- Counselling and family support.

**Introduction**

The human immunodeficiency virus (HIV) epidemic has spread to all corners of the world, affecting millions of infants, children and adults. It is the most common cause of acquired immune deficiency in children. The timely and early diagnosis of neonates, infants and children with HIV is vital. However, the healthcare system of resource-limited countries has its own strengths and limitations. Pitfalls in accurate testing, poor access to health, and high financial costs are a few of the many factors that hamper efforts to limit the spread of diseases such as HIV. In addition, the management of HIV is complex and intricate. Many factors, including proper assessment and indication, counselling, availability and choice of antiretroviral drugs, toxicity, monitoring, financial burden, and social and psychosocial support have to be addressed for HIV care to be successful. Education, evaluation, building expertise, establishing HIV referral centres with diagnostic testing (including virological testing), ensuring availability of antiretroviral drugs, monitoring and follow-up are some of the key elements necessary for programmes to have adequate impact.

**Epidemiology**
- There are two major strains of the human immunodeficiency virus: HIV1 and HIV2. HIV1 is the more pathogenic, and is responsible for the global epidemic. HIV2 is largely confined to West Africa. This subsection reflects current management of HIV1, but the principles apply to both strains.
- Infection with HIV leads to progressive destruction of the cellular immune system, ultimately resulting in an acquired immune deficiency syndrome (AIDS) in the vast majority of infected individuals.
- HIV/AIDS is now one of the leading causes of death in children.
- Mother-to-child transmission results in approximately 1000 children becoming infected with HIV each day worldwide. There were 2.5 million children under 15 years old living with HIV in 2009.
- Around 97% of the world’s new HIV infections occur in people living in low- and middle-income countries. About 92% of children living with HIV are from sub-Saharan Africa.
- The number of new infections fell from a peak in the late 1990s, but has now plateaued at a high incidence of 2.6 million new infections per year, just below the maximum level reached previously.
- Deaths from AIDS have decreased by 19% between 2004 and 2009 with increasing access to antiretroviral therapy.
- Around 95% of the world’s HIV-infected children have been from resource-limited countries. About 90% have been from sub-Saharan Africa, but the prevalence elsewhere is rising, particularly in India, South-East Asia, and countries of the former Soviet Union.
More than 90% of children acquire HIV perinatally (vertically) from their mothers. The rest are infected through transfusion of infected blood products or via unsterilised needles (extent unknown but probably small), or via sexual transmission among adolescents, or in younger children through child sexual abuse.

In non-breastfed infants, vertical transmission occurs mainly around the time of delivery, with transmission rates in resource-limited countries ranging from 17% to 24%. Breastfeeding roughly doubles the risk of transmission. In breastfed cohorts from resource-limited countries the rates of transmission are 25–45%.

Management ideally begins before birth, with counselling and voluntary testing of HIV-infected women during pregnancy, and institution of measures to reduce transmission. In almost all countries, antiretroviral therapy for mothers and infants, elective (pre-labour) Caesarean section and avoidance of breastfeeding have reduced transmission rates to less than 2%.

Without prenatal counselling and screening, as is frequently the case in resource-limited countries, management begins only when the child becomes symptomatic, with subsequent identification of the HIV infection in the mother.

Treatment may not be successful if presentation is at an advanced stage of immunosuppression.

In all societies, even those with a high prevalence, HIV is a potentially stigmatising condition, and the mother or both parents may be reluctant to undergo testing. Confidentiality is essential.

Counselling must be confidential, requires time and should be undertaken by trained staff.

Even if a child born to an infected mother is uninfected, he or she will inevitably be affected. Between 14.4 and 18.8 million children were estimated to have lost one or both parents to AIDS in 2010 (UNAIDS data). These children may be abandoned by relatives, ostracised by the community, poorly educated and highly vulnerable. Many support themselves and surviving siblings by commercial sex work, and may acquire HIV infection as a result.

Natural history data

Before the advent of highly active antiretroviral therapy (HAART), infant mortality doubled and mortality in children aged 1–5 years increased from 8 to 20 per 1000 in Harare between 1990 and 1996.

However, even in resource-limited countries, some children may be symptom-free into the second decade of life. There is no upper age limit at which it is appropriate to test for HIV if the mother does not have a negative test after the child’s birth.

Data from large long-term prospective perinatally recruited cohort studies are limited in resource-limited countries.

Growth failure, generalised lymphadenopathy, hepatosplenomegaly, persistent diarrhoea, pulmonary infections, chronic cough and recurrent fevers are the most frequent clinical manifestations.

The most common causes of death are pneumonia, diarrhoea and malnutrition. Post-mortem studies from the Cote d’Ivoire and clinical studies in Malawi and South Africa showed that Pneumocystis jiroveci pneumonia (PCP) is a frequent cause of death in children under 15 months of age.

Malignancy is a relatively rare AIDS-defining illness in children, compared with HIV-infected adults. However, substantial increases in Kaposi’s sarcoma in children have been reported from East and Central Africa. Co-infection with the human herpes virus (HHV8) is a crucial aetiological factor. Kaposi’s sarcoma typically presents with large non-tender firm mobile lymph nodes in the head and neck region, and there may be skin lesions and pulmonary disorders. Median survival in one series was only 3 months.

Diagnostic issues

Confirming a diagnosis of HIV infection in young children can be difficult in resource-limited settings.

Early infant diagnosis of HIV: exposed infants should be tested at 6 weeks or as soon as possible thereafter. Infant blood samples are sent as dried blood spots to a laboratory that has the required equipment for HIV PCR testing. This laboratory may be close by, but could also be far from the site. The results then need to be sent back to sites and returned to caregivers in a timely manner. Finally, infants who have tested positive must be started on ART.

In areas of high HIV prevalence, WHO Integrated Management of the Child recommends that, when

### TABLE 6.2.D.1 Signs and symptoms for use in endemic areas with limited access to diagnostic laboratories

<table>
<thead>
<tr>
<th>Signs or illness specific to HIV infection</th>
<th>Signs or illness uncommon in HIV-negative children</th>
<th>Signs common in both HIV-positive and ill non-HIV-infected children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumocystis pneumonia</td>
<td>Molluscum contagiosum with multiple lesions</td>
<td>Persistent diarrhoea (&gt; 14 days)</td>
</tr>
<tr>
<td>Oesophageal candidiasis</td>
<td>Oral thrush (especially after the neonatal period) without antibiotic treatment and lasting &gt; 1 month or recurrent</td>
<td>Failure to thrive</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>Generalised pruritic dermatitis</td>
<td>Persistent cough &gt; 1 month</td>
</tr>
<tr>
<td>Lymphoid interstitial pneumonia</td>
<td>Recurrent severe infections (three or more per year)</td>
<td>Generalised lymphadenopathy</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>Persistent and/or recurrent fever lasting &gt; 1 week</td>
<td>Hepatosplenomegaly</td>
</tr>
<tr>
<td>Chronic parotid enlargement</td>
<td>Neurological dysfunction (progressive neurological impairment, delayed development, intellectual impairment, hypertonia)</td>
<td>Chronic otitis media</td>
</tr>
<tr>
<td>Recto-vaginal fistula (rare)</td>
<td>Failure to thrive in a fully breastfed infant &lt; 6 months of age</td>
<td>Moderate or severe malnutrition</td>
</tr>
</tbody>
</table>
assessing sick children aged 2 months to 5 years, health-care workers ask about a history of pneumonia, persistent diarrhoea, ear discharge or very low weight, and look for oral thrush, parotid enlargement and generalised persistent lymphadenopathy. If there are two or more of the above, HIV infection should be suspected and an HIV antibody test performed.

Clinical diagnosis

- The symptoms and signs are often non-specific. The most recent modified WHO clinical case definition for paediatric AIDS is a useful tool for epidemiological surveillance, but lacks sensitivity and has a low positive predictive value (PPV). It is therefore not useful for confirming a diagnosis of HIV infection in an individual child.
- The presence of oral candidiasis does not distinguish HIV-infected from HIV-uninfected children. However, failure of oral candidiasis to respond to treatment or rapid relapse is a highly specific sign of HIV infection. After the neonatal period, the presence of oral thrush without antibiotic treatment, or lasting over 30 days despite treatment, or recurring, or extending beyond the tongue, is highly suggestive of HIV infection. Also typical is extension to the back of the throat, which indicates oesophageal candidiasis.
- Chronic parotitis, the presence of unilateral or bilateral parotid swelling (just in front of the ear) for 14 or more days, with or without associated pain or fever or shingles, is highly suggestive of HIV infection.
- Shingles is unusual in healthy children. Herpes zoster ophthalmicus (i.e. shingles around one eye) is said to have greater than 95% PPV for HIV infection in African children.
- Geographical variation in patterns of disease must be recognised. *Penicillium marneffei* infection, an opportunistic fungal disease that presents with nodular skin lesions, is an AIDS-defining illness that has been reported in South-East Asia. Giant molluscum contagiosum has been a presenting sign in children in Eastern Europe.
- None of these clinical features is a sensitive marker of HIV infection in childhood populations, in that a minority of HIV-infected children manifest them.

There are many clinical signs or conditions that are quite specific to HIV infection, which should be strongly suspected if these conditions are present (see Table 6.2.D.1).

Some of these features are listed below.

1 **Signs or conditions that are very specific to HIV-infected children:**
   - Pneumocystis pneumonia (PCP).
   - Oesophageal candidiasis.
   - Lymphoid interstitial pneumonia (LIP).
   - Kaposis sarcoma.

2 **Signs that may indicate possible HIV infection:**
   - **Recurrent infection:** three or more severe episodes of a bacterial infection (e.g. pneumonia, meningitis, sepsis, cellulitis) in the past 12 months.
   - **Oral thrush:** after the neonatal period, the presence of oral thrush in the absence of antibiotic treatment, or lasting over 30 days despite treatment, or recurring, or extending beyond the tongue.
   - **Chronic parotitis:** the presence of unilateral or bilateral parotid swelling for 14 or more days.
   - **Generalised lymphadenopathy:** the presence of enlarged lymph nodes in two or more non-inguinal regions without any apparent underlying cause.
   - **Hepatomegaly** with no apparent cause.
   - **Persistent and/or recurrent fever.**
   - **Neurological dysfunction:** progressive neurological impairment, microcephaly, developmental delay, hypertonia, encephalopathy.
   - **Herpes zoster.**
   - **HIV dermatitis:** typical skin rashes include erythematous papular rashes, extensive fungal infections of the skin, scalp and nails, and extensive molluscum contagiosum.
   - **Chronic suppurative lung disease.**

**Counselling and testing**

If there are reasons to suspect HIV infection, and the child’s HIV status is not known, the family should be offered diagnostic testing for HIV.

Counselling used to be more complex when there was no treatment available. There is now no question that it is in the child’s best interest to be tested so that treatment can be given to prolong life if they are HIV-positive. The lessons of obtaining informed consent still apply, just as with any other important investigation. If the mother has not already been tested, a positive result in a child is most likely to mean that the mother is infected, too. However, if the mother is not present when the child presents, the onus of responsibility of the paediatrician is to the child, and testing should not be delayed.

The additional consideration with testing for HIV is the stigma associated with the diagnosis. When HIV meant inevitable death, there was enormous fear of the diagnosis. The potentially better prognosis has been hard to accept when so many present too late. Stigma is also associated with the fact that it is a sexually transmitted disease. This raises issues of where the infection was acquired and contact tracing. The fear of domestic violence and social ostracisation sometimes creates reluctance to allow children to be tested.

The process of counselling starts with always ensuring that the test is done with consent. The person giving consent should be the carer at the time when the test is indicated. If the child is of an age at which they can be responsible for taking their own medicines, they can give their own consent for testing. There are no surrogate tests for HIV, such as lymphocyte counts; the appropriate test according to what is available should always be done. If there is delay in getting a result it may be necessary to start appropriate treatment – for example, for suspected PCP pneumonia with IV co-trimoxazole.

If there is refusal to allow testing, the test cannot be carried out. If the test is positive, the family need to have confidence in the healthcare professionals to ensure adherence to treatment. Counselling requires time, and must 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 organisations. A time limit should be set to prevent repeated
procrastination and the risk of death from opportunistic infection.

HIV counselling should take account of the child as part of a family. This should include the psychological implications of HIV infection for the child, mother, father and other family members. Counselling should stress that, although cure is currently not possible, there is much that can be done to improve the quality and duration of the child’s life. Antiretroviral treatment (ART) is available and greatly improves survival and the quality of life of the child and the 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 centre or hospital early in an illness, even if this is only to ask questions.

HIV is talked about much more openly now than was the case at the start of the epidemic, and testing is seen as an expected part of routine healthcare. The request for testing should not be built up as a major event, but included as part of the diagnostic work-up along with malaria, TB and other investigations.

As mentioned above, counselling requires time, and must be done by trained staff.

**Indications for HIV counselling**

**Child with unknown HIV status presenting with clinical signs of HIV infection and/or risk factors (e.g. a mother or sibling with HIV/AIDS)**

- Make time for the counselling session.
- Take advice from local people experienced in offering testing, so that any advice given is consistent with what the mother will receive from professional counsellors at a later stage.
- Where available, arrange an HIV test, according to national guidelines, to confirm the clinical diagnosis, alert the mother to HIV-related problems, and discuss prevention of future mother-to-child transmission.

Note the following:
1. If HIV testing is not available, discuss the presumptive diagnosis of HIV infection in the light of the existing signs and symptoms and risk factors.
2. In countries with generalised HIV epidemics, routine healthcare provider-initiated testing and counselling (PICT) is recommended for all children seen in paediatric health services (World Health Organization, 2007).

**Child known to be HIV-infected but responding poorly to treatment, or needing further investigations**

Discuss the following:
- the parents’ understanding of HIV infection
- management of current problems
- the role of ART and adherence to regular drug administration
- the need to refer to a higher level, if necessary
- support from community-based groups (if available).

**Child known to be HIV-infected who has responded well to treatment and is to be discharged (or referred to a community-based care programme)**

Discuss the following:
- the reason for referral to a community-based care programme, if appropriate
- follow-up care

- risk factors for future illness
- immunisation and HIV
- adherence and ART treatment support.

**Laboratory diagnosis**

The definitive diagnosis of HIV requires laboratory confirmatory testing. The HIV antibody test is commonly used as a screening test. However, in the neonatal and infantile period, the antibody test is not recommended. This is because the maternal HIV antibodies readily cross the placenta and persist in the neonate for up to 18 months. Also, all screening tests should be confirmed by a second test. The following are some of the tests used for laboratory diagnosis of HIV in children:

- **Antibody tests:**
  - HIV IgG antibody tests.
  - Rapid Test.
- **Virological tests:**
  - HIV DNA polymerase chain reaction (PCR).
  - HIV RNA PCR.
  - HIV culture.
- **P24 antigen assay:**
  - Direct.
  - Acid hydrolysis.

DNA-based assays are the most reliable for diagnosis, and are recommended for diagnosis in infants. However, the cost and availability of tests may be an issue in resource-limited countries. The simplest laboratory test is an HIV antibody test, usually done by enzyme-linked immunosorbent assay (ELISA). However, even this may not be affordable or available in many settings.

The WHO recommends the use of a presumptive clinical diagnosis of severe HIV disease in the absence of virologic testing if:

- an infant’s HIV exposure is confirmed by antibody testing and if either:
  - clinical stage 3 or 4 or AIDS-indicator condition(s) are present or
  - the child has two or more of the following: oral thrush, severe pneumonia, severe sepsis.

A presumptive diagnosis of AIDS can also be made in an antibody-positive infant if CD4 percentages are below 20% or other factors are present, including recent HIV-related maternal death or advanced HIV disease in the mother.

Infants acquire maternal HIV IgG transplacentally, and this can be detected by ELISA up to 18 months of age. Thus antibody tests cannot reliably distinguish infected from uninfected children until they are 18 months old. Additional diagnostic challenges arise if the child is still breastfeeding or has been breastfed. Although HIV infection cannot be ruled out until 18 months for some children, many children will have lost HIV antibodies between 9 and 18 months of age. The importance of this is that a rapid antibody test can be done if the mother is unwilling or unavailable to be tested herself. If the antibody test is negative and the child has not been breastfed in the last 6 weeks, there is then no need for further testing unless there is ongoing exposure (e.g. through breastfeeding). If the antibody is positive, this does not mean that the child is infected, but if other signs of immune deficiency are present it may warrant empirical treatment according to WHO guidelines if PCR testing is not available.
Many children born to HIV-infected mothers may die before this age, and a diagnosis of HIV infection may be presumptive, dependent on signs and symptoms. Thus, based on age, the clinical, serological and virological tests and status of breastfeeding will determine the diagnosis of a child undergoing evaluation (see Table 6.2.D.2).

**FIGURE 6.2.D.1** Algorithm for diagnosing HIV infection in infants and children less than 18 months of age.

**TABLE 6.2.D.2** Proposed methods for diagnosing HIV in children (born to mothers identified as HIV-positive or with unknown HIV status) in resource-limited settings* (see Figure 6.2.D.1)

<table>
<thead>
<tr>
<th>Age of child</th>
<th>&lt; 12 months</th>
<th>12–18 months</th>
<th>&gt; 18 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic method</td>
<td>Clinical staging</td>
<td>Serological (antibody)</td>
<td>Virological</td>
</tr>
<tr>
<td>*If the child is breastfeeding, a negative diagnostic test, either serological or virological, would have to be repeated 6 weeks after cessation of all breastfeeding.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>*If the child is breastfeeding, a negative diagnostic test, either serological or virological, would have to be repeated 6 weeks after cessation of all breastfeeding.</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

* A positive antibody test in a child under 12 months of age defines the exposure status of the child and may be helpful when the mother’s HIV status is unknown.

† By the age of 12 months, HIV antibody-positive testing can be considered indicative of probable HIV infection, and should be confirmed by a second antibody test after 18 months.
Algorithms for diagnosis are shown in Figures 6.2.D.1 and 6.2.D.2.

**Notes to Figure 6.2.D.1.**
1. If HIV exposure is not certain, consider testing the mother first before doing a virological test on the child. If the mother tests negative for HIV, explore other risk factors for HIV transmission.
2. In infants and children under 18 months of age considered to be HIV-uninfected who develop signs or symptoms suggestive of HIV, virological testing should be performed.
3. If virological testing is not available, antibody testing can be performed. By the age of 12 months most uninfected children will have lost maternal antibody, and positive antibody testing at this time usually indicates HIV infection in the child (96% specificity). In infants younger than 12 months where antibody testing is still positive, a presumptive clinical diagnosis of severe HIV disease may need to be made, as it is not possible to reliably establish HIV infection with antibody testing before the age of 12 months (i.e. specificity at age 9–12 months is 74–96%). In this situation, confirmation of the presumptive clinical diagnosis of HIV infection by virological testing should be sought as soon as possible.
4. Antibody testing can be performed at the age of 12 months (see above).
5. Where the infant is being considered to be HIV-infected based upon a positive antibody test performed at 12 months of age or older, the result should be confirmed by virological testing (in children less than 18 months of age) or by antibody testing (once they are over 18 months of age).

**Notes to Figure 6.2.D.2.**
1. A definitive diagnosis of HIV infection in children aged ≥ 18 months can be made with antibody testing. HIV testing procedures for children aged ≥ 18 months follow the national HIV testing guidelines for adults. Virological testing can be used to diagnose HIV infection at any age.
2. One positive HIV antibody test (rapid test or ELISA) should be confirmed by a second HIV antibody test.
(rapid test or ELISA) using an assay that relies on a different antigen or has different operating characteristics. In low-HIV-prevalence settings, a third confirmatory test may be required.

3 Children who are breastfed have an ongoing risk of acquiring HIV infection. Therefore HIV infection can be excluded only after stopping breastfeeding for more than 6 weeks.

**HIV antibody test (ELISA or rapid tests)**

Rapid tests are widely available and are safe, effective, sensitive and reliable for diagnosing HIV infection in children above the age of 18 months. For those under 18 months, HIV antibody tests are a sensitive reliable way to exclude HIV infection in non-breastfeeding children. For those children under 18 months, confirm all positive HIV antibody tests by virological tests as soon as possible (see below). Where this is not possible, repeat antibody testing at 18 months.

Rapid HIV tests can be used to exclude HIV infection in a child presenting with malnutrition or other serious clinical events in areas with high HIV prevalence.

To confirm the diagnosis, it is necessary to use assays that detect the virus itself or viral components. Such tests include antigen detection tests, viral culture, amplification techniques and HIV-specific IgA tests.

**Virological testing**

Virological testing for HIV-specific RNA or DNA is the most reliable method of diagnosing HIV infection in children under 18 months of age. This requires sending a blood sample to a specialised laboratory that can perform this test, and these are becoming increasingly available in large centres in many countries. It is relatively inexpensive, easy to standardise, and can be done using dried blood spots. In infants and children undergoing virological testing, the following assays (and respective specimen types) are potentially available:

- HIV DNA on whole blood specimens or dried blood spots (DBS)
- HIV RNA on plasma or DBS
- ultrasensitive p24 antigen (Up24 Ag) on plasma or DBS.

The new ultrasensitive p24 assay is as accurate as PCR virology, significantly less expensive, and less resource demanding when used to diagnose HIV. It is particularly valuable in infants under 12 months old.

A test at birth will only detect in-utero infection, whereas most infection occurs at delivery. Infected infants can suffer life-threatening infections in the first weeks of life. Where there is a high risk of infection (e.g. a mother who seroconverts in pregnancy, has a low CD4 count or other genital lesions and has had no antiretrovirals), testing should be done at 2 weeks of age. Where the risk is low (e.g. a mother who has been on HAART throughout pregnancy), the test can be delayed until 6 weeks of age. At the first DTP immunisation of all infants, the maternal HIV status should be checked from records or rapid testing. If it is positive or unavailable, the child should be tested. All HIV-exposed infants should have HIV virological testing at 4–6 weeks of age or at the earliest opportunity thereafter.

If the child has had zidovudine (ZDV) prophylaxis during and after delivery, virological testing is not recommended until 4–8 weeks after delivery, as ZDV interferes with the reliability of the test.

One virological test that is positive at 4–8 weeks is sufficient to diagnose infection in a young infant. If the young infant is still breastfeeding, and the DNA virological test is negative, it needs to be repeated 6 weeks after the complete cessation of breastfeeding to confirm that the child is not HIV infected.

Infants with signs or symptoms suggestive of HIV infection must undergo HIV serological testing and, if this is positive, virological testing. In breastfeeding infants or children it is strongly recommended that breastfeeding is not discontinued in order to perform any kind of diagnostic HIV test. In sick infants in whom HIV infection is being considered as an underlying cause of symptoms and signs, and virological testing is not available, HIV serological testing and the use of a clinical algorithm for presumptive clinical diagnosis of HIV infection are strongly recommended.

In infants with an initial positive virological test result, it is strongly recommended that ART be started without delay and, at the same time, a second specimen be collected to confirm the initial positive virological test result. **Do not delay ART.** In infected infants, immediate initiation of ART saves lives, and commencement of ART should not be delayed while waiting for the results of the confirmatory test. Results from the CHER trial suggest initiation of ART before 12 weeks of age in results at a 75% reduction in early mortality.


Test results from virological testing in infants should be returned to the clinic and the child and their mother or carer as soon as possible, but at the very latest within 4 weeks of specimen collection. Positive test results should be fast-tracked to the mother–baby pair as soon as possible to enable prompt initiation of ART.

All infants with unknown or uncertain HIV exposure who are being seen in healthcare facilities at or around the time of birth or at the first postnatal visit (usually 4–6 weeks), or at another child health visit, should have their HIV exposure status ascertained.

Clinically well, HIV-exposed infants should undergo HIV serological testing at around 9 months of age (or at the time of the last immunisation visit). Those who have positive serological assays at 9 months should have a virological test to identify whether they need ART.

Recently the WHO Technical Reference Group for Paediatric HIV/ART and Care made the following key recommendations with regard to when and how to test for HIV in children:

1. **Infants known to have been exposed to HIV should have a virological test (HIV nucleic acid test) at 4–6 weeks of age, or at the earliest opportunity for infants seen after 4–6 weeks.**
2. **Urgent HIV testing is recommended for any infant presenting to healthcare facilities with signs, symptoms or medical conditions that could indicate HIV.**
3. **All infants should have their HIV exposure status established at their first contact with the healthcare system, ideally before 6 weeks of age.**
4. **Infants under 6 weeks of age, of unknown HIV exposure status and in settings where local or national antenatal HIV seroprevalence is greater than 1%, should be offered maternal or infant HIV antibody testing and counselling in order to establish their exposure status.**
**Other laboratory tests**
- A low CD4 count or CD4:CD8 ratio suggests HIV infection, but requires specialised equipment. A low total lymphocyte count is a much less expensive though less specific surrogate marker of HIV infection and immunosuppression.
- HIV infection can also cause anaemia or thrombocytopenia. It is appropriate to test for HIV in children who present with low platelet counts.
- Lack of thymic shadow on chest X-ray is a feature of advanced disease, but is clearly not specific, as the thymus tends to shrink in volume in response to a variety of acute infections in childhood.

**Assessment of HIV-infected and HIV-exposed children**
Any child with an illness compatible with HIV infection should be properly evaluated irrespective of HIV exposure. This includes neonates, infants and children with perinatal exposure, and those with specific signs and symptoms suggestive of HIV infection, chronic or unexplained illness, or known exposure during childhood. Figure 6.2.D.3 shows a useful algorithm that can be used by paediatricians and other clinical care providers for the initial evaluation and management of children with known exposure to HIV, or sick children with symptoms suggestive of HIV infection but unknown history of exposure.

**Notes to Figure 6.2.D.3.**
1. An expert in the management of children with HIV should be consulted wherever this is feasible.
2. If HIV is suspected, compassionate counselling before HIV testing should be arranged.
3. Maternal advanced HIV disease and low CD4 are risk factors for HIV transmission.
4. Successful treatment with ART in mothers reduces the risk of transmission.
5. PMTCT using ZDV monotherapy alone, ZDV plus NVP single dose, and NVP single dose alone is associated

![Figure 6.2.D.3](#) Initial assessment of a child with known HIV exposure or a sick child with unknown HIV exposure but with suspected HIV infection. MTCT, mother-to-child transmission; ART, antiretroviral therapy; PCP, pneumocystis pneumonia.
with transmission rates of approximately 5–10%, 3–5% and 10–20%, respectively.

6 An infant remains at risk of acquiring HIV for as long as he or she is breastfed.

Perinatally acquired HIV infection
HIV1 transmission occurs more frequently than that of HIV2. It occurs in late pregnancy, during delivery and through breastfeeding, and transmission is more likely if any of the following factors are present:
- advanced maternal HIV disease
- prematurity labour
- prolonged rupture of membranes
- contact with maternal blood
- in the first twin
- maternal genital infection.

Prevention of mother-to-child transmission (PMTCT) of HIV and infant feeding in the context of HIV
HIV transmission may occur during pregnancy, labour and delivery, or through breastfeeding. The best way to prevent transmission is to prevent sexually acquired HIV infection, especially in pregnant women, and to prevent unintended pregnancies in HIV-positive women. If an HIV-infected woman becomes pregnant, she should be provided with services including antiretroviral drugs, safe obstetric practices, and infant feeding counselling and support (see Section 2.8.C).

The key recommendations of the 2010 WHO guidance on ARV drugs for treatment of pregnant women and prevention of HIV in infants are as follows:

Women who are immunocompromised
As early as possible, provide ART for all HIV-positive pregnant women both to benefit the health of the mother and to prevent HIV transmission to her child during pregnancy and breastfeeding.

Start lifelong ART for all pregnant women with severe or advanced clinical disease (stage 3 or 4), or with a CD4 count of ≤ 350 cells/mm³, regardless of symptoms. HIV-positive pregnant women in need of treatment for their own health (i.e. as soon as the eligibility criteria are met) should start ART irrespective of gestational age, and should continue with it throughout pregnancy, delivery, during breastfeeding and thereafter.

The recommended first-line regimens for pregnant women are as follows:
- AZT + 3TC + NVP or
- AZT + 3TC + EFV or
- TDF + 3TC (or FTC) + NVP or
- TDF + 3TC (or FTC) + EFV.

The infant is given NVP or AZT starting as soon as possible after birth (aim for less than 6 hours postpartum) and continued for 4–6 weeks.

Women who are not immunocompromised
Antiretroviral (ARV) prophylaxis is indicated for HIV-positive pregnant women with relatively strong immune systems who do not need ART for their own health. This would reduce the risk of HIV transmission from mother to child. There are two options, both of which should start early in pregnancy, at 14 weeks or as soon as possible thereafter.

The two options provide a significant reduction in MTCT with equal efficacy in this group of women who are not eligible for ART.

Option A: Twice daily AZT for the mother during pregnancy; if the mother has less than 4 weeks of AZT, give single-dose nevirapine during labour, and AZT and lamivudine during labour and for 7 days postpartum. Give the infant prophylaxis with either AZT or NVP for 6 weeks after birth if he or she is not breastfeeding. If the infant is breastfeeding, daily NVP infant prophylaxis should be continued for 1 week after the end of the breastfeeding period.

or

Option B: a three-drug prophylactic regimen for the mother, taken during pregnancy and throughout the breastfeeding period, as well as infant prophylaxis for 6 weeks after birth, whether or not the infant is breastfeeding.

Option B+: all pregnant and breastfeeding women infected with HIV should initiate ART as lifelong treatment.

Breastfeeding
The global availability of ART means that there is enough evidence for the WHO to recommend breastfeeding for mothers with HIV.

Even with ART there is still a small risk of HIV transmission, particularly if there is any interruption to treatment, either in supply or absorption (due to diarrhoea or vomiting). HIV can be transmitted through breast milk at any point during lactation, so the rate of infection in breastfed infants increases with duration of breastfeeding.

In many countries, public health services where there is poor access to clean drinking water and alternatives to breastfeeding have not been able to adequately support and provide safe replacement feeding. HIV-positive mothers have faced the dilemma of whether to give their babies all the benefits of breastfeeding but expose them to the risk of HIV infection, or avoid all breastfeeding and increase the risk of their baby’s death from diarrhoea and malnutrition.

The effectiveness of ART in reducing transmission through breastfeeding has resulted in two major changes in 2012 from previous guidelines:

1 National health authorities should decide whether health services will principally counsel and support HIV-positive mothers to either:
   - breastfeed and receive ARV interventions or
   - avoid all breastfeeding, as the strategy that is most likely to give infants the greatest chance of HIV-free survival.

2 In settings where national authorities recommend that HIV-positive mothers should breastfeed, and provide ARVs to prevent transmission, mothers should exclusively breastfeed their infants for the first 6 months of life, introducing appropriate complementary foods thereafter, and should continue breastfeeding for the first 12 months of life.

Mothers who are known to be HIV infected and who decide to stop breastfeeding at any time should stop gradually over 1 month. Stopping breastfeeding abruptly is not advisable (World Health Organization, 2010).

These new guidelines have great potential to improve the mother’s own health and to reduce the mother-to-child HIV transmission risk to 5% or lower in a breastfeeding population in the absence of any interventions and with continued breastfeeding. With ART the WHO is aiming...
for complete prevention of mother-to-child transmission worldwide by 2015.

Where a decision has been made to continue breastfeeding because the child is already infected, infant feeding options should be discussed for future pregnancies. This should be carried out by a trained and experienced counsellor.

If a child is known to be HIV-infected and is being breastfed, encourage the mother to continue breastfeeding if living in a resource-limited country, as there is usually a high risk of gastroenteritis in such regions.

If the mother is known to be HIV-positive and the child's HIV status is unknown, the mother should be counselled about the benefits of breastfeeding as well as the risk of HIV transmission through breastfeeding. If replacement feeding is acceptable, feasible, affordable, sustainable and safe, avoidance of further breastfeeding is recommended.

Otherwise, exclusive breastfeeding should be practiced if the child is less than 6 months of age, and breastfeeding should be discontinued as soon as these conditions are in place.

Infants born to HIV-positive mothers who have escaped perinatal infection have a lower risk of acquiring HIV if they are not breastfed. However, their risk of death may be increased if they are not breastfed in situations where there is no regular access to nutritionally adequate, safely prepared breast milk substitutes, and there is a high risk of gastroenteritis.

Counselling should be provided by a trained and experienced counsellor. Take advice from local people experienced in counselling so that any advice given is consistent with what the mother will receive from professional counsellors at a later stage.

If the mother decides to use breast milk substitutes, counsel her about their correct use and demonstrate their safe preparation.

Management of the child with a suspected or proven HIV infection

- The aim of treatment should be to maintain the best possible quality of life for the child for as long as possible, without bankrupting the family. This disease affects the whole family, and the child must be treated in the context of the needs of all of the family.
- Currently there are far more questions than evidence-based answers; published data on many management issues in the context of resource-limited countries are not available.
- Much can be achieved with compassionate supportive care, by applying existing guidelines (such as integrated Management of Childhood Illness algorithms) with an awareness of the need for early diagnosis and intervention in the HIV-infected child.
- Diagnosis of infections such as tuberculosis, lower respiratory infections, bacteremia (particularly with non-typhoid salmonellae, staphylococci or streptococci) and opportunistic infections can be difficult, and often relies on empirical trials of therapy.

A low threshold for antibiotic use is appropriate, but may exacerbate diarrhoea and candidiasis, and may only be effective if given IV or IM, in the presence of diarrhoea and malabsorption.

Most infections in HIV-positive children are caused by the same pathogens as in HIV-negative children, although they may be more frequent, more severe and occur repeatedly. There is recent evidence that Staphylococcus aureus may be more invasive in children with HIV.

Clinical staging of HIV infection

In a child with diagnosed or highly suspected HIV infection, a clinical staging system helps to identify 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 as to when to start, stop or substitute ARV therapy in HIV-infected children.

The clinical stages identify a progressive sequence from least to most severe, such that the higher the clinical stage the poorer the prognosis. For classification purposes, once a stage 3 clinical condition has occurred, the child's prognosis will probably remain that of stage 3, and will not improve to that of stage 2, even with resolution of the original condition, or the appearance of a new stage 2 clinical event. ART with good adherence dramatically improves the 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.

TABLE 6.2.D.3 WHO paediatric clinical staging system for use in children under 13 years with confirmed laboratory evidence of HIV infection (HIV antibody where age is > 18 months, DNA or RNA virological testing where age is < 18 months)

| Stage 1 | Asymptomatic | Persistent generalised lymphadenopathy (PGL) |
| Stage 2 | Unexplained persistent hepatosplenomegaly | Fungal nail infections | Lineal gingival erythema (LGE) | Extensive wart virus infection | Extensive molluscum infection (> 5% of body area) | Recurrent oral ulcerations (two or more episodes in 6 months) | Parotid enlargement | Herpes zoster | Recurrent or chronic upper respiratory tract infections (otitis media, otorhhea, sinusitis, two or more episodes in any 6-month period) |
| Stage 3 | Unexplained moderate malnutrition not responding to standard therapy | Unexplained persistent diarrhoea (for > 14 days) | Unexplained persistent fever (intermittent or constant, for > 1 month) | Oral candidiasis (outside the neonatal period) | Oral hairy leukoplaikia | Pulmonary tuberculosis | Severe recurrent presumed bacterial pneumonia (two or more episodes in 6 months) | Acute necrotising ulcerative gingivitis or periodontitis | Lymphoid interstitial pneumonia (LIP) | Unexplained anaemia (< 8 gram/dL) | Neutropenia (< 500/mm³) | Thrombocytopenia (< 30 000/mm³) | for > 1 month |

(continued)
Antiretroviral therapy (ART)

Antiretroviral (ARV) drugs are becoming more widely available, and have revolutionised the care of children with HIV/AIDS. ARV drugs are not a cure for HIV, but they have dramatically reduced mortality and morbidity, and improved the quality and length of life. The WHO recommends that in resource-limited settings, HIV-infected adults and children should start ARV therapy based upon clinical or immunological criteria, and using simplified standardised treatment guidelines.

Resistance to single or dual agents is quick to emerge, so **single-drug regimens are contraindicated**. Indeed at least three drugs are the **recommended minimum standard for all settings**. Although new ARV drugs are coming on to the market, frequently these are not available for use in children, due to lack of suitable formulations or dosage data, or their high costs.

As children with HIV are often part of a household that includes an adult with HIV, ideally access to treatment and ARV drugs needs to be ensured for other family members, and where possible similar drug regimens should be used. Fixed-dose combinations are increasingly available, and are preferred as they promote and support treatment adherence, as well as reducing the cost of treatment. Existing tablets often cannot be divided into lower dosages for children (under 10kg), so syrups or solutions and suspensions are needed.

The underlying principles of ART and the choice of first-line ART in children are largely the same as for adults. However, it is also important to consider the following:

- availability of a suitable formulation that can be taken in appropriate doses
- simplicity of the dosage schedule
- taste/palatability and thus compliance in young children
- the ART regimen that the parent(s) or carers are or will be taking.

Suitable formulations for children are not available for some ARVs (particularly the protease inhibitor class of drugs).

**Antiretroviral drugs**

Antiretroviral drugs fall into three main classes, namely nucleoside analogue reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (Pis) (see Table 6.2.D.4).

**Triple therapy is the standard of care.**

The WHO currently recommends that first-line regimens should be based upon two nucleoside analogue reverse transcriptase inhibitors (NRTIs) plus one non-nucleoside drug (NNRTI). The use of triple NRTI as first-line therapy is currently considered a secondary alternative because of recent research findings in adults. Protease inhibitors are usually recommended as part of second-line regimens in most resource-limited settings.

Efavirenz (EFV) is the NNRTI of choice in children who are on rifampicin, if treatment needs to start before antituberculous therapy is completed.

**For drug dosages and regimens, see Appendix 4.**

**Calculation of drug dosages**

Drug doses are given per kg for some drugs and per m² surface area of the child for others. A table giving the equivalent weights of various surface area values is provided in Section 9 of this textbook, to aid dosage calculation. In general, children metabolise PI and NNRTI drugs faster than adults, and require higher than adult equivalent doses to achieve appropriate drug levels. Drug doses have to be increased as the child grows, otherwise there is a risk of under-dosage and development of resistance.

**Formulations**

Liquid formulations may not be readily available, are more expensive, and may have a reduced shelf-life. As the child gets older, the amount of syrup that needs to be taken becomes quite considerable. Therefore, in patients over 10kg in weight, it is preferable to give parts of scored tablets or combination preparations (see Appendix 4).

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**Table 6.2.D.4**

<table>
<thead>
<tr>
<th>Stage 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Unexplained severe wasting or severe malnutrition not responding to standard therapy</td>
</tr>
<tr>
<td>● Pneumocystis pneumonia</td>
</tr>
<tr>
<td>● Recurrent severe presumed bacterial infections (two or more episodes within 1 year, e.g. empyema, pyomyositis, bone or joint infection, or meningitis, but excluding pneumonia)</td>
</tr>
<tr>
<td>● Chronic oralabial or cutaneous herpes simplex infection (for &gt; 1 month)</td>
</tr>
<tr>
<td>● Disseminated or extrapulmonary tuberculosis</td>
</tr>
<tr>
<td>● Kaposi’s sarcoma</td>
</tr>
<tr>
<td>● Oesophageal candidiasis</td>
</tr>
<tr>
<td>● Symptomatic HIV seropositive infant &lt; 18 months of age with two or more of the following: oral thrush, with or without severe pneumonia, or with or without failure to thrive, with or without severe sepsis</td>
</tr>
<tr>
<td>● CMV retinitis</td>
</tr>
<tr>
<td>● CNS toxoplasmosis</td>
</tr>
<tr>
<td>● Any disseminated endemic mycosis, including cryptococcal meningitis (e.g. extrapulmonary cryptococcosis, histoplasmosis, coccidiomycosis, penicilliosis)</td>
</tr>
<tr>
<td>● Cryptosporidiosis or isosporiasis (with diarrhoea for &gt; 1 month)</td>
</tr>
<tr>
<td>● Cytomegalovirus infection (onset at age &gt; 1 month in an organ other than liver, spleen or lymph nodes)</td>
</tr>
<tr>
<td>● Disseminated mycobacterial disease other than tuberculosis</td>
</tr>
<tr>
<td>● Candida of trachea, bronchi or lungs</td>
</tr>
<tr>
<td>● Acquired HIV-related recto-vesical fistula</td>
</tr>
<tr>
<td>● Cerebral or B-cell non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>● Progressive multifocal leukoencephalopathy (PML)</td>
</tr>
<tr>
<td>● HIV encephalopathy</td>
</tr>
<tr>
<td>● HIV-related cardiomyopathy</td>
</tr>
<tr>
<td>● HIV-related nephropathy</td>
</tr>
</tbody>
</table>

1 TB may occur at any CD4 count, and CD4% should be considered where available.

2 Presumptive diagnosis of stage 4 disease in seropositive children under 18 months of age requires confirmation with HIV virological tests, or with HIV antibody test if over 18 months of age.
First-line ART for children under 3 years of age

An LPV/r-based regimen should be used as first-line ART for all children infected with HIV who are under 3 years (36 months) of age, regardless of NNRTI exposure. If LPV/r is not feasible, treatment should be initiated with an NVP-based regimen.

Where viral load monitoring is available, consideration can be given to substituting LPV/r with an NNRTI after virological suppression is sustained.

For infants and children under 3 years of age who are infected with HIV, ABC + 3TC + AZT is recommended as an option for children who develop TB while on an ART regimen containing NVP or LPV/r. Once TB therapy has been completed, this regimen should be stopped and the initial regimen should be restarted.

For infants and children under 3 years of age who are infected with HIV, the NRTI backbone for an ART regimen should be ABC + 3TC or AZT + 3TC (this is a strong recommendation but with low-quality evidence).

**First-line ART for children aged 3 years or older (including adolescents)**

For children aged 3 years or older (including adolescents) who are infected with HIV, EFV is the preferred NNRTI for first-line treatment, and NVP is the alternative.

For children aged 3–9 years (and adolescents weighing less than 35 kg) who are infected with HIV, the NRTI backbone for an ART regimen should be one of the following, in order of preference:
- ABC + 3TC
- AZT + TDF + 3TC (or FTC).

For adolescents who are infected with HIV (10–19 years old, weighing 35 kg or more), the NRTI backbone for an ART regimen should align with that of adults and be one of the following, in order of preference:
- TDF + 3TC (or FTC)
- AZT + 3TC
- ABC + 3TC.

**When to start ART**

About 20% of HIV-infected infants in developing countries progress to AIDS or death by 12 months of age (with a substantial contribution from PCP infections in infants under 6 months of age who are not receiving co-trimoxazole treatment).

ART should be initiated in all children infected with HIV below 5 years of age, regardless of WHO clinical stage or CD4 count, that is:
- Infants diagnosed in the first year of life.
- Children infected with HIV when aged 1–4 years.

ART should be initiated in all children infected with HIV aged 5 years or older with a CD4 cell count of less than 500 cells/mm³, regardless of WHO clinical stage, that is:
- CD4 count less than 350 cells/mm³.
- CD4 count between 350 and 500 cells/mm³.

ART should be initiated in all children infected with HIV with severe or advanced symptomatic disease (WHO clinical stage 3 or 4) regardless of age and CD4 count.

ART should be initiated in any child younger than 18 months who has been given a presumptive clinical diagnosis of HIV infection.

**Infants and children with specific conditions**

- For children or adolescents with severe anaemia (< 7.5 g/dL) or severe neutropenia (< 0.5/mm³), avoid AZT.
- For adolescents over 12 years of age with hepatitis B, the preferred regimen is tenofovir (TDF) + emtricitabine (FTC) or 3TC + NNRTI.

**Side effects of antiretroviral therapy and monitoring**

The response to antiretroviral treatment and the side effects of treatment both need to be monitored. Where CD4 cell count or viral load monitoring is available, this should be done every 3 to 6 months and can provide information on the success or failure of the response to treatment, and therefore guide changes to treatment. Where this is not possible, clinical parameters, including clinical staging events, need to be used (see Table 6.1.D.3).

**Monitoring the response after ARV initiation**

- After ARV initiation or a change in ARVs see the child at 2 and 4 weeks after the start or change.
- All children should be seen if there are any problems that concern the caregiver, or inter-current illness.

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**TABLE 6.2.D.4 Classes of antiretroviral drugs recommended for use in children in resource-limited settings**

<table>
<thead>
<tr>
<th>Nucleoside analogue reverse transcriptase inhibitors (NRTIs)</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine (ZDV/AZT)</td>
<td>180–240 mg/m² twice daily</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>4 mg/kg twice daily up to a maximum of 150 mg twice daily</td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>1 mg/kg twice daily up to 30 mg twice daily</td>
</tr>
<tr>
<td>Didanosine (ddI)</td>
<td>90–120 mg/m²/dose twice daily</td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td>8 mg/kg/dose given twice daily up to 300 mg twice daily</td>
</tr>
</tbody>
</table>

**Non-nucleoside reverse transcriptase inhibitors (NNRTIs)**

| Nevirapine (NVP) | 160–200 mg/m² up to a maximum of 200 mg twice daily |
| Efavirenz (EFV) | 15 mg/kg/day up to 600 mg once daily |
| Etravirine (ETV) | 200 mg twice daily for adolescents |

**Protease inhibitors (PIs)**

| Lopinavir/ritonavir (LPV/r) | 230–350 mg/m² twice daily |
| Darunavir (DRV) | 10–20 mg/kg twice daily |
| Atazanavir (ATV) | 7 mg/kg once daily |
| Ritonavir (RTV) | Given as a ‘booster’ with another PI |

**Integrase inhibitors**

| Raltegravir (RAL) | 400 mg twice daily for adolescents |
Long-term follow-up

- A clinician should see the child at least every 3 months.
- A non-clinician (ideally the provider of ARV medication, such as a pharmacist, who would assess adherence and provide adherence counselling) should see the child monthly.
- The child should be seen more frequently, preferably by a clinician, if clinically unstable.

Monitoring the response (see Appendix 1)

At entry into care and at initiation of ART, and then at regular intervals and as required by symptoms, monitor the following:

- weight and height (monthly)
- neurodevelopment (monthly)
- adherence (monthly)
- CD4 (%) if available (then every 3 to 6 months)
- viral load if available (every 3 to 6 months)
- baseline haemoglobin or haematocrit (if on ZDV/AZT), full chemistry (renal function, liver enzymes, especially ALT for liver toxicity) and lipids (if available)
- symptom-related determination: haemoglobin or haematocrit or full blood count, ALT.

General long-term side effects of antiretroviral therapy include lipodystrophy. The specific side effects of individual antiretroviral drugs are summarised in Appendix 5.

When to change treatment

Drugs need to be substituted for others when there is:

- treatment-limiting toxicity, such as:
  - Stevens–Johnson syndrome (SJS)
  - severe liver toxicity
  - severe haematological findings
- drug interaction (e.g. tuberculosis treatment with rifampin interfering with NVP or PI)
- potential lack of adherence by the patient if they cannot tolerate the regimen.

<table>
<thead>
<tr>
<th>Clinical criteria</th>
<th>CD4 criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of or decline in growth among children with an initial growth response to ARV</td>
<td>Return of CD4% if aged &lt; 6 years (% or count if aged ≥ 6 years) to pre-therapy baseline or below, without other cause</td>
</tr>
<tr>
<td>Loss of neurodevelopmental milestones or onset of encephalopathy</td>
<td>≥ 50% fall from peak CD4% if aged &lt; 6 years (% or count if aged ≥ 6 years), without other aetiology</td>
</tr>
<tr>
<td>New or recurrent WHO clinical Stage 4 conditions</td>
<td></td>
</tr>
</tbody>
</table>

First-line regimen treatment failure; when to switch regimens

1. A switch to a second-line regimen is recommended when:
   - clinical failure is recognised and/or
   - immunological failure is recognised and/or
   - virological failure is recognised.

2. Clinical failure is defined as the appearance or re-appearance of WHO clinical stage 3 or stage 4 events after at least 24 weeks on ART in a treatment-adherent child. It is important to exclude TB as a cause of clinical failure, especially when there is poor growth.

3. Immunological failure is defined as developing or returning to the following age-related immunological thresholds after at least 24 weeks on ART, in a treatment-adherent child:
   - CD4 count of < 200 cells/mm$^2$ or CD4+% < 10% for a child between 2 and 4 years of age
   - CD4 count of < 100 cells/mm$^2$ for a child aged 5 years or older.

4. Virological failure is defined as a persistent viral load above 5000 RNA copies/mL, after at least 24 weeks on ART, in a treatment-adherent child.

Principles

Virological failure is due to resistance mutations acquired either at the time of infection or as a result of poor adherence. Even a resistance test before starting treatment (not widely available) will not always show archived mutations (not in the majority of the virus tested). Acquired resistance is more likely if there is initial improvement (ideally documented virologically). A history of missed doses is usually not given readily, but it is essential that support to ensure 100% adherence is put in place before second-line treatment is started.

In the absence of routine CD4 or viral load assays, judgements should be made about treatment failure based on:

- clinical progression
- CD4 decline as defined in Table 6.2.D.8.

Generally, patients should have received 6 months or more of ARV therapy, and adherence problems must be ruled out where possible before considering treatment failure and switching ARV regimens.

If an apparent deterioration is due to the immune reconstitution inflammatory syndrome (IRIS), this is not a reason for switching therapy. IRIS usually starts within weeks or the first few months after starting ART in children who have very low CD4 counts (< 15%). The most common initiator is TB which has been latent, but the symptoms of other opportunistic infections can develop as the immune recovery enables a response. Treatment is of the infection, and ART should be continued.

Immune reconstitution inflammatory syndrome (IRIS)

It is important to differentiate IRIS clinically from treatment failure, because the symptoms may be similar. IRIS can be confused with several other clinical events that are also observed in children with advanced HIV disease, such as opportunistic infections, ARV-related toxicity, or HIV disease clinical progression.

What is IRIS?

IRIS is an exaggerated immune response to antigens or organisms. The related organisms could be mycobacteria (e.g. *Mycobacterium tuberculosis*, non-tuberculosis mycobacteria), viruses (e.g. herpes zoster, herpes simplex) or fungi (e.g. *Cryptococcus neoformans*).
Who is at risk of developing IRIS?
It usually occurs in a child with low baseline CD4 or WHO clinical stage 3 or 4 before initiation of ART. The incidence rate of IRIS could be as high as 15–25%.

When does IRIS develop?
It usually occurs during the first 6 months after initiation of ART, although it commonly manifests during the first month. During the initial period of ART, antiretroviral drugs cause a rapid decline in HIV viral load and a rapid rise in CD4, so a brisk immune response to antigen is developed.

What are the common manifestations of IRIS?
There are two types of IRIS:
- **Worsening type**: clinical worsening of a previously treated opportunistic infection. For example:
  - worsening of respiratory symptoms and/or chest X-ray finding in a child with previously treated pulmonary tuberculosis
  - severe headache in a child with previously treated cryptococcal meningitis.
- **Unmasking type**: unmasking of a previously subclinical infection with exaggerated inflammatory response. For example:
  - suppurative lymphadenitis from *Mycobacterium* infection
  - development of an abscess at the BCG vaccination site.

How should IRIS be managed?
- ARVs should be continued.
- For the ‘unmasking type’, the appropriate anti-infective agents are needed.
- In most cases, the symptoms of IRIS resolve after a few weeks. However, some reactions can be severe or life-threatening, requiring a short course of steroid treatment (e.g. IRIS from pulmonary tuberculosis with acute respiratory distress syndrome (ARDS), IRIS from *M. avium* complex infection with high-grade fever and severe abdominal pain, IRIS from cryptococcal meningitis with a severe increase in intracranial pressure).

Second-line treatment regimens in the event of treatment failure
After failure of a first-line NNRTI-based regimen, a boosted PI plus two NRTIs are recommended for second-line ART. LPV/r is the preferred boosted PI.

After failure of a first-line LPV/r-based regimen, children younger than 3 years should remain on their first-line regimen, and measures to improve adherence should be undertaken.

After failure of a first-line LPV/r-based regimen, children aged 3 years or older should be switched to a second-line regimen containing an NNRTI plus two NRTIs. EFV is the preferred NNRTI.

After failure of a first-line regimen of ABC or TDF + 3TC (or FTC), the preferred NRTI backbone option for second-line ART is AZT + 3TC.

After failure of a first-line regimen containing AZT or d4T + 3TC (or FTC), the preferred NRTI backbone option for second-line ART is ABC or TDF + 3TC (or FTC).

Third-line ART
Third-line regimens should include new drugs with minimal risk of cross-resistance to previously used regimens, such as integrase inhibitors and second-generation NNRTIs and PIs.

Patients on a failing second-line regimen with no new ARV options should continue with a tolerated regimen.

Strategies that balance the benefits and risks for children need to be explored when second-line treatment fails.
- For older children and adolescents who have more therapeutic options available to them, constructing third-line ARV regimens with novel drugs used to treat adults, such as ETV, DRV and RAL, may be possible.
- Children on a second-line regimen that is failing with no new ARV drug options should continue with a tolerated regimen. If ART is stopped, opportunistic infections still need to be prevented, symptoms relieved and pain managed.

Nutritional care and failure to thrive (see Appendix 3)
Nutrition is a long-term concern in all HIV-infected children. Stunting frequently develops within the first 12 months, although most children maintain normal weight-for-height ratios. Close monitoring of growth, and early protein/calorie, vitamin A and other micronutrient supplementation need to be evaluated.

- Regular vitamin A as per WHO guidelines.
- Supplementary feeding if possible (aim for 150 kcal/kg/day).
- Exclude or treat Candida.
- Exclude or treat enteric infection.
- Consider zinc deficiency (see Section 5.10.A).
- Consider fever.
- Consider depression.
- Consider pain.

Clinical management
1. HIV-infected children should be assessed routinely for nutritional status, including weight and height, at scheduled visits, particularly after the initiation of ART.
2. HIV-infected children on or off ART who are symptomatic, who have conditions requiring increased energy (e.g. TB, chronic lung disease, chronic oral infections, malignancies) or who have weight loss or evidence of poor growth, should be provided with 25–30% additional energy.
3. HIV-infected children who are severely malnourished should be managed as per the guidelines for uninfected children and provided with 50–100% additional energy.
4. HIV-infected children should receive one recommended daily allowance of micronutrients daily. If this cannot be ensured through the diet, or there is evidence of deficiency, supplementation should be given.
5. HIV-infected infants and children should receive high-dose vitamin A supplementation every 6 months between 6 and 59 months of age, as per the guidelines for uninfected children (see Section 5.10.A).
6. HIV-infected children who have diarrhoea should receive zinc supplementation as part of management, as per the guidelines for uninfected children.
7 For infants and young children who are known to be HIV infected, mothers are strongly encouraged to exclusively breastfeed for 6 months and to continue breastfeeding as per recommendations for the general population (i.e. up to 2 years of age and beyond).

Respiratory disorders in children with HIV infection

Symptoms include cough, shortness of breath, fever, sweat and cyanosis.

The aetiology of acute respiratory infections is similar to that of community-acquired infections in immunocompetent children (Mycobacterium tuberculosis, Pneumococcus, Haemophilus influenzae, Staphylococcus aureus, Mycoplasma pneumonia) (see Section 5.3.A and Section 6.1.N). However, children with HIV may require more prolonged courses of treatment.

Studies on the aetiology of pneumonia among HIV-infected children in resource-limited countries have identified Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae and Klebsiella species as the major bacterial pathogens in HIV-infected children. HIV-negative children are affected by the same pathogens, although at lower rates. The post-mortem studies showed similar results, except that H. influenzae was slightly less prominent. M. tuberculosis was prevalent regardless of HIV status, reflecting its significance in resource-limited countries. From the limited data available, RSV and parainfluenza appear to be the most prevalent viral causes of pneumonia.

In cases of failed treatment, consider using a second-line antibiotic.

Treatment of recurrent infections is the same, regardless of the number of recurrences.

Specific HIV-related causes of infection and illness

Pneumocystis jiroveci (formerly carinii) pneumonia (PCP)

• PCP should be suspected and anti-pneumocystis therapy considered in any HIV-positive infant with severe pneumonia.
• Severe generalised pneumonia usually includes ventilation/perfusion mismatch and severe hypoxaemia.
• High fever is uncommon compared with bacterial pneumonia.

PCP is most likely to develop in a child whose HIV infection occurred in the previous 12 months (the peak time is 4–6 months), or over 12 months if they have a low CD4 count and are not on co-trimoxazole prophylaxis. There is an absent or low-grade fever, non-productive cough and difficulty breathing. Signs include severe respiratory distress (tachypnoea, chest indrawing), which is disproportionate to findings on auscultation (usually normal breath sounds or only a few crackles). If an oxygen saturation monitor is available, check at rest and, if normal, again after exercise. The latter may show hypoxia or, if there is a severe infection, cyanosis.

There may be a history of a poor response to 48 hours of first-line antibiotics, and elevated levels of lactate dehydrogenase.

PCP is often the first clinical indicator of HIV infection, and is a WHO clinical stage 4 criterion.

Clinical and radiological signs are not diagnostic. However, a clear chest or diffuse chest signs on auscultation are typical with PCP infection, as is the presence of diffuse infiltrates and areas of hyperinflation rather than focal signs on a chest X ray.

Induced sputum and nasopharyngeal aspiration are useful for obtaining sputum for examination. Nasopharyngeal aspirate has a low sensitivity with conventional staining techniques, and requires PCR. Induced sputum techniques greatly increase the diagnostic yield. Beware the risk of infection being transmitted to operators, especially of multiple drug-resistant tuberculosis, for example.

Bronchoalveolar lavage may provide a diagnosis if adequate resources are available.

Treatment of PCP

Severe disease (severe respiratory distress, severe hypoxia): treat with co-trimoxazole 60–90 mg/kg IV 12-hourly for a minimum of 7 days, followed by oral drugs in the same doses for another 2 weeks (IV if there is severe nausea). In addition, give high-dose dexamethasone for the first 5 days (150 micrograms/kg/dose 6-hourly for 4 days) or prednisolone 0.5 mg/kg 12-hourly for 5 days, then 0.25 mg/kg 12-hourly for 5 days, then 0.25 mg/kg daily for 5 days. The response usually occurs after more than 5–7 days of appropriate high-dose therapy.

Less severe disease: treat with oral co-trimoxazole 30 mg/kg 6-hourly for 21 days (trimethoprim (TMP) 5 mg/kg; sulfamethoxazole (SMX) 25 mg/kg).

If the child has a severe drug reaction, change to penicillin (4 mg/kg once a day by IV infusion) for 3 weeks, or trimethoprim 5 mg/kg/dose orally 6-hourly and dapsone 100 mg/kg once a day for 21 days.

Continue co-trimoxazole prophylaxis (see below) on recovery, and ensure that ART is being given.

Co-trimoxazole prophylaxis

Co-trimoxazole prophylaxis has been shown to be very effective in HIV-infected infants and children in reducing mortality and the likelihood of PCP as a cause of severe pneumonia. PCP is now unusual in countries where prophylaxis is routine.

Co-trimoxazole also protects against common bacterial infections, toxoplasmosis and malaria.

Who should be given co-trimoxazole?

• All HIV-exposed children (children born to HIV-infected mothers) from 4–6 weeks of age, whether or not they are part of a prevention of mother-to-child transmission (PMTCT) programme.
• Any child under 5 years old identified as HIV-infected, regardless of CD4 count.
• Any child over 5 years old with a CD4 count of less than 25%.
• Any child with a history of PCP.

See Appendix 2 for management.

For how long should co-trimoxazole be given?

• HIV-exposed children: for the first year, or until HIV infection has been definitively ruled out and the mother is no longer breastfeeding.
What doses of co-trimoxazole should be used?

- **Recommended dosages of 6–8 mg/kg TMP once daily should be used.**
  - For children under 6 months of age, give 2.5 mL of suspension (40/200 mg in 5 mL) or 1 paediatric tablet (or ½ adult tablet, 20 mg TMP/100 mg SMX; tablets can be crushed).
  - For children aged 6 months to 5 years, give 5 mL of suspension or 2 paediatric tablets (or ½ adult tablet).
  - For children aged 6–14 years, give 10 mL of suspension or 1 adult tablet.
  - For children over 14 years, give 2 adult tablets.
- **Use weight-band dosages rather than body-surface-area doses.**
- **If the child is allergic to co-trimoxazole, dapsone is the best alternative.** Give dapsone after 4 weeks of age in an oral dose of 2 mg/kg/24 hours once daily.
- **If the patient is G6PD-positive, consider giving pentamidine or atovaquone.**

Under what circumstances should co-trimoxazole be discontinued?

- **If severe cutaneous reactions such as Stevens–Johnson syndrome occur with co-trimoxazole or other sulpha drugs, or if there is renal and/or hepatic insufficiency or severe haematological toxicity (severe anaemia or pancytopenia).** It is contraindicated in children with glucose-6-phosphate dehydrogenase (G6PD) deficiency.
- **In an HIV-exposed child, only after HIV infection has confidently been excluded:**
  - For a non-breastfeeding child under 18 months of age, this is by negative DNA or RNA virological HIV testing.
  - For a breastfed HIV-exposed child under 18 months of age, negative virological testing is only reliable if performed 6 weeks after cessation of breastfeeding.
  - For a breastfed HIV-exposed child over 18 months of age, negative HIV antibody testing 6 weeks after stopping breastfeeding.
- **In an HIV-infected child:**
  - If the child is on ARV therapy, co-trimoxazole can be continued to provide benefit even after the child has clinically improved.
  - If ARV therapy is not available, co-trimoxazole should not be discontinued.

What follow-up is required?

Co-trimoxazole prophylaxis should be a routine part of the care of HIV-infected children, and must be assessed for tolerance and adherence at all regular clinic visits or follow-up visits by healthcare workers and/or other members of the multidisciplinary care team. It is suggested that initial clinic follow-up in children takes place monthly, and then every 3 months if co-trimoxazole is well tolerated.

**Lymphocytic interstitial pneumonitis (LIP)**

LIP is a non-infectious pulmonary disorder caused by white cell infiltration into alveoli. It is most common in children over 2 years old, and is a clinical stage criterion which is an indication for starting ART.

LIP is common in children (it occurs in at least 40% of children with perinatal HIV), but rare in adults (it occurs in about 3% of adults with HIV). Various studies in Africa have documented a 30–40% prevalence of LIP in HIV-infected children, and up to 60% prevalence in those with chronic lung disease. LIP is often mistaken for pulmonary TB (miliary) because of the chronic cough and the miliary-like pattern on chest X-ray.

**Pathogenesis:** Possible explanations for LIP include a co-infection of the lungs by HIV and Epstein–Barr virus (EBV), leading to immune stimulation with lymphoid infiltration and chronic inflammation.

The child is often asymptomatic in the early stages, but may later have a mild persistent cough, with or without difficulty in breathing, bilateral parotid swelling, persistent generalised lymphadenopathy, poor growth, hepatomegaly and other signs of heart failure (tender hepatomegaly, bilateral pitting pedal oedema, loud second heart sound and finger clubbing). Chest auscultation may be normal, or there may be widespread crackles. It may produce severe ventilatory perfusion mismatch with hypoxaemia, but may be asymptomatic.

There is an increased risk of lower respiratory tract infection, including bronchiectasis. It is also associated with parotid, adenoid and tonsillar enlargement (and may produce sleep-related upper airway obstruction; see Section 5.1.D). LIP may be mistaken for miliary TB, but the child is systematically too well.

Suspect LIP if the chest X-ray shows a bilateral reticulonodular interstitial pattern that is prominent in the lower lobes, nodules less than 5 mm in diameter, a single patchy alveolar opacity, hyperinflation or isolated bullae. It must be distinguished from pulmonary tuberculosis and bilateral infiltrates.

**FIGURE 6.2.D.4** Chest X ray showing lymphocytic interstitial pneumonia (LIP): typical is hilar lymphadenopathy and lacelike infiltrates.
hilar adenopathy (see Figure 6.2.D.4). Chest X-ray diffuse infiltrations and hilar lymphadenopathy persisting for more than 2 months despite antibiotic treatment are also a clue. X-ray appearances are often more severe than the clinical features.

**FIGURE 6.2.D.5** Pneumocystis jiroveci pneumonia (PCP): typical is a ground glass appearance.

**Treatment of LIP**
- Give oxygen therapy during episodes of hypoxia.
- Give a trial of antibiotic treatment for bacterial pneumonia before starting treatment with prednisolone.
- Start treatment with steroids only if there are chest X-ray findings suggesting lymphocytic interstitial pneumonitis, plus any of the following signs:
  - fast or difficult breathing
  - cyanosis
  - pulse oximetry reading of oxygen saturation < 90% (normal value is > 93%).
- Bronchodilators (e.g. salbutamol) are of benefit where wheezing is a problem. For moderate symptoms give oral prednisone, 1–2 mg/kg daily for 3 days, and for more severe symptoms for up to 4 weeks. Then slowly decrease the dose over 2–4 weeks depending on the treatment response. If there is no response by 4 months, slowly taper the dose to stop over a further 2 months.
- Only start steroid treatment if it is possible to complete the full treatment course (which may take several months depending on the resolution of signs of hypoxia), as partial treatment is not effective and could be harmful. Beware of reactivation of TB.

**Tuberculosis (see also Section 6.1.N)**

In a child with suspected or proven HIV infection, it is important always to consider the co-diagnosis of tuberculosis, a diagnosis which is often difficult. Early in HIV infection, when immunity is not impaired, the signs of tuberculosis are similar to those in a child without HIV infection. Pulmonary tuberculosis is still the commonest form of tuberculosis, even in HIV-infected children. As HIV infection progresses and immunity declines, dissemination of tuberculosis becomes more common. Tuberculous meningitis, miliary tuberculosis and widespread tuberculous lymphadenopathy occur.

All children with HIV should be screened for TB.

Avoid, if practicable, children with HIV being in contact with a TB-infected person.

**Isoniazid preventive therapy (IPT)**
1. All HIV-infected infants and children who are exposed to TB through household contacts, but show no evidence of active disease, should begin isoniazid preventive therapy (IPT).
2. Children who have either poor weight gain, fever, cough or a contact with TB should be evaluated for active TB. If TB is excluded, give IPT.
3. Children living with HIV (over 12 months of age, and including those previously treated for TB), who are not likely to have active TB, and who are not known to be exposed to TB, should receive 6 months of IPT as part of a comprehensive package of HIV care.
4. Infants living with HIV, who have been exposed to TB but are evaluated as not having active TB, should receive IPT as part of a comprehensive package of HIV care.
5. The recommended dose of isoniazid (INH) for preventive therapy in HIV co-infection is 10 mg/kg daily for 6 months (maximum 300 mg/day).
6. See the child monthly and give a 1-month supply of isoniazid at each visit.

**Investigations**

A tuberculin skin test (TST, Mantoux) is unreliable in HIV and should not be used. Since a definitive diagnosis of TB in children is difficult, there could be clinical features that are very suggestive of TB, leading to a high index of suspicion. In such cases a negative TST should not prevent you from starting anti-TB treatment. Furthermore, several people develop TB infection when they come into contact with the TB pathogens, but they do not go on to develop signs and symptoms of TB disease, because their immune systems control the infection. When the immune systems break down, such individuals develop signs and symptoms suggestive of TB disease. A TST can be positive in either state, and without signs and symptoms would be suggestive of TB infection and not TB disease.

**Chest X-ray:** this may be normal, or it may show non-specific infiltrates, hilar or paratracheal lymphadenopathy, persistent opacities after an antibiotic trial, or a miliary pattern.

**Microscopy** (alcohol and acid-fast bacilli, AAFB), Ziehl-Neelsen (ZN) stain and culture: this is the most important investigation. Sputum which may need to be induced by saline nebuliser (in an isolation room with staff wearing a fine-particle (FFP3) mask), and gastric aspirate (if the child is coughing, take this in the early morning before they have had anything to eat or drink). Collect at least three specimens.

**Treatment of infants and children diagnosed with TB and HIV**

Treat TB in HIV-infected children with the same anti-TB drug regimen as for non-HIV-infected children with TB.

**Thiacetazone is associated with a high risk of severe, and sometimes fatal, skin reactions in HIV-infected children, and must not be given.** These reactions can start with itching, but progress to severe reactions.

**Recommended ART regimens for children who need TB treatment**

Recommended regimens for children and adolescents initiating ART while on TB treatment:

- **Younger than 3 years**

Two NRTIs + NVP, ensuring that the dose is 200 mg/m² or
Triple NRTI (AZT + 3TC + ABC).

3 years or older
Two NRTIs + EFV
or
Triple NRTI (AZT + 3TC + ABC).

Recommended regimen for children and infants
initiating TB treatment while receiving ART
Child on standard NNRTI-based regimen (two NRTIs + EFV or NVP)

Younger than 3 years
Continue NVP, ensuring that the dose is 200 mg/m²
or
Triple NRTI (AZT + 3TC + ABC).

3 years or older
If the child is receiving EFV, continue the same regimen.
If the child is receiving NVP, substitute with EFV or
Triple NRTI (AZT + 3TC + ABC).

- TB should be treated with standard regimes, the emphasis being on achieving high adherence rates. The development of multi-drug-resistant TB is a very real threat if compliance is poor. Directly observed therapy (DOT) may be the best approach.
- Any child with active TB disease and HIV infection should begin TB treatment immediately, and start ART as soon as tolerated in the first 8 weeks of TB therapy, irrespective of CD4 count and clinical stage.
- For all HIV-infected children, anti-TB therapy should be started immediately upon the diagnosis of TB, and ART should continue.

**Bronchiectasis**

Suspect bronchiectasis if there is a persistent cough productive of copious sputum (in vomit in young children) or haemoptysis associated with fever, anorexia and failure to thrive. There may be clubbing and localized coarse crackles on auscultation. Obtain a chest X-ray and sputum for Gram stain and culture as well as AFB; differential diagnoses include TB and LIP. Treatment consists of physiotherapy with postural drainage, bronchodilators and antibiotics. Intravenous amoxicillin (50 mg/kg 6-hourly) and gentamicin (7.5 mg/kg daily) may be required for 2 weeks.

**Cytomegalovirus (CMV)**

CMV can present with pneumonia with fever, dry cough, respiratory distress and hypoxia. CMV also causes oesophagitis and gastroenteritis presenting with nausea, difficulty swallowing, diarrhoea and vomiting. CMV retinitis is often asymptomatic or may cause blurred vision, strabismus and ultimately blindness. The fundi show white perivascular infiltrates and haemorrhages, reduced acuity and field defects.

A chest X-ray may show diffuse interstitial infiltrates. Oesophageal endoscopy may show linear, localized or punctate ulcers. Biopsies show typical inclusion cells.

Treatment is with ganciclovir 6 mg/kg 12-hourly for 14 days.

**Other lung infections**

Other opportunistic lung infections that may occur include Pseudomonas aeruginosa, Chlamydia, Mycoplasma, Cryptococcus neoformans, Aspergillus, cytomegalovirus, Histoplasma, Coccidioides, Legionella and Nocardia.

**Gastrointestinal disorders**

**Oral and oesophageal problems**

**Oral candidiasis**

This is the most common form of fungal infection and the most common orofacial manifestation encountered in HIV-infected children. It progresses to involve the oesophagus in 20% of cases, and denotes significantly impaired T-cell function.

It presents as white plaques on mucosa that are difficult to remove, loss of taste, pain on swallowing, reluctance to eat, increased salivation and crying during feeds.

**Treatment for oral candida**

- Nystatin 100 000 IU/mL oral suspension, 1–2 mL four to six times a day for 7 days or
- Local gentian violet 0.5% aqueous solution twice daily for 7 days (dissolve one teaspoonful (5 mL) of crystals in 1 litre of water, filter off the residue, and use within 7 days) or
- Clotrimazole 1%, miconazole 2% gel, or amphotericin B suspension/lozenges three times daily or
- Fluconazole 3–6 mg/kg on the first day, then 3 mg/kg (maximum 100 mg) daily for 1–2 weeks. If there is rare resistance to fluconazole, give ketoconazole oral tablets, 3.3–6.6 mg daily.

**Oesophageal candidiasis**

Oesophageal candidiasis is a stage 4 clinical feature indicating profound immune impairment (advanced HIV disease). The only clinical symptom may be reluctance to feed. It presents as difficulty or pain while vomiting or swallowing, reluctance to take food, excessive salivation, or crying during feeding. The condition may occur with or without evidence of oral candida. If oral candida is not found, give a trial of treatment with fluconazole (3–6 mg/kg once a day). Exclude other causes of painful swallowing (e.g. cytomegalovirus, herpes simplex, lymphoma and, rarely, Kaposi’s sarcoma), if necessary by referral to a larger hospital where appropriate testing is possible.

**Treatment for oesophageal candidiasis**

- Give oral fluconazole, 3–6 mg/kg once a day for 7 days, except if the child has active liver disease.
- Give amphotericin B, 0.5–1 mg/kg/dose once a day by IV infusion for 10–14 days to children with liver disease and in cases where there is a lack of response to oral therapy, inability to tolerate oral medications, or the risk of disseminated candidiasis (e.g. in a child with leukaemia).

**Viral oesophagitis**

**Herpes simplex virus (HSV)**

Herpes simplex virus (HSV) infection may either be primary (herpetic gingivostomatitis) or secondary (herpes labialis). The prevalence of oral HSV infection ranges from 10% to 35% in adults and children with HIV infection. The presence...
of HSV infection for more than 1 month constitutes an AIDS-defining condition.

Clinical appearance
HSV infection appears as a crop of vesicles, usually localised on the keratinised mucosa (hard palate, gingiva) and/or the vermilion borders of the lips and perioral skin. The vesicles rupture and form irregular painful ulcers. They may interfere with mastication and swallowing, resulting in decreased oral intake and dehydration.

Systemic therapy with antiviral agents is recommended. The treatment is more effective if it is instituted in the prodromal stage of infection. Treat with aciclovir 20–40 mg/kg orally or IV four times daily for 7 days (maximum single dose is 800 mg).

Cytomegalovirus (CMV) infection: treat with ganciclovir IV 5 mg/kg every 12 hours for 14–21 days.

Reflux oesophagitis may also be present. Treat with an H2-antagonist, such as ranitidine 2 mg/kg twice daily (see Section 5.12.E).

Idiopathic aphthous ulcers: if possible these need to be differentiated from HSV by viral culture. Pay attention to oral hygiene. Thalidomide is useful if they are severe.

Severe periodontal and gingival disease (cancrum oris)
Periodontal (gum) disease is common among HIV-infected patients. It is characterised by bleeding gums, bad breath, pain or discomfort, mobile teeth, and sometimes sores. Its reported prevalence ranges widely, from 0% to 50%. If left untreated, HIV-associated periodontal disease may progress to life-threatening infections, such as Ludwig’s angina and noma (cancrum oris).

Noma is a gangrenous condition that primarily affects children. It is a multifactorial disease. The most important risk factors are poverty, chronic malnutrition, poor oral hygiene and severe immunosuppression. Although it is considered to be a preventable disease, noma has a case-fatality rate of 70–90% if left untreated.

1. Treat with benzylpenicillin 50 mg/kg 4-hourly or amoxicillin 40–60 mg/kg IV 8-hourly. Change to oral antibiotics once the child is able to swallow (usually after 24–48 hours).
2. Provide materials for and education on dental hygiene.

Rarely, malignancy (Kaposi’s sarcoma or non-Hodgkin’s lymphoma) or oral hairy leukoplakia (white lacy markings on the sides of the tongue associated with Epstein–Barr virus infection; no treatment required) occur. Visceral Kaposi’s sarcoma may present with persistent diarrhoea, intestinal obstruction and abdominal pain.

Persistent diarrhoea (see Section 5.12.B)
Case management should start with management of dehydration with oral rehydration solution. Dysentery (loose stools with blood) should be managed in the same way as for non-HIV-infected children (e.g. for Shigella infection). Concur with the local prevalence of treatable infections. Giardiasis, cryptosporidiosis, microsporidiosis, Shigella, Salmonella, Campylobacter, enteropathogenic E. coli and Yersinia may each contribute to gastrointestinal dysfunction. HIV itself may cause an enteropathy, and in highly immunosuppressed children, atypical mycobacterial infection and protozoa such as Blastocystis hominis may cause diarrhoea. Even with sophisticated microbiology, no pathogen may be found, and malabsorption due to lactase deficiency and other brush-border defects should be considered. All antiretroviral drugs (except AZT) can cause diarrhoea, particularly ritonavir.

Chronic or recurrent diarrhoea
Normal endemic pathogens may be responsible, such as rotavirus, Giardia lamblia, Campylobacter jejuni (see Section 5.12.A and Section 5.12.B), salmonellae (typhoid and non-typhoid), E. coli, Shigella, Entamoeba histolytica and Strongyloides stercoralis.

Investigations
- Fresh stool microscopy and culture: Giardia, Entamoeba.
- Ova and cysts: helminths.
- ZN stain: cryptosporidia, cyclospora.
- pH and reducing substances: lactose intolerance.
- CD4 count < 50: CMV, mycobacterium avium intracellulare
- CD4 count < 100: cryptococcosis, microsporidiosis.

Look for signs of vitamin deficiencies:
- Vitamin A: night blindness, dry eyes, Bitot’s spots (on conjunctivae).
- Vitamin D: rickets (wide wrist, double malleoli, bow legs, rachitic rosary, Harrison’s sulcus).
- Vitamin E: dry rough skin.
- Vitamin K: ecchymosis, purpura.

Opportunistic infections such as those listed below may be responsible:
- Bacterial: atypical mycobacterial infections, such as Mycobacterium avium complex (MAC) (see below).
- Protozoa and parasites: cryptosporidia, microsporidia, Isospora belli. Treat with azithromycin 10 mg/kg once daily.
- Viral: cytomegalovirus, herpes simplex virus.
- Fungal: histoplasmosis, coccidiomycosis, Candida. If severe, treat with fluconazole 3 mg/kg once daily.

Diarhoea may be secondary to antibiotics, either by direct effects or through Clostridium difficile. Stop antibiotics as soon as possible. Give live yoghurt with or without oral vancomycin.

If lactose intolerance is present, give lactose-free feeds. Treat dysentery with ciprofloxacin 15 mg/kg 12-hourly for 3 days, or ceftriaxone 50 mg/kg once a day for 2–5 days, plus metronidazole 7.5 mg/kg 8-hourly for 7 days.

Nutritional management includes calorie replacement, which may need to be nasogastric, but always encourage eating. Ensure that additional food is not just recommended but actually given. Vitamin A, multivitamins and zinc (10–20 mg once a day for 10–14 days) supplementation may be of benefit (see Section 5.10.A).

Prevention: Use hygienic practices during food preparation, always use clean water, avoid bird and animal faeces, avoid swimming in fresh water, and avoid reptiles (salmonellae).

Abdominal pain
This is most frequently related to infections, but occasionally is caused by tumours (non-Hodgkin’s lymphoma and Kaposi’s sarcoma).
Malabsorption
HIV can be directly associated with an enteropathy. Lactase deficiency and other brush-border defects can also be responsible. Consider trial of a lactose-free diet.

Central nervous system disorders
A myriad of HIV-related CNS diseases have been described. Primary CNS infection by HIV is quite common, as it is a neurotropic virus. Various abnormalities of the central nervous system (CNS) and peripheral nervous system (PNS) are associated with HIV and AIDS. These abnormalities may be attributable to the following causes: HIV infection, complications related to immunosuppression, neurotoxic effects of antiretroviral treatments, and other systemic complications of HIV that affect brain function.

Neurological disorders in people with HIV infection include peripheral neuropathies (nerve disorders that affect the limbs or feet and hands), myelopathy (disorders of the spinal cord), focal cerebral mass lesions (brain tumours such as CNS lymphoma), CNS complications of opportunistic infections, vascular (blood vessel) abnormalities, seizures and encephalopathies. Developmental delays and regression are also important CNS-related problems in HIV-infected children.

The neurological manifestations of HIV infection include the following:
- progressive or static encephalopathy
- seizures
- strokes
- HIV myopathy
- HIV myelopathy
- peripheral neuropathy
- psychiatric manifestations
- sleep problems.

The effect of HIV on the brain ranges from severe effects, found in more than 50% of patients dying of AIDS at post-mortem, to the much more common and milder effects on the developing brain in children, which result in mild learning difficulties. It is particularly important to recognise this so that appropriate support can be given (e.g. reminding the patient to take ART).

### TABLE 6.2.D.10 Comparison of features of major CNS mass lesions in HIV

<table>
<thead>
<tr>
<th>Disease</th>
<th>Timing</th>
<th>Fever</th>
<th>Number of lesions</th>
<th>Type of lesions</th>
<th>Location of lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral toxoplasmosis</td>
<td>Acute onset of symptom</td>
<td>Common</td>
<td>Multiple</td>
<td>Enhancing spherical rings; mass effect</td>
<td>Basal ganglia</td>
</tr>
<tr>
<td>Primary CNS lymphoma</td>
<td>Insidious onset of symptom</td>
<td>Usually absent</td>
<td>One or few</td>
<td>Irregular shape, weakly enhancing, mass effect</td>
<td>Periventricular, peri-ependymal, corpus callosum</td>
</tr>
<tr>
<td>Tuberculoma</td>
<td>Insidious onset of symptom</td>
<td>Common</td>
<td>One or few</td>
<td>Discrete lesions, significant surrounding oedema, mass effect</td>
<td>Supratentorial in adults, infratentorial in children (at the base of the brain near the cerebellum)</td>
</tr>
<tr>
<td>Cryptococcoma</td>
<td>Acute onset of symptom</td>
<td>Common</td>
<td>Variable</td>
<td>Mass lesions, dilated perivascular spaces, oedema</td>
<td>Basal ganglia</td>
</tr>
</tbody>
</table>

Care of HIV-infected children with CNS involvement requires a thorough evaluation and stepwise therapy according to the underlying aetiology. A multidisciplinary approach is usually needed for appropriate care.

### Specific neurological problems
**HIV encephalopathy**
- Rapid onset or chronic and relapsing forms.
- Hypertonic (spastic) diplegia and expressive language delay.
- Acquired microcephaly with developmental regression (loss of skills).
- White-matter disease predominates. It does not cause seizures, and therefore seizures need to be fully investigated for another pathology.

**Encephalitis**
**Toxoplasma gondii**
- Prevention: avoid cats and cat faeces:
  - avoid raw uncooked or partially cooked food
  - can be acquired congenitally.
- Diagnosis: CT/MRI of the brain, and serology (if available).
- Treat with co-trimoxazole 60 mg/kg orally (IV if there is severe nausea) 12-hourly for 2 weeks.
- Then give lifelong prophylaxis: sulfadiazine 85–120 mg/kg/day in two doses, pyrimethamine 1 mg/kg/day (maximum 25 mg) and folinic acid 5 mg every 3 days.

**JC virus (papovavirus)**
The JC virus is associated with progressive multifocal leukoencephalopathy, a disease characterised by altered mental status, limb weakness, or both. Patients may also exhibit personality changes with frequent emotional outbursts. There is no treatment for this illness, but strong antiretroviral medications (if available) can sometimes improve the symptoms.

**Fungal lesion**
This is rare.

### Diffuse CMV encephalitis
Treat with ganciclovir 5 mg/kg orally or IV 12-hourly for 14–21 days.

**Malaria**
See Section 6.3.A.d.

**Meningitis**
**Bacterial meningitis**
This has the usual spectrum of pathogens, such as...
Pneumococcus, Haemophilus influenzae, Meningococcus and Mycobacterium TB. (see Section 5.16.B).

Viral meningitis
See Section 5.16.C.

Cryptococcosis and other fungi
- Prevention: avoid bird faeces.
- Clinical features: chronic onset, headache (common), fever, meningism (usually but not always present), and there may be a change in mental state.
- Diagnosis: based on staining of CSF sample with Indian ink.
- Treatment:
  - Fluconazole 6–12 mg/kg orally or, if there is severe nausea, IV once daily for 14 days. There is a high relapse rate, therefore give prophylactic fluconazole 3–6 mg/kg/day or amphotericin IV 0.5–1.5 mg/kg/day for 14 days followed by oral fluconazole for 8 weeks.

Syphilis
Treat with benzylpenicillin IV 50 mg/kg every 6 hours for 48 hours, then oral penicillin 25 mg/kg 6-hourly for 3 weeks (20% of cases may have a systemic febrile response to penicillin).

Tuberculosis
See Section 6.1.N.

Cerebral abscess
Acute bacterial or tuberculosis.

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**TABLE 6.2.D.11 Neurological manifestations of paediatric HIV infection**

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Clinical findings</th>
<th>Diagnostic studies (if available)</th>
</tr>
</thead>
</table>
| Focal cerebral mass lesions        | Headache, nausea/vomiting, motor deficits (usually asymmetrical), discoordination, visual changes, altered mental status | CT/MRI: enhancing lesions
|                                    |                                                                                  | Lumbar puncture: CSF may reveal abnormal cytology or Epstein–Barr virus via PCR |
|                                    |                                                                                  | Brain biopsy: sometimes needed to confirm diagnoses                    |
| Myelopathy                         | Gait disturbances, lower-extremity weakness/spasticity incontinence, sensory abnormalities, abnormal lower-extremity reflexes | CT/MRI on mass lesions seen; nerve-root thickening may be present
|                                    |                                                                                  | CSF: polymorphonuclear pleocytosis                                      |
| Myopathy                           | Muscle weakness, muscle soreness, weight loss                                      | EMG: irritative myopathy                                                |
|                                    |                                                                                  | Muscle biopsy: inflammation, degeneration                                |
| Opportunistic infections           | Headache, nausea/vomiting, fever, seizures, altered mental status, malaise        | CT/MRI: multiple enhancing lesions (toxoplasmosis), periventricular and meningeal abnormalities (CMV) |
| Peripheral neuropathy              | Distal symmetrical neuropathy
|                                    | • Distal numbness/pain                                                            | Distal symmetrical neuropathy                                           |
|                                    | • Parasthesias                                                                    | EMG: distal axonopathy                                                  |
|                                    | • Stocking/glove sensory loss                                                     |                                                                        |
|                                    | • Decreased ankle reflexes                                                       |                                                                        |
|                                    | Inflammatory demyelinating polyneuropathy                                        | Inflammatory demyelinating polyneuropathy                              |
|                                    | • Progressive weakness                                                           | EMG: demyelination                                                      |
|                                    | • Parasthesias                                                                    |                                                                        |
|                                    | • Areflexia                                                                       |                                                                        |
|                                    | • Mild sensory loss                                                                |                                                                        |
| Progressive polyradiculopathy      | Lower-extremity weakness                                                          | Progressive polyradiculopathy                                           |
|                                    | Paraesthesias                                                                     | EMG: polyradiculopathy                                                  |
|                                    | Urinary incontinence and retention                                               | Serum: increased creatine kinase                                        |
|                                    | Diminished reflexes                                                               |                                                                        |
| Progressive encephalopathy         | Fine and gross motor deficits (usually symmetrical), abnormal tone, neurodevelopmental delay, microcephaly, altered mental status | CT/MRI: brain atrophy, white-matter abnormalities                        |
| Strokes (cerebrovascular accidents) | Focal or generalised seizures, post-ictal stare (fatigue and confusion following seizure) | EEG: abnormal patterns
|                                    |                                                                                  | CT/MRI and CSF studies: mass lesions may be seen via imaging, and CSF may be positive for pathogens and abnormal cells if aetiology is infectious or neoplastic
|                                    |                                                                                  | Lumbar puncture: may reveal infection                                  |
|                                    | Rapid onset of focal neurological signs, seizures, altered mental status         | CT/MRI: extent of bleeding seen (in ischaemic strokes, CT may not show changes during the first 2–1 hours); contributing factors such as CNS neoplasms may be identified
|                                    |                                                                                  | Lumbar puncture: with subarachnoid haemorrhages, blood will be present in the CSF |

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### TABLE 6.2.D.12 Care guidelines for children with neurological manifestations of paediatric HIV infection

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Care guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal cerebral mass lesions</td>
<td>* Assess for signs of increased intracranial pressure, fever, focal neurological signs and behavioural changes</td>
</tr>
<tr>
<td></td>
<td>* Administer chemotherapy or antibiotics as needed</td>
</tr>
<tr>
<td></td>
<td>* Provide support to family and education regarding specific medications needed by patients</td>
</tr>
<tr>
<td>Myelopathy</td>
<td>* Assess for pain, muscle weakness, lower-extremity weakness, incontinence and spasticity</td>
</tr>
<tr>
<td></td>
<td>* Administer HAART to reverse immune suppression</td>
</tr>
<tr>
<td></td>
<td>* Administer muscle relaxants as needed</td>
</tr>
<tr>
<td></td>
<td>* Provide physical therapy for weakened muscles and to maintain range of motion</td>
</tr>
<tr>
<td></td>
<td>* Teach exercises to the family so that they can help the patient at home</td>
</tr>
<tr>
<td>Myopathy</td>
<td>* Assess for pain, muscle weakness and range of motion</td>
</tr>
<tr>
<td></td>
<td>* Consider discontinuing medications that may be contributing to the condition</td>
</tr>
<tr>
<td></td>
<td>* Administer corticosteroids and pain medications as needed</td>
</tr>
<tr>
<td></td>
<td>* Provide physical therapy for weakened muscles and to maintain range of motion</td>
</tr>
<tr>
<td></td>
<td>* Teach exercises to the family so that they can help the patient at home</td>
</tr>
<tr>
<td>Opportunistic infections</td>
<td>* Assess for signs of increased intracranial pressure, fever, focal neurological signs and behavioural changes</td>
</tr>
<tr>
<td></td>
<td>* Administer appropriate medication based on the suspected or confirmed pathogen:</td>
</tr>
<tr>
<td></td>
<td>- toxoplasmosis: pyrimethamine, sulfadiazine, clindamycin</td>
</tr>
<tr>
<td></td>
<td>- cryptococcosis: fluconazole, flucytosine, amphotericin B</td>
</tr>
<tr>
<td></td>
<td>- herpes simplex: aciclovir</td>
</tr>
<tr>
<td></td>
<td>- cytomegalovirus: ganciclovir, foscarnet</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>* Assess for numbness, paraesthesias, pain and weakness</td>
</tr>
<tr>
<td></td>
<td>* Administer analgesics, tricyclic antidepressants, anticonvulsants and steroids as needed</td>
</tr>
<tr>
<td></td>
<td>* Provide support to the family regarding progression of symptoms</td>
</tr>
<tr>
<td>Progressive encephalopathy</td>
<td>* Assess for progressive motor dysfunction, and failure to reach or loss of age-appropriate milestones</td>
</tr>
<tr>
<td></td>
<td>* Administer antiretroviral medications and muscle relaxants as needed</td>
</tr>
<tr>
<td></td>
<td>* Assist with ambulation and activities of daily living</td>
</tr>
<tr>
<td></td>
<td>* Provide information to the family regarding progression of symptoms</td>
</tr>
<tr>
<td>Seizures</td>
<td>* Assess for seizure activity</td>
</tr>
<tr>
<td></td>
<td>* Protect the patient from injury during seizure activity</td>
</tr>
<tr>
<td></td>
<td>* Monitor respiratory status: suction airway and administer oxygen as needed</td>
</tr>
<tr>
<td></td>
<td>* Administer anticonvulsant medications as needed</td>
</tr>
<tr>
<td></td>
<td>* Provide support to the family during seizures</td>
</tr>
<tr>
<td></td>
<td>* Educate the patient and the family about long-term use of anticonvulsant medications and seizure precautions (e.g., patients with seizures should never swim alone or climb to high places from which they could fall during a seizure)</td>
</tr>
<tr>
<td>Strokes</td>
<td>* Intensive care, including neurosurgical intervention, is often needed immediately after a stroke occurs</td>
</tr>
<tr>
<td></td>
<td>* Look for contributing factors, such as low platelet levels, which may be correctable</td>
</tr>
<tr>
<td></td>
<td>* Assess for seizures</td>
</tr>
<tr>
<td></td>
<td>* Assist with ambulation and activities of daily living</td>
</tr>
<tr>
<td></td>
<td>* Provide physical therapy as needed</td>
</tr>
<tr>
<td></td>
<td>* Provide support and education to the family regarding the long-term prognosis</td>
</tr>
</tbody>
</table>

### Skin disorders
Cutaneous lesions are often the first manifestation of HIV noted by patients and healthcare professionals. These can be due to infectious or non-infectious causes. Viral, bacterial and fungal infections have been very frequently reported in HIV-infected children. These usually tend to be more severe and resistant to therapy. Common skin diseases may present with unusual skin lesions such as Norwegian scabies and disseminated, confluent and large lesions of molluscum contagiosum (see Table 6.2.D.13).

#### Seroconversion rash
Maculopapular erythematous rash (very rarely observed in infants).

#### Viral infections

**Varicella**
- Chickenpox: can be very severe (affecting the lungs and brain) or even fatal.
- Herpes zoster: can involve single or multiple dermatomes and may affect the eyes.

**Treat with:**
1. IV aciclovir (poorly absorbed by the oral route):
   - Age < 3 months: 10 mg/kg 8-hourly.
   - Age > 3 months: 20 mg/kg 8-hourly.
2. Valacyclovir is the prodrug of aciclovir, and achieves better blood levels orally and is an alternative to IV aciclovir (if available).
3. VZIG within 96 hours of contact (if available).

**HSV 1 and 2**
Infection appears as a crop of localised vesicles. It may affect the lips, mouth and anogenital areas (rare in children unless sexually abused). The vesicles rupture and form irregular painful ulcers. They may interfere with mastication and swallowing, resulting in decreased oral intake and dehydration.
Fungal infections
- Candida
- Tinea onychomycosis

Bacterial infections
- Impetigo
- Scabies

Fungal infection
Fungal infection is common and involves the feet, hands and groin. Treat with topical imidazole (e.g. miconazole 2% cream twice daily until healed) or terbinafine cream. If severe, widespread, or for nail infections, use itraconazole or terbinafine. Treatment will be needed for 4–6 weeks. Antifungal drugs commonly used in paediatric patients include the following:
- **Itraconazole**: children aged 1–12 years: course (‘pulse’) of 5 mg/kg (maximum 200 mg) daily for 7 days, with subsequent courses repeated after 21-day intervals; fingernails need two courses, and toenails need three courses. For children aged 12–18 years: either 200 mg once daily for 3 months or course (‘pulse’) of 200 mg twice daily for 7 days, with subsequent courses repeated after 21-day intervals; fingernails need two courses, and toenails need three courses.
- **Terbinafine**: children aged over 1 year: body weight 10–20 kg, 62.5 mg once daily; body weight 20–40 kg, 125 mg once daily; body weight over 40 kg, 250 mg once daily, for 6 weeks to 3 months.
- **Fluconazole**: 6 mg/kg weekly.
- **Griseofulvin**: 20–25 mg/kg/day (micronized formulation) or 10–15 mg/kg/day (ultramicronized formulation) for 6–12 weeks.

Seborrhoeic dermatitis and pityriasis versicolor
Seborrhoeic dermatitis occurs in up to 85% of adults and children with HIV infection. It may be an early sign of HIV. It is caused by the yeast Malassezia furfur.

It is characterised by thick yellow hypopigmented scaly macules occurring on the scalp but also on the face or in the diaper (nappy) area. Older children may also have involvement of the nasolabial folds, the skin behind the ears, and the eyebrows.

Treatment consists of selenium-based or ketoconazole shampoo, topical coal tar or antifungal creams, aqueous cream, UBV light therapy or salicylic acid. To decrease inflammation, 1% hydrocortisone cream can be applied to the affected area (except for the face) three times per day. Parents should be instructed to use 1% hydrocortisone cream sparingly in the diaper area.

If the condition is severe, give oral fluconazole 3 mg/kg once daily.

Non-specific pruritic papular rash
This is a common and severe problem in children with HIV infection. In a previously untested child it should be an indication for HIV testing. In a child who is known to have HIV, the CD4 count should be checked and ARV started if appropriate.

Treatment
- Bathe in a skin antiseptic wash (e.g. dilute chlorhexidine solution).
- **Antihistamines**: give chlorpheniramine:
  - Age < 1 year: 1 mg twice daily.
  - Age 1–5 years: 1–2 mg three times daily.
  - Age 6–12 years: 2–4 mg three times daily.
  - Age > 12 years: 4 mg three times daily.
- **Aqueous cream and calamine lotion may be of benefit.**

Drug side effects
Drug eruptions can occur in patients who are receiving treatment for HIV infection. These can be severe (e.g. erythema multiforme, Stevens–Johnson syndrome, toxic epidermal necrolysis).

Drug side effects are most common with co-trimoxazole, sulfadiazine, anti-tuberculous drugs (e.g. thiacetazone, which is contraindicated in HIV infection), penicillin, cephalosporins and dapsone.

Drug eruptions usually appear as pink to erythematous papules that run together and create a blotty appearance, but may include elevated patches (hives), mucous membrane ulceration, scaling and light sensitivity.

NRTIs (nevirapine and efavirenz) have been associated with pruritic maculopapular eruptions. Most eruptions are mild, and the medication can be continued with eventual spontaneous resolution of the eruption.

To promote comfort, the patient can be given oral anti-histamine such as diphenhydramine hydrochloride 1 mg/kg

**Table 6.2.D.13 Common infectious and non-infectious skin lesions in paediatric HIV**

<table>
<thead>
<tr>
<th>Infectious disorders and lesions</th>
<th>Non-infectious disorders and lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral infections</td>
<td>Seborrhoeic dermatitis, atopic dermatitis, general dermatitis, Nutritional deficiency, Eczema, Psoriasis, Drug eruptions, Vasculitis, Alopecia</td>
</tr>
<tr>
<td>- Herpes simplex, herpes zoster</td>
<td></td>
</tr>
<tr>
<td>- Molluscum contagiosum</td>
<td></td>
</tr>
<tr>
<td>- CMV</td>
<td></td>
</tr>
<tr>
<td>- Warts</td>
<td></td>
</tr>
<tr>
<td>Fungal infections</td>
<td></td>
</tr>
<tr>
<td>- Candida</td>
<td></td>
</tr>
<tr>
<td>- Tinea onychomycosis</td>
<td></td>
</tr>
<tr>
<td>Bacterial infections</td>
<td></td>
</tr>
<tr>
<td>- Impetigo</td>
<td></td>
</tr>
<tr>
<td>- Scabies</td>
<td></td>
</tr>
</tbody>
</table>

- May be recurrent and severe.
- Treat with oral aciclovir, 20 mg/kg four times daily for 5–7 days (maximum single dose 800 mg).

**Molluscum contagiosum**
Umbilicated papular lesions. Treat with ARVs (no other measures are effective). If neglected, giant lesions can result which require surgical excision.

**Measles**
- Prevent by immunisation (see below and Section 6.2.E).
- May not have a rash.
- Giant-cell pneumonitis may occur.
- Treat with Vitamin A and human immunoglobulin (if available).

**Viral warts**
These can be persistent and severe. Topical treatment is ineffective (see molluscum contagiosum above), and ARVs are the only effective treatment.

**Bacterial infections**
Impetigo and furunculitis due to Staphylococcus aureus are common. Treat with (flucloxacillin, 12.5–25 mg/kg four times daily orally, or a first-generation cephalosporin such as cephradine.

**Alopecia**

**Vasculitis**

**Psoriasis**

**Seborrhoeic dermatitis**

**Atopic dermatitis**

**Seborrhoeic dermatitis and pityriasis versicolor**

**Herpes simplex, herpes zoster**

**Herpes zoster**

**Impetigo and furunculitis due to Staphylococcus aureus**

**Staphylococcus aureus**

**CMV**

**Cytomegalovirus (CMV)**

**Drug eruptions**
Drug eruptions usually appear as pink to erythematous papules that run together and create a blotty appearance, but may include elevated patches (hives), mucous membrane ulceration, scaling and light sensitivity.

**NRTIs (nevirapine and efavirenz)** have been associated with pruritic maculopapular eruptions. Most eruptions are mild, and the medication can be continued with eventual spontaneous resolution of the eruption.

To promote comfort, the patient can be given oral anti-histamine such as diphenhydramine hydrochloride 1 mg/kg
Prophylaxis can often be stopped after sustained immune reconstitution secondary to ART, but not in all cases.

Mycobacterium avium complex (MAC)
- This produces a systemic infection with fever, chronic diarrhoea, abdominal pain, chronic malabsorption, generalised lymphadenopathy and obstructive jaundice (from lymph node enlargement around the porta hepatis).
- Treat with clarithromycin 7.5 mg/kg twice daily IV or orally or azithromycin 10 mg/kg once daily and ciprofloxacin and rifabutin.
- Consider prophylaxis with the above drugs if CD4 cell counts are persistently < 50/mm³ despite antiretroviral therapy, as the risk of MAC is high. The opportunistic infection guidelines recommend that all HIV-infected individuals with CD4 counts of < 50 cells/mm³ should have primary prophylaxis against disseminated MAC initiated. Prior to initiating prophylaxis, patients should be evaluated for active MAC infection by clinical assessment.

Fever of unknown origin
- HIV infection itself can cause fever.
- In an endemic area, always treat for malaria (ideally after a blood film). Malaria has not usually been reported to be more severe in HIV-infected children in terms of parasite density or response to treatment. The main interaction between the two diseases has been the acquisition of HIV by children through blood transfusion for malaria-associated anaemia.
- Have a low threshold for diagnosing septicaemia and meningitis and giving powerful empirical antibiotics if severe sepsis is suspected.
- Consider tuberculosis and non-Hodgkin’s lymphoma.

Immunisation
Early immunisations can help HIV-infected children who are more likely to acquire diseases that are preventable by immunisation because of their compromised immune system. Appropriate immunisations vary according to geographical location.

Routine immunisations appear to be generally safe for children with HIV infection without fever. Although immune responses may be suboptimal in some HIV-infected children, because of the severe nature of infections and associated mortality, routine immunisation of all children with HIV exposure or confirmed HIV infection is recommended with few exceptions.

Immunisations should generally follow the Expanded Programme on Immunisation (EPI) scheme. The current EPI schedule includes DTP, OPV, hepatitis B, Haemophilus influenzae type B vaccine (Hib) and measles vaccine. The difference in HIV-infected children is an extra dose of measles vaccine to be given at the age of 6 months. BCG and yellow fever vaccines should not be given to HIV-symptomatic children.

In HIV-endemic areas, BCG is routinely administered postnatally. This should be given even to infants of mothers known to be HIV-infected, as the damage to the immune system generally occurs after the onset of viraemia (i.e. after the first 6 weeks of life). There is no evidence of frequent dissemination occurring after neonatal administration of BCG, although BCG-osis is not an easy diagnosis to establish, and there may be unrecognised cases.

Because most HIV-positive children have an effective immune response in the first year of life, EPI should be
started as early as possible after the recommended age of vaccination.

There are theoretical risks associated with giving live oral polio vaccine, particularly to other immunocompromised members of the household. However, cases of vaccine-associated paralytic illness are rare, and oral polomyelitis vaccine (OPV) continues to be recommended.

Live attenuated measles vaccine is recommended by the WHO for children in resource-limited countries, where the risks from wild-type measles virus are high. Responses to the vaccine tend to be lower in HIV-infected children with more advanced disease. The WHO recommends giving an extra dose of measles vaccine at 6 months, as well as the standard dose at 9 months, to HIV-infected children. It is important to be aware of measles in the differential diagnosis of any child with fever or pneumonia and HIV, as a typical morbilliform rash and standard symptoms may not be present.

Other non-EPI vaccines are encouraged and recommended, especially in children whose immune systems have recovered. These more expensive but strongly recommended vaccines include MMR, pneumococcal conjugate vaccine, hepatitis A, typhoid and varicella vaccines. Diseases caused by these organisms have a greater propensity to cause severe life-threatening infections in HIV-infected children.

**Terminal care of children dying from HIV infection**

*See also Section 1.16.*

Despite the increased availability and effectiveness of ARVs, death is still a possible outcome of HIV/AIDS. Each year, millions of children lose one or both parents to AIDS. Although relatives often go to heroic lengths to provide orphans with food, shelter and housing, often the children’s psychosocial needs are overlooked, and these young people are not given full recognition or support after their loss. This is usually due to the belief that children are too young to understand what is happening or are better off not dwelling on their loss. Consequently, they are not properly supported in their time of mourning.

Local groups for the support of families with HIV infection are essential, and ideally should be funded by local government.

*Give end-of-life (terminal) care if:*
- the child has had a progressively worsening illness
- everything possible has been done to treat the presenting illness.

Keep up to date on how to contact local community-based home care programmes and HIV/AIDS counselling groups. Find out whether the carers are receiving support from these groups. If not, discuss the family’s attitude towards these groups and the possibility of linking the family with them.

**Pain control for children with HIV**

*See Section 1.15.*

**Need for referral**

Often the facilities or expertise that are needed will not be available at the health centre or hospital to which a child with suspected or confirmed HIV has come for treatment. If the child is not suffering from a life-threatening condition that requires urgent treatment, and referral can be arranged, it is advisable to refer the child to a paediatric infectious disease specialist or HIV treatment centre for the following:
- HIV testing with pre- and post-test counselling
- further investigations to confirm the diagnosis
- evaluation of immunological status and the need to initiate ART
- management of complicated HIV-related conditions and infections
- evaluation of possible treatment failure
- second-line treatment if there has been little or no response to treatment
- HIV medication-related toxicities
- HIV-related expert counselling.

**Summary**

*The major practical focus should be on prevention of childhood HIV infection. This means implementing effective strategies for reduction of mother-to-infant transmission, such as prenatal screening of mothers and administration of ARV drugs for mother and baby. Unfortunately, establishing the infrastructure that is required to implement effective interventions is lagging far behind the scientific advances in this field. Surmounting the sense of hopelessness among health-care professionals who are dealing with overwhelming numbers of patients without resources is a critical issue. This may come in part from research that identifies practical interventions which improve the quality of life for HIV-infected children and their families.*

- Limiting the use of blood transfusions and ensuring that the blood supply is safe, and preventing sexual transmission among adolescents, are vital public health issues.
- Positive education is required to encourage testing in the knowledge that there is now accessible safe treatment to keep children alive so that they can have a full healthy life.
- The key to successful treatment is 100% adherence. Do not start outpatient treatment until the child’s carer and ideally all the family have expressed a commitment to treatment. Choose ART regimes which are simple, and ensure that there is no problem with swallowing.
- Predict growth for dosing so that the child is never under-dosed.
- Frequent review is necessary to re-emphasise the importance of adherence and education of young people.
- It is essential that resource-limited countries are permitted by multinational drug companies to develop low-cost and effective forms of HAART, without being limited by international patent regulations.
- Without question, health system strengthening is essential if the advent of ARVs for all is to be adequately managed.

This is a very optimistic time in the field of paediatric HIV, with the potential to aim for eradication of mother-to-child transmission, and to provide successful treatment.
## TABLE 6.2.D.14 Monitoring children on ART

<table>
<thead>
<tr>
<th>Item</th>
<th>Before or at ART initiation</th>
<th>Month (M) 1</th>
<th>M 2</th>
<th>M 3</th>
<th>M 4</th>
<th>M 5</th>
<th>M 6</th>
<th>Every 2–3 months</th>
<th>Symptom-directed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical evaluation: history and physical examination (including neurodevelopment)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Weight and height</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Calculation of ART dose&lt;sup&gt;1&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Concomitant medications&lt;sup&gt;2&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Check ART adherence&lt;sup&gt;3&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin and white blood cell count&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Full chemistry&lt;sup&gt;5&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4% or count&lt;sup&gt;6&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X*</td>
<td></td>
</tr>
<tr>
<td>HIV viral load measurement&lt;sup&gt;7&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

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

- The child should be seen again within 1 week of starting ART to resolve any problems.
- If the child has missed a visit, attempts should be made to call or visit the child’s home.
- In addition to these suggested appointments, caregivers should be encouraged to bring the child in if he or she is sick, especially during the first few months of ART when the child may experience ART side effects and intolerance.

1 Children may show rapid weight and height gain after ART, in addition to expected normal growth. Therefore the ART dose should be recalculated at every visit. Under-dosing of ART can lead to the development of resistance.

2 Concomitant drugs should be asked for at every visit to ensure that the child is on appropriate CTX dosing (if indicated) and is not taking drugs that have potential interactions with ART.

3 ART adherence can be assessed by asking questions about missed doses and the times when the child takes ART. Performing a pill count is time consuming, but may give a more accurate indication of adherence, if done correctly.

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

5 Full chemistry includes but is not restricted to liver enzymes, renal function, glucose, lipids, amylase, lipase and serum electrolytes. Monitoring depends on symptoms and regimens. Regular liver enzyme monitoring during the first 3 months of treatment may be considered for certain children using nevirapine-based regimens, in particular for adolescent girls with a CD4 count of > 250 cells/mm³, and for infants and children who are co-infected with hepatitis B or hepatitis C virus, or other hepatic disease.

6 TLC is not suitable for monitoring of therapy; therefore it cannot be a substitute for CD4. If CD4 is not available, clinical monitoring alone is used.

7 At present, viral load measurement is not recommended for decision making about 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, and to assess discordant clinical and CD4 findings in children in whom ART is suspected of failing.
Appendix 2
Treatment of PCP infection

TABLE 6.2.D.15 Starting co-trimoxazole (CTX) prophylaxis for *Pneumocystis jiroveci* pneumonia (PCP)

<table>
<thead>
<tr>
<th>HIV-exposed infants and children</th>
<th>Confirmed HIV-infected infants and children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Under 1 year</td>
</tr>
<tr>
<td>CTX 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</td>
<td>CTX prophylaxis is indicated regardless of CD4 percentage or clinical status</td>
</tr>
</tbody>
</table>

*Patient information:* It needs to be explained to patients that although CTX does not cure HIV, regular dosing is essential for protection of children from infections that are more common or more likely to occur in HIV infection. CTX does not replace the need for antiretroviral therapy.

TABLE 6.2.D.16 Dosing for PCP: once-daily CTX dosing

<table>
<thead>
<tr>
<th>Weight</th>
<th>Suspension: 40 mg TMP + 200 mg SMX/5mL</th>
<th>Tablets (SS): 80 mg TMP/400 mg SMX</th>
<th>Tablets (DS): 160 mg TMP/800 mg SMX</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–4 kg</td>
<td>2.5 mL</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5–8 kg</td>
<td>5 mL</td>
<td>½ tablet</td>
<td>–</td>
</tr>
<tr>
<td>9–16 kg</td>
<td>10 mL</td>
<td>1 tablet</td>
<td>½ tab</td>
</tr>
<tr>
<td>17–50 kg</td>
<td>20 mL</td>
<td>2 tablets</td>
<td>1 tablet</td>
</tr>
<tr>
<td>&gt; 50 kg</td>
<td>20 mL</td>
<td>2 tablets</td>
<td>1 tablet</td>
</tr>
</tbody>
</table>

Appendix 3
Summary of nutritional recommendations and support for HIV-infected children

- Regular growth monitoring.
- Safe infant feeding advice (the emphasis is on an exclusive infant feeding option). Substitute feeds if they are acceptable, affordable, feasible, sustainable and safe, otherwise exclusive breastfeeding, and early weaning. Avoid all mixed feeding.
- Dietary counselling for asymptomatic children to increase energy intake by 10% compared with HIV-uninfected children.
- Dietary counselling for symptomatic children to increase energy intake by 20–30% compared with HIV-uninfected children.
- Counselling on the importance of a balanced diet, including affordable choices from all food groups (micro-nutrient requirement of 1 RDA for age).
- Counselling on high-energy affordable food options for children with growth failure.
- Counselling on the use of clean water and hygienic food preparation.
- Vitamin A supplementation to prevent vitamin A deficiency in children aged 6 to 59 months with dosing schedule as follows:
  - Children aged 6–11 months: 100 000 IU (30 mg) once every 6 months.
  - Children aged 12–59 months: 200 000 IU (60 mg) once every 6 months.
- Zinc supplementation during diarrhoeal episodes: 10 mg once daily for 10 days in children older than 6 months if weight is < 10 kg, and 20 mg if weight is > 10 kg.
- Assessment and management for underlying HIV-associated illnesses.
- Assessment for need to initiate ART.
- Referral to outreach service providers for food assistance, if needed.
### Formulations and dosages of ART drugs for children

<table>
<thead>
<tr>
<th>Name of drug</th>
<th>Formulation</th>
<th>Age</th>
<th>Age (weight), dose and dose frequency</th>
<th>Other comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleoside analogue reverse transcriptase inhibitors (NRTIs)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine (ZDV) AZT</td>
<td>Syrup: 10 mg/mL Capsules: 100 mg, 250 mg Tablet: 300 mg</td>
<td>All ages</td>
<td>&lt; 4 weeks: 4 mg/kg/dose twice daily 4 weeks to 13 years: 180–240 mg/m²/dose twice daily Maximum dose: ≥ 13 years: 300 mg/dose twice daily</td>
<td>Large volume of syrup is not well tolerated in older children. Syrup needs to be stored in glass jars and is light sensitive Can give with food Doses of 600 mg/m²/dose per day required for HIV encephalopathy Capsule can be opened and its contents dispersed, or tablet crushed and its contents mixed with a small amount of water or food and immediately taken (solution is stable at room temperature) Do not use with d4T (antagonistic antiretroviral effect)</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>Oral solution: 10 mg/mL Tablet: 150 mg</td>
<td>All ages</td>
<td>&lt; 30 days: 2 mg/kg/dose twice daily ≥ 30 days or &lt; 60 kg: 4 mg/kg/dose twice daily Maximum dose: &gt; 60 kg: 150 mg/dose twice daily</td>
<td>Well tolerated Can give with food Store solution at room temperature (use within 1 month of opening) Tablet can be crushed and its contents mixed with a small amount of water or food and immediately taken</td>
</tr>
<tr>
<td><strong>Fixed-dose combination of ZDV plus 3TC</strong></td>
<td>No liquid formulation available Tablet: 300 mg ZDV plus 150 mg 3TC</td>
<td>Adolescents and adults</td>
<td>Maximum dose: ≥ 13 years old or weight &gt; 60 kg: 1 tablet per dose twice daily (should not be given if weight is &lt; 30 kg)</td>
<td>Ideally, tablet should not be split Tablet can be crushed and its contents mixed with a small amount of water or food and immediately taken At weights of &lt; 30 kg, ZDV and 3TC cannot be dosed accurately in tablet form</td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>Oral solution: 1 mg/mL Capsules: 15 mg, 20 mg, 30 mg, 40 mg</td>
<td>All ages</td>
<td>&lt; 30 kg: 1 mg/kg/dose twice daily 30–60 kg: 30 mg/dose twice daily Maximum dose: &gt; 60 kg: 40 mg/dose twice daily</td>
<td>Large volume of solution Keep solution refrigerated; it is stable for 30 days, but must be shaken well. It needs to be stored in glass bottles Capsules can be opened and their contents mixed with a small amount of food or water (stable in solution for 24 hours if kept refrigerated) Do not use with ZDV (antagonistic antiretroviral effect)</td>
</tr>
<tr>
<td>Didanosine (ddI, dideoxyinosine)</td>
<td>Oral suspension paediatric powder/ water: 10 mg/mL (in many countries needs to be made up with additional antacid) Chewable tablets: 25 mg, 50 mg, 100 mg, 150 mg, 200 mg Enteric-coated beadlets in capsules: 125 mg, 200 mg, 250 mg, 400 mg</td>
<td>All ages</td>
<td>&lt; 3 months: 50 mg/m²/dose twice daily 3 months to &lt; 13 years: 90–120 mg/m²/dose twice daily or 240 mg/m²/dose once daily Maximum dose: ≥ 13 years or &gt; 60 kg: 200 mg/dose twice daily or 400 mg once daily</td>
<td>Keep suspension refrigerated; it is stable for 30 days, but must be shaken well Administer on an empty stomach, at least 30 minutes before or 2 hours after eating If tablets are dispersed in water, at least 2 appropriate-strength tablets should be dissolved for adequate buffering Enteric-coated beadlets in capsules can be opened and sprinkled on a small amount of food</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Name of drug</th>
<th>Formulation</th>
<th>Age</th>
<th>Age (weight), dose and dose frequency</th>
<th>Other comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abacavir (ABC)</strong></td>
<td>Oral solution: 20 mg/mL; Tablet: 300 mg</td>
<td>Over 3 months</td>
<td>&lt; 16 years or &lt; 37.5 kg: 8 mg/kg/dose twice daily; Maximum dose: &gt; 16 years or ≥ 37.5 kg: 300 mg/dose twice daily</td>
<td>Can give with food; Tablet can be crushed and its contents mixed with a small amount of water or food and immediately ingested; Warn parents about hypersensitivity reaction; ABC should be stopped permanently if a hypersensitivity reaction occurs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Can give with food</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tablet can be crushed and its contents mixed with a small amount of water or food and immediately ingested</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Warn parents about hypersensitivity reaction</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ABC should be stopped permanently if a hypersensitivity reaction occurs</td>
<td></td>
</tr>
<tr>
<td><strong>Non-nucleoside reverse transcriptase inhibitors (NNRTIs)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nevirapine (NVP)</strong></td>
<td>Oral suspension: 10 mg/mL; Tablet: 200 mg</td>
<td>All ages</td>
<td>15–30 days: 5 mg/kg/dose once daily for 2 weeks, then 120 mg/m^2/dose twice daily for 2 weeks, then 200 mg/m^2/dose twice daily; &gt; 30 days to 13 years: 120 mg/m^2/dose once daily for 2 weeks, then 120–200 mg/m^2/dose twice daily; Maximum dose: &gt; 13 yrs: 200 mg/dose once daily for first 2 weeks, then 200 mg/dose twice daily</td>
<td>If rifampicin co-administration, avoid use; Store suspension at room temperature, but it must be shaken well; Can give with food; Tablets are scored and can be divided into two equal halves to give a 100 mg dose; can be crushed and combined with a small amount of water or food and immediately administered; Warn parents about rash; Do not dose escalate if rash occurs (if mild or moderate rash, hold drug; when rash has cleared, restart dosing from beginning of dose escalation; if severe rash, discontinue drug)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>If rifampicin co-administration, avoid use</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Store suspension at room temperature, but it must be shaken well</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Can give with food</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tablets are scored and can be divided into two equal halves to give a 100 mg dose; can be crushed and combined with a small amount of water or food and immediately administered</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Warn parents about rash; Do not dose escalate if rash occurs (if mild or moderate rash, hold drug; when rash has cleared, restart dosing from beginning of dose escalation; if severe rash, discontinue drug)</td>
<td></td>
</tr>
<tr>
<td><strong>Efavirenz (EFV)</strong></td>
<td>Syrup: 30 mg/mL (note that syrup requires higher doses than capsules; see dosing chart); Capsules: 50 mg, 100 mg, 200 mg</td>
<td>Only for children over 3 years of age or who weigh &gt; 10 kg</td>
<td>Capsule (liquid) dose: 10–15 kg: 200 mg (270 mg = 9 mL) once daily; 15–19 kg: 250 mg (300 mg = 10 mL) once daily; 20–24 kg: 300 mg (360 mg = 12 mL) once daily; 25–32 kg: 350 mg (450 mg = 15 mL) once daily; 33–39 kg: 400 mg (510 mg = 17 mL) once daily; Maximum dose: ≥ 40 kg: 600 mg once daily</td>
<td>Capsules may be opened and added to food, but have a very peppery taste; however, can mix with sweet foods or jam to disguise taste; Can give with food (but avoid giving after high-fat meals which increase absorption by 50%); Best given at bedtime, especially in the first 2 weeks, to reduce CNS side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Capsules may be opened and added to food, but have a very peppery taste; however, can mix with sweet foods or jam to disguise taste</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Can give with food (but avoid giving after high-fat meals which increase absorption by 50%); Best given at bedtime, especially in the first 2 weeks, to reduce CNS side effects</td>
<td></td>
</tr>
<tr>
<td><strong>Etravirine</strong></td>
<td>100 mg, 200 mg dispersible tablets</td>
<td>Child over 6 years</td>
<td>16–20 kg, 100 mg twice a day; 21–25 kg, 125 mg twice a day; 26–30 kg, 150 mg twice a day; &gt; 30 kg, 200 mg twice a day; AUC decreased by 50% if taken on an empty stomach</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AUC decreased by 50% if taken on an empty stomach</td>
<td></td>
</tr>
<tr>
<td><strong>Protease inhibitors (PIs)</strong></td>
<td>Powder for oral suspension (mix with liquid; 200 mg per level teaspoon (50 mg per 1.25 mL scoop): 5 mL; Tablet: 250 mg (tablets can be halved; can be crushed and added to food or dissolved in water)</td>
<td>All ages</td>
<td>&lt; 1 year: 50 mg/kg/dose three times daily or 75 mg/kg/dose twice daily; 1 year to &lt; 13 years: 55–65 mg/kg/dose twice daily; Maximum dose: ≥ 13 years: 1250 mg/dose twice daily</td>
<td>Powder is sweet, faintly bitter, but gritty and hard to dissolve; must be reconstituted immediately prior to administration in water, milk, formula, pudding, etc.; do not use acidic food or juice (which increase the bitter taste); solution is stable for 6 hours; Because of difficulties with use of powder, the use of crushed tablets is preferred (even for infants) if the appropriate dose can be given</td>
</tr>
</tbody>
</table>
| | | | Powder is sweet, faintly bitter, but gritty and hard to dissolve; must be reconstituted immediately prior to administration in water, milk, formula, pudding, etc.; do not use acidic food or juice (which increase the bitter taste); solution is stable for 6 hours; Because of difficulties with use of powder, the use of crushed tablets is preferred (even for infants) if the appropriate dose can be given | (continued)
| Name of drug                  | Formulation                                      | Age            | Age (weight), dose and dose frequency                                                                 | Other comments                                                                                             |
|------------------------------|--------------------------------------------------|----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nelfinavir (NFV) (cont.)     | Powder and tablets can be stored at room temperature | > 6 months to 13 years: 225 mg/m² LPV and 57.5 mg/m² ritonavir twice daily, or weight-based dosing as follows: 7–15 kg: 12 mg/kg LPV and 3 mg/kg ritonavir twice daily 16–40 kg: 10 mg/kg lopinavir and 5 mg/kg ritonavir twice daily Maximum dose: > 40 kg: 400 mg LPV and 100 mg ritonavir (3 capsules or 5 mL) twice daily | Preferably oral solution and capsules should be refrigerated; however, they can be stored at room temperature up to 25°C (77°F) for 2 months; at temperatures > 25°C (77°F) the drug degrades more rapidly |
| Lopinavir/ritonavir (LPV/r) | Oral solution: 80 mg/mL lopinavir plus 20 mg/mL ritonavir Note that oral solution contains 42% alcohol Capsules: 133.3 mg lopinavir plus 33.3 mg ritonavir | 6 months or older | > 25 kg | Approved dosing in adults: SQV 1000 mg and RTV 100 mg twice daily There are no data for children For children who weigh > 25 kg, the approved adult dosing can be used If possible, monitoring of SQV level is recommended | Capsules are large Capsules should not be crushed or opened, but must be swallowed whole Should be taken with food |
| Saquinavir/r                  | Soft gel capsule: 200 mg Hard gel capsule: 200 mg, 500 mg | > 25 kg | Approved dosing in adults: SQV 1000 mg and RTV 100 mg twice daily There are no data for children For children who weigh > 25 kg, the approved adult dosing can be used If possible, monitoring of SQV level is recommended | Capsules are large Capsules should not be crushed or opened, but must be swallowed whole Should be taken with food |
| Darunavir plus Ritonavir (RTV)| 75 mg (white), 150 mg (white), 400 mg (light orange), 600 mg (orange) | PI experienced, 3–6 years: 10–11 kg: 200 mg twice a day + RTV 32 mg twice a day 11–12 kg: 220 mg twice daily + RTV 32 mg twice a day 12–13 kg: 240 mg twice a day + RTV 40 mg twice a day 13–14 kg: 260 mg twice a day + RTV 40 mg twice a day 14–15 kg: 280 mg twice a day + RTV 48 mg twice a day 6 years: 15–30 kg: 375 mg twice a day + RTV 50 mg twice a day 31–40 kg: 450 mg twice a day + RTV 60 mg twice a day, > 40 kg: 600 mg twice a day + RTV 100 mg twice a day | DRV and RTV levels reduce in combination |
| Integrase inhibitor          |                                                  |                |                                                                                                           |                                                                                                            |
| Raltegravir                  | 400 mg tablets (pink)                            | > 6 years      | > 25 kg: 400 mg twice a day With or without food Avoid indigestion remedies                                 |                                                                                                            |

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### TABLE 6.2.D.18 Side effects of ARVs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Side effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleoside analogue reverse transcriptase inhibitors (NRTIs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine 3TC</td>
<td>Headache, nausea, abdominal pain, diarrhoea, fatigue, pancreatitis</td>
<td>Well tolerated, can be crushed</td>
</tr>
<tr>
<td>Stavudine d4T</td>
<td>Headache, abdominal pain, neuropathy, pancreatitis, lactic acidosis, hepatitis, lipodystrophy</td>
<td>Large volume of suspension, capsules can be opened</td>
</tr>
<tr>
<td>Zidovudine AZT</td>
<td>Headache, anaemia, neutropenia, nausea, hepatitis, neuropathy, nail pigmentation</td>
<td>Do not use with d4T (antagonistic ARV effect)</td>
</tr>
<tr>
<td>Abacavir ABC</td>
<td>Hypersensitivity reaction, with fever, mucositis and rash; this is rare, but if it occurs stop the drug</td>
<td>Tablets can be crushed</td>
</tr>
<tr>
<td>Didanosine ddI</td>
<td>Peripheral neuropathy, diarrhoea, nausea, abdominal pain, lipodystrophy. Lactic acidosis and pancreatitis (especially with d4T)</td>
<td>On empty stomach, give with antacid</td>
</tr>
<tr>
<td><strong>Non-nucleoside reverse transcriptase inhibitors (NNRTIs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz EVF</td>
<td>Vivid dreams, sleepiness, rash, mood changes, hypercholesterolaemia</td>
<td>Take at night, avoid taking with fatty food</td>
</tr>
<tr>
<td>Nevirapine NVP</td>
<td>Rash (Stevens–Johnson syndrome), liver toxicity (check liver function tests at 2, 4 and 8 weeks)</td>
<td>When given with rifampicin, increase NVP dose by 30% or avoid use</td>
</tr>
<tr>
<td><strong>Protease inhibitors (PIs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopinavir/ritonavir* LPV/r</td>
<td>Diarrhoea, nausea, vomiting, headache</td>
<td>Liquid: bitter taste. Take with food. Take within 2 hours of food</td>
</tr>
<tr>
<td>Darunavir DRV</td>
<td>Rash, nausea, diarrhoea, headache</td>
<td></td>
</tr>
<tr>
<td>Atazanavir ATV</td>
<td>Rash, nausea, jaundice, headache</td>
<td>Avoid antacids</td>
</tr>
<tr>
<td>Ritonavir* RTV</td>
<td>Rash, nausea, diarrhoea, peri-oral paraesthesia, flushing, hepatitis</td>
<td>Liquid: bitter taste</td>
</tr>
<tr>
<td><strong>Integrase inhibitor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raltegravir</td>
<td>Nausea, dizziness, insomnia, rash, pancreatitis, elevated ALT, AST, GGT</td>
<td>Avoid indigestion remedies</td>
</tr>
</tbody>
</table>

*Requires cold storage and cold chain for transport.
### Table 6.2.D.19: Number of tablets of child-friendly solid formulations for twice daily dosage (morning and evening)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Strength of paediatric tablet (mg)</th>
<th>Children aged ≥ 6 weeks</th>
<th>Strength of adult tablet (mg)</th>
<th>Number of tablets by weight-band morning and evening</th>
<th>Number of tablets by weight-band</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Number of tablets by weight-band</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3–5.9 kg</td>
<td>6–9.9 kg</td>
<td>10–13.9 kg</td>
<td>14–19.9 kg</td>
<td>20–24.9 kg</td>
</tr>
<tr>
<td></td>
<td>am pm</td>
<td>am pm</td>
<td>am pm</td>
<td>am pm</td>
<td>am pm</td>
</tr>
<tr>
<td>Single drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZT</td>
<td>60</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
<td>2.5</td>
</tr>
<tr>
<td>ABC</td>
<td>60</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
<td>2.5</td>
</tr>
<tr>
<td>NVP</td>
<td>50</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
<td>2.5</td>
</tr>
<tr>
<td>Ddp</td>
<td>25</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2.5</td>
</tr>
<tr>
<td>Combinations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZT/3TC</td>
<td>60/30</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
<td>2.5</td>
</tr>
<tr>
<td>AZT/3TC/NVP</td>
<td>60/30/50</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
<td>2.5</td>
</tr>
<tr>
<td>ABC/AZT/3TC</td>
<td>60/60/30</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
<td>2.5</td>
</tr>
<tr>
<td>ABC/3TC</td>
<td>60/30</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
<td>2.5</td>
</tr>
<tr>
<td>d4T/3TC</td>
<td>6/30</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
<td>2.5</td>
</tr>
<tr>
<td>d4T/3TC/NVP</td>
<td>6/30/50</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
<td>2.5</td>
</tr>
<tr>
<td>LPWrc</td>
<td>100/25</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>2</td>
</tr>
</tbody>
</table>
* This dose of Ddp is only approximate for children aged 3 months or older and weighing between 6 kg and 6.9 kg.
* See ABC/3TC FDC dosing table.
* Higher doses of LPWrc may be required when co-administered with enzyme-inducing drugs such as NVP, EFV, fos-amprenavir (FPV) and rifampicin.

### Table 6.2.D.20: Number of tablets or capsules of child-friendly solid formulations for once-daily dosage

<table>
<thead>
<tr>
<th>Drug</th>
<th>Strength of tablet or capsule (mg)</th>
<th>Number of tablets or capsules by weight-band once daily</th>
<th>Strength of tablet or capsule (mg)</th>
<th>Number of tablets or capsules by weight-band once daily</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3–5.9 kg</td>
<td>6–9.9 kg</td>
<td>10–13.9 kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Once daily</td>
<td>Once daily</td>
<td>Once daily</td>
</tr>
<tr>
<td>Single drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EFVa</td>
<td>200 mg</td>
<td>NR</td>
<td>NR</td>
<td>1</td>
</tr>
<tr>
<td>Ddpb</td>
<td>125 mg or 200 mg EC</td>
<td>NR</td>
<td>NR</td>
<td>1 (125 mg)</td>
</tr>
</tbody>
</table>
* EFV is not recommended for children under 3 years and weighing less than 10 kg.
* Ddp EC is not recommended for children weighing less than 10 kg.
* NR, not recommended; EC, enteric coated.

**Further reading**

6.2.E Measles

BOX 6.2.E.1 Minimum standards
- Immunisation.
- Vitamin A.
- Oral rehydration solution and nutritional provision.
- Antibiotics for secondary infection.
- Oxygen.
- Nebulised adrenaline and corticosteroids for croup.
- Eye pads.
- Public health measures.

Introduction
Measles is an acute viral disease characterised by fever, cough, coryza, conjunctivitis, an erythematous maculopapular rash, and typical oral lesions (Koplik’s spots). It is caused by an RNA virus, a member of the genus Morbillivirus in the Paramyxoviridae family. Humans are the only natural hosts. It is transmitted by direct contact with infectious droplets or, less commonly, by airborne spread. It has a high incidence in winter. Measles is one of the most highly communicable of all infectious diseases.

Measles occurs worldwide, and is a significant cause of morbidity and mortality worldwide. It is the fifth most common cause of death in children under 5 years of age. There has been a 78% reduction in measles mortality worldwide in recent years, largely as a result of immunisation, from 733,000 deaths in 2000 to 164,000 in 2008, and a reduction in the total number of cases from 39.9 to 20 million.

Epidemiology
- Measles is transmitted by droplet spread of virus in nasopharyngeal secretions. It is most infectious before the appearance of rash, and for at least 7 days after the onset of the first symptoms. The incubation period is 10–12 days. Quarantine can be lifted 2 days after the fever subsides.
- Epidemic cycles of infection in urban areas may occur every 2 years. In isolated communities, all age groups are affected. In resource-limited countries, the population peak incidence is at 1–2 years, with a mortality of 1–5%, although during epidemics it may rise to 30%. Mortality is low in the well nourished. Children who acquire infection in overcrowded conditions tend to have more severe disease, probably due to a larger infecting dose of the virus.
- Pneumonia and upper airway obstruction account for about 75% of measles deaths. Measles is more severe in HIV-infected children.
- In resource-limited countries, measles commonly occurs in previously vaccinated children. This is partly explained by a persistent maternal antibody at 9 months of age when vaccine is usually given, and also a relatively poor efficacy of the vaccine and waning immunity.
- It rarely occurs in infants under 3 months of age because of maternal immunity transferred in utero.

Clinical features
Prodromal period (3–5 days): acute coryza-like illness with high-grade fever, cough and conjunctivitis. Febrile seizures may occur. Koplik’s spots (tiny bluish-white specks on a red base on the buccal mucosa of the cheeks, resembling grains of salt) appear by days 2–4.

A maculopapular rash commences on day 4 on the face and neck, behind the ears and along the hairline, and spreads to become generalised and reaches the feet after 3 more days. Fades after 5–6 days in order of appearance, developing a brownish colour and often becoming scaly. If severe, there may be petechiae and ecchymoses. The rash is due to infiltration of lymphocytes into areas of virus replication in skin.

Persistence of fever beyond day 3 of the rash is usually due to complications (see below).

Diagnosis
This is mostly clinical (diagnosis is based on the specific pattern of rash, history of contact with a measles patient, and Koplik’s spots). Serology, viral culture or PCR may be used to confirm it.

Laboratory findings
Leukopenia and thrombocytopenia may be observed during measles infection. Chest radiography may demonstrate interstitial pneumonitis.

Complications
Recovery following acute measles may be delayed for weeks or months due to failure to thrive, recurrent infections, persistent pneumonia and diarrhoea.

Pneumonia (see Section 5.3.A)
- Bacterial pneumonia usually occurs during convalescence and after several days of an afebrile period. It is the most frequent cause of death with an incidence of 10–25% of hospitalised cases in developing countries.
- Viral pneumonia occurs during the acute phase of measles, and may progress to giant-cell pneumonia in the immunosuppressed (e.g. leukaemia, HIV).
- Mediastinal emphysema occurs in 1 in 300 measles cases, and may lead to subcutaneous emphysema.

Diarrhoea
Incidence 20–40%. May become persistent and frequently precipitates malnutrition (see Section 5.12.A).

Tracheobronchitis
This presents as croup. Laryngeal tissue sometimes becomes necrotic, which may lead to laryngeal obstruction (see Section 5.1.A).

Otitis media
This is common, especially in infants. Mastoiditis may develop. It is an important cause of chronic otitis media and hearing impairment (see Section 5.1.C).

Stomatitis
There is mucosal inflammation and ulceration with bleeding gums and secondary Candida albicans and herpes simplex infections. Stomatitis causes difficulty in eating and worsens malnutrition. Cancrum oris (noma) may develop.
**Xerophthalmia**
Vitamin A deficiency may combine with measles to precipitate xerophthalmia and blindness (see Section 5.10.A).

**Malnutrition**
Malnutrition secondary to measles results from anorexia and poor nutrition following infection. Mortality is high (> 15%) (see Section 5.10.B).

**Tuberculosis**
Tuberculosis, including tuberculous meningitis, may first be noticed in the post-measles period (see Section 6.1.N).

**Encephalitis**
- Acute allergic encephalitis: this is a demyelinating disorder and the most common CNS complication of measles. Onset is often in the second week as exanthema is clearing. It occurs in one or two per 1000 cases of measles, and can be fatal. Virus is not found in the brain.
- Acute measles inclusion-body encephalitis: this results from direct invasion of brain cells by virus (which may be isolated from CSF). There is a more rapid onset if there is immunosuppression or malignancy.
- Subacute sclerosing panencephalitis (SSPE): there is a long latent period (several years) between infection and the onset of symptoms. Commonly, measles occurred at an early age. SSPE is characterised by lethargy, psychological changes, myoclonic jerks and mental deterioration, eventually leading to death. Virus has been isolated from brain biopsy specimens.
- Atypical measles may have prolonged fever and present with pneumonia or rarely encephalitis. Rash may or may not appear. Prolonged fever for 2–3 weeks with diarrhoea may simulate enteric fever.

**Differential diagnosis**
- Other exanthema and drug reactions.
- Koplik’s spots are the most helpful diagnostic feature in the prodromal period.

**Case assessment and classification**
Cases may be classified into:
- uncomplicated measles
- severe measles requiring treatment or urgent referral.

**TABLE 6.2.E.1 Clinical features of severe disease**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough, tachypnoea or indrawing</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Stridor when quiet</td>
<td>Croup, necrotising tracheitis</td>
</tr>
<tr>
<td>Severe diarrhoea</td>
<td>Dehydration</td>
</tr>
<tr>
<td>Recent severe weight loss</td>
<td>Malnutrition</td>
</tr>
<tr>
<td>Corneal damage or Bitot spots</td>
<td>Blindness</td>
</tr>
<tr>
<td>Ear discharge</td>
<td>Otitis media, deafness</td>
</tr>
<tr>
<td>Lethargy, convulsions</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>Inability to drink or eat</td>
<td>Dehydration, malnutrition</td>
</tr>
<tr>
<td>Blood in the stools</td>
<td>Dysesthesy, haemorrhagic measles</td>
</tr>
<tr>
<td>Severe stomatitis</td>
<td>Cancrum oris</td>
</tr>
</tbody>
</table>

**Danger signs**
These include the following:
- breathing difficulty
- cyanosis
- bleeding
- corneal/mouth ulcers
- coma/lethargy
- seizures
- inability to eat or drink.

**Management**

**Mild measles**
- Give small frequent feeds. Infants should continue breastfeeding. Extra energy should be provided by adding vegetable oil or sugar to cereals (1 teaspoon of each). Follow-up nutritional support is needed.
- Give paracetamol for temperature > 39°C. Saline drops for blocked nose.
- Maintain oral hygiene by rinsing the mouth several times daily. Apply 1% gentian violet to mouth sores. Treat oral thrush with nystatin drops.
- If mouth ulcers are secondarily infected, give an antibiotic (penicillin or metronidazole orally for 5 days).
- If the mouth is too sore to feed or drink, a nasogastric tube may be required.
- Maintain ocular hygiene for purulent conjunctivitis, with daily washings with sterile 0.9% saline or boiled water (using cotton-wool swabs) and the application of tetracycline eye ointment three times daily. **Never use topical steroids.** Consider using protective eye pads.
- **Vitamin A treatment** of children with measles in developing countries has been associated with decreased morbidity and mortality rates. The dose is 100000 IU as a capsule (in children under 1 year old) or 200000 IU (in those over 1 year old). **Give a second capsule the next day.**
- Give oral rehydration solution (ORS) for diarrhoea.
- Give an oral antibiotic (co-trimoxazole, amoxicillin, ampicillin) if there is a clear indication of lower respiratory tract infection (see Section 5.3.A).
- Admit the child to hospital if they show signs or symptoms of severe measles.

**Severe measles**
Admit the child to hospital and isolate them. Airborne transmission precautions are indicated for 4 days after the onset of rash in otherwise healthy children, and for the duration of illness in immunocompromised patients.

In addition to the care for mild measles described above:
- Give parenteral antibiotics for pneumonia or septicaemia (e.g. benzylpenicillin or ceftriaxone/cefotaxime if available). Give (flu)cloxacillin plus gentamicin or cefuroxime (if available) if *Staphylococcus aureus* is suspected. If stridor associated with fever is present use ceftriaxone/cefotaxime (if available) or chloramphenicol. Rapidly spreading pulmonary tuberculosis may be difficult to distinguish from a progressive pyogenic pneumonia.
- Give oxygen as required to keep SpO₂ ≥ 94%.
- Croup: nebulised adrenaline, 1 mL adrenaline (1 in 1000) mixed with 1 mL of saline every 2 hours, **careful observation** (see Section 5.1.A, which also describes the use of oral steroids or nebulised budesonide, either of which can be life-saving in this situation).
- Diarrhoea: give oral rehydration and appropriate treatment.
antibiotic if the child passes bloody stools. Persistent diarrhoea requires nutritional support.

- Otitis media: give antibiotics and maintain regular aural hygiene. Screen for hearing impairment during follow-up.
- Xerophthalmia: use protective eye pads, and give vitamin A capsules (see above).
- Malnutrition: treat according to management guidelines (see Section 5.10.B).
- Encephalopathy: follow the management guidelines for coma and convulsions (see Section 5.16.A and Section 5.16.E).

Prevention and follow-up

- Give ‘normal immunoglobulin’ (if available) for susceptible immunocompromised contacts of measles cases or those under 1 year old. It is given intramuscularly to prevent or modify measles in a susceptible child within 6 days of exposure. The usual recommended dose is 0.25 mL/kg given intramuscularly; immunocompromised children (e.g. those with HIV) should receive 0.5 mL/kg intramuscularly (the maximum dose is 15 mL).
- Improve vaccination coverage (see Section 1.17).
- Give a follow-up vitamin A dose (after 2 weeks) if the child is malnourished or has an eye disorder.
- Measles control by immunisation is one of the most important public health interventions in reducing child mortality. If a child with measles is admitted, immunise all other unimmunised children under 6 months of age in the hospital, with a follow-up second dose in all aged 6–9 months as soon after 9 months as possible. A second dose is given at 12–15 months of age.

6.2.F Mumps

**BOX 6.2.F.1 Minimum standards**

Measles, mumps, rubella (MMR) vaccination two-dose schedule.

**Introduction**

Mumps is a systemic disease characterised by swelling of one or more of the salivary glands, usually the parotid glands. It is caused by a virus of the paramyxovirus family (which also includes measles and parainfluenza). The virus is spread by airborne droplets through the respiratory tract, mouth and possibly the conjunctivae and urine, and is present in saliva, CSF, blood and urine. Other viruses and bacteria (cytomegalovirus, parainfluenza virus types 1 and 3, influenza A virus, coxsackieviruses and other enteroviruses, human immunodeficiency virus (HIV), *Staphylococcus aureus* and non-tuberculous *Mycobacterium*) may also cause parotitis.

**Clinical presentation**

- The incubation period is 14–24 days. Onset is with painful swelling of parotid glands, fever, general malaise, and occasionally headache. Parotid swelling may be unilateral at first, followed a couple of days later by swelling of the opposite parotid gland, with pain on opening the dry mouth.
- Mild meningoencephalitis is common and usually neither serious nor recognised clinically. There may be nausea and vomiting, and abdominal pain.
- Orchitis presents with fever and tender oedematous swelling of the testis. In 10–20% of cases the second testicle may be affected. However, infertility is rare.
- Differential diagnosis of parotitis includes cervical adenitis, pyogenic parotitis, recurrent parotitis, tumours of the parotid and tooth infections.

- Mumps orchitis can mimic hernias, tumours, haematomas, epididymo-orchitis and testicular torsion.

**Complications**

Complications include oophoritis, mastitis, pancreatitis, nephritis, myocarditis, thyroiditis, labyrinthine disturbance, painful swelling of the lacrimal glands, optic neuritis, uveokeratitis, rapid loss of vision, arthritis, jaundice, pneumonia and thrombocytopenia. Transient or permanent unilateral nerve deafness has been reported. Infection during pregnancy very rarely causes disease of the fetus (e.g. aqueductal stenosis, hydrocephalus).

**Management**

Symptomatic treatment includes analgesics, fluids, and scrotal support for orchitis. Antibiotics are usually not warranted for the uncomplicated disease, but each complication should be treated on its own merits with antibiotics (in the case of pneumonia or wherever a secondary bacterial infection is suspected), or with appropriate local treatment and monitoring. The value of corticosteroids for orchitis is not established.

**Prevention**

Measles, mumps, rubella (MMR) immunisation is routine in well-resourced countries, and has reduced mumps by over 90%. The recommended two-dose vaccine schedule has an effectiveness of approximately 90% (range 88–95%).
6.2.G Poliomyelitis

**Introduction**

Poliomyelitis is caused by polioviruses type 1, 2 and 3, which are ingested and then multiply in the tonsils and Peyer’s patches of the gut. In most cases, infection is contained at this point and the child is asymptomatic.

Due to both vertical and mass vaccination campaigns, the number of reported cases has fallen by 90% since 1988. Wild poliovirus is now mainly found in Afghanistan and a few countries in sub-Saharan Africa.

**Severity**

**Minor illness**

This is associated with viraemia and non-specific symptoms, such as nausea, vomiting, abdominal pain and sore throat.

**Major illness**

**Non-paralytic poliomyelitis**

This occurs in a minority of symptomatic children. Incubation period is 10–14 days and symptoms include: fever, headache and two to five days later, signs of meningeal irritation with severe pain and stiffness of neck, back and limbs.

**Paralytic poliomyelitis**

- Paralysis occurs within the first 2 days of major illness.
- It can affect any muscles, but particularly large ones and those of the lower limbs.
- Asymmetrical paralysis, flaccid muscles and absent tendon reflexes are characteristic. There is intact sensation. Paralysis is maximal within 3–5 days of onset, and rarely extends once the temperature has settled.
- In bulbar form, the involvement of cranial nerve nuclei and vital centres in the brainstem results in paralysis of the facial, pharyngeal, laryngeal and tongue muscles, causing swallowing difficulties, aspiration and respiratory failure.
- Hypertension may occur, as well as transient bladder paralysis.

**Diagnosis**

CSF initially shows neutrophil predominance, but after 5–7 days is mainly lymphocytic. CSF protein levels are normal or slightly elevated. CSF glucose levels are normal. Virus can be isolated from throat and stool for up to 3 months after onset. The differential diagnosis includes other causes of acute flaccid paralysis (see Section 5.16.F).

**Prognosis**

- This depends on the extent of paralysis and the quality of care during the acute phase.
- Early identification of and intervention for respiratory and bulbar paralysis will reduce mortality to 5–10%.
- With appropriate physiotherapy, improvement in the function of paralysed muscles can occur for up to 18 months.
- Factors that adversely affect outcome include intramuscular injections, muscle fatigue, corticosteroid therapy and immunocompromised states. Removal of tonsils or teeth during the incubation period increases the risk of bulbar paralysis.

**Management**

**Acute phase**

- Absolute bed rest is mandatory. Avoid intramuscular injections and exercise.
- Analgesics should be given for severe pain. Keep paralysed muscles in a neutral position to prevent contractures.
- Gentle passive exercises and warm compresses should be used to help to relieve pain. Active exercises are introduced a few days after the temperature has settled.
- Respiratory paralysis requires ventilatory support (if available) (see Sections 1.25 and 8.3).
- Bulbar paralysis requires nasogastric tube feeding and, to protect the airway, may require tracheostomy.

**Convalescent phase**

- Aim to improve motor function, prevent deformities and generally reintegrate the child into society.
- Encourage active participation by the parents in the rehabilitation process. The educational and emotional needs of the child must not be neglected. The services of an orthopaedic surgeon and an orthoptist may be required.
- See Sections 4.2.C, 4.2.D and 4.2.E for further information on the long-term care of children with a disability.

**Prevention**

See Section 1.17 on immunisation.
Rabies encephalitis
Furious and paralytic (dumb) forms of human rabies can occur. Furious rabies is characterised by agitation, hyperexcitability and hydrophobia, which is due to spasms of the inspiratory muscles, accompanied by an inexplicable feeling of terror. Spasms occur on attempting to drink water or from a draught of air. Flaccid paralysis without hydrophobia occurs in some patients, but this paralytic rabies is rarely recognised. It is likely to be misdiagnosed as another encephalitis or cerebral malaria. Once symptoms of encephalitis have begun there is no treatment. The disease is always fatal in Asia, Africa and Europe. A very few patients have survived infection after contact with bats in the Americas. North and South American bat rabies viruses appear to be less pathogenic.

Management
The treatment of established rabies is palliative. Sedatives (e.g. diazepam, midazolam) and strong analgesics (e.g. morphine) may be given parenterally to control symptoms and relieve anxiety. An IV infusion assuages the feeling of thirst. Relatives and staff should wear gloves when handling the child, their vomitus or their saliva. Close attendants are at risk of exposure to the virus, but there is no documented case of transmission of rabies to a carer. However, if antirabies vaccine is available it should be offered to them, but rabies immunoglobulin (RIG) is not needed.

Rabies prophylaxis
Dog bites are the usual cause of rabies in humans, but cats, foxes, bats, jackals, wolves, mongooses and domestic mammals may also transmit the infection.

Estimating the risk of exposure to rabies
1. Is there a bite wound with broken skin? Have mucous membranes or an existing skin lesion been contaminated by virus in the animal’s saliva? Intact skin is a barrier against the virus.
2. How did the animal behave? An unprovoked attack by a frantic dog is a high risk, but so is contact with a paralysed animal, or an unusually tame wild mammal.
3. Is rabies known to occur in the biting animal species?
4. Regularly vaccinated animals are unlikely to be rabid, but vaccinated dogs or cats can transmit the infection.
5. Try to have the animal’s brain examined for rabies. If this is not possible, the animal may be kept under safe observation, but post-exposure treatment must not be delayed. If the animal is still healthy after 10 days, vaccine treatment of the patient can be stopped.

Post-exposure treatment
Table 6.2.H.1 lists the criteria for initiating treatment. All three parts of post-exposure therapy are always urgent. The aim is to chemically kill or neutralise the rabies virus at the wound site before it can enter a nerve ending and travel to the brain. Neutralising antibody is provided by local injection of rabies immunoglobulin, or it may be present already in previously vaccinated individuals.

1. Wound care: this is important for all bites, irrespective of the rabies risk.
2. Rabies vaccine (active immunisation).
3. Rabies immunoglobulin (RIG) is passive immunisation which provides antibody locally for the first week, until the vaccine-induced antibody appears.

Wound care
- Scrub and flush the lesion repeatedly and energetically with soap or detergent and water. Remove any foreign material. Local anaesthesia may be necessary.
- Apply povidone iodine (or 70% ethyl alcohol, but this is painful).
- Do not suture the wound, or at least delay suturing.
- Give tetanus immunisation if appropriate.
- Treat bacterial infection of wounds with an oral antibiotic, such as amoxicillin/clavulanic acid or tetracycline.

Rabies vaccine
Active immunisation with vaccine should be given whenever there is a risk from contact with a suspect rabid animal. Rabies vaccines are suitable for people of all ages, including pregnant women.

Vaccines accredited by the WHO include the following:
- Purified chick embryo cell vaccine (PCEC) (Rabipur®, RabAvert®) (1.0 mL/ampoule).
- Purified vero cell vaccine (PVRV) (Verorab®) (0.5 mL/ampoule).
- Purified duck embryo vaccine (PDEV) (Vaxirab®) (1.0 mL/ampoule).
- Human diploid cell vaccine (HDCV) by Sanofi (1.0 mL/ampoule).

These vaccines are interchangeable, so a change may be made to a different vaccine during a course of treatment. The side effects of these vaccines are mild local or non-specific generalised symptoms. Transient maculopapular or urticarial rashes are occasionally seen.

Other vaccines
1. Tissue culture rabies vaccines not listed above should be used according to the manufacturer’s instructions.
2. Vaccines of nervous tissue origin (e.g. Semple vaccine and suckling mouse brain vaccine) should only be used if no other vaccine is available.

Three post-exposure regimens (see Table 6.2.H.2)

Standard five-dose intramuscular (IM) ‘Essen’ regimen
- Days 0, 3, 7, 14 and 28: Inject one IM dose (1 mL or 0.5 mL) into the deltoid or ante-ro-lateral thigh in small children. Do not inject into the gluteal region.

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6.2.H Rabies management and prevention after animal bites

Box 6.2.H.1 Minimum standards
- Palliative care, including morphine.
- Wound care.
- Rabies vaccine.
- Rabies immunoglobulin.
Economical four-site intradermal (ID) regimen
The intradermal dose is 0.1 mL per site for vaccines containing 0.5 mL/ampoule (e.g. Verorab®), and 0.2 mL per site for vaccines containing 1 mL/ampoule (e.g. Rabipur®).
- Day 0: draw up a whole ampoule of vaccine into a 1-mL (Mantoux-type) syringe. Give intradermal injections at four sites (deltoid, and either thigh or suprascapular areas) using all of the vaccine.
- Day 7: give an intradermal dose (0.1 mL or 0.2 mL) at two sites (deltoid areas).
- Day 28: give one intradermal dose.

Practical points
- Intradermal injections should raise a papule as with BCG vaccine.
- Inject using strict aseptic precautions. If ampoules are shared, use a new sterile needle and syringe for each patient. If there is difficulty in injecting 0.2 mL intradermally, withdraw the needle and inject the remainder at an adjacent site.
- Do not waste vaccine. Ampoules shared between patients must be stored at 5°C and used on the same day.
- If few patients are treated, on day 0 ask the patient to bring their relatives and friends for pre-exposure vaccine on day 7.
- If vaccine is very scarce or unaffordable, and 1-mL vaccines (e.g. Rabipur®) are used, half the dose (i.e. 0.1 mL per intradermal site) may be used.
- The timing of the final dose can be varied for economy. A clinic could assign 1 or 2 days a week for intradermal rabies vaccination for the day 28 doses and pre-exposure immunisation (see below).
- This is the most economical rabies post-exposure regimen both for the healthcare provider and for the patient.
- This regimen is as immunogenic as IM vaccination, and may become the treatment of choice in Asia and Africa.

Economical two-site ID regimen
The intradermal dose is 0.1 mL per site for vaccines containing 0.5 mL/ampoule (e.g. Verorab®). The equivalent dose is 0.2 mL for vaccines containing 1 mL (e.g. Rabipur®), but half the dose (i.e. 0.1 mL per site) is used.
- Days 0, 3, 7 and 28: give an intradermal dose at two sites (deltoids).

The same precautions for intradermal use as described above apply. This regimen is less economical if few patients are being treated. It has mainly been used in large clinics.

Rabies immunoglobulin (RIG)
- Passive immunisation with RIG is recommended to accompany vaccine following contact with suspected rabid animals where the skin has been broken or mucous membranes have been contaminated (see Table 6.2.H.2).
- It is vital for bites with a high risk of infection (on the head, neck or hands) or for multiple bites.
- If supplies are limited, ensure that the high-risk, severely exposed patients have access to RIG.
- If RIG is not available immediately, it should be given up to 7 days after the first dose of vaccine. After that it is no longer needed.
- RIG is not required if a course of vaccine has been completed previously.

Dosage: equine RIG (40 IU/kg) or human RIG (20 IU/kg) is infiltrated into and around the wound on day 0. If this is not anatomically possible (e.g. on a finger), inject any remainder IM, at a site remote from the vaccine site, but not into the gluteal region.
- Skin tests are not useful for predicting anaphylactoid reactions to equine RIG, and should not be used.
- If in very rare cases there may be anaphylaxis.

Anaphylaxis treatment (see also Section 5.1.B)
Adrenaline (epinephrine) intramuscular treatment is essential.
Dosage:
- Age < 6 years: 150 micrograms or 0.15 mL of 1:1000 (1 mg/mL).
- Age 6–12 years: 300 micrograms or 0.3 mL of 1:1000.
- Age > 12 years: 500 micrograms or 0.5 mL of 1:1000.

The dose can be repeated at 5-minute intervals if necessary. In addition, if available give the following: Chlorpheniramine maleate IM or by slow IV infusion
Dosage:
- Age 6 months to 6 years: 2.5 mg.
- Age 6–12 years: 5 mg.
- Age > 12 years: 10 mg.

Hydrocortisone sodium succinate by slow IV infusion or IM
Dosage:
- Age 1–5 years: 50 mg.
- Age 6–12 years: 100 mg.
- Age > 12 years: 200 mg.

Post-exposure treatment for previously vaccinated adults
Thorough wound care and vaccine treatment are always urgent following possible exposure to a rabid animal. Patients who have previously had a complete pre-exposure (three doses) or post-exposure course of vaccine only require a short booster course, and RIG is not necessary.

Two post-exposure booster regimens (see Table 6.2.H.2)

Standard two-dose IM regimen
- Days 0 and 3: inject one IM vaccine dose.

Economical single-day four-site ID regimen
- Day 0: Give 0.1 mL intradermal injections at four sites (deltoids, and either thigh or suprascapular areas).
- The intradermal dose is 0.1 mL, which is sufficient for vaccines of any volume. For Verorab® (0.5 mL/ampoule) a whole ampoule is used.
- For 1 mL vaccines, the total dose is half an ampoule. Do not waste vaccine. Ampoules may be shared between patients or used as pre-exposure prophylaxis for relatives, hospital staff, etc. on the same day. See above for precautions when sharing ampoules. If the ampoule cannot be shared, give the whole 1 mL to the patient at four sites, as for the primary four-site intradermal regimen described above.
Pre-exposure treatment

Pre-exposure vaccination is the best means of rabies prophylaxis. No one who has had pre-exposure treatment and a post-exposure booster injection is known to have died of rabies.

Indications for pre-exposure rabies prophylaxis

People working with dogs, bats or other wild mammals should be immunised. Anyone in an area where dog rabies is enzootic is at risk of infection, especially children. Ideally, rabies should be included as part of the routine Expanded Programme on Immunisation (EPI). Pre-exposure vaccine should be given whenever it is affordable to residents of dog rabies areas, and should be strongly encouraged if RIG may not be available locally.

Pre-exposure three-dose regimen (see Table 6.2.H.2)

Days 0, 7 and 28: Inject one dose of a vaccine IM (1 ampoule) or intradermally (0.1 mL). Variation in timing does not matter. The final dose may be given from day 21 to months later, but aim for a total of three doses. Having had one or two doses is still an advantage if the individual is exposed to rabies in the future, especially if RIG may not be available locally.

- Patients on chloroquine, steroids or other immunosuppressive drugs should have IM not intradermal injections for pre-exposure treatment.
- Patients who have been vaccinated should keep a record of their immunisations.
- Routine booster doses are only recommended for people at high occupational risk of exposure.
- If contact with a rabid animal occurs, post-exposure booster vaccine treatment is still required.

Summary

- The only treatment for rabies encephalitis is palliative care.
- Rabies can be prevented by education about the dangers of animal contact, the need for vaccination of pets, first-aid cleaning of wounds with soap, and the need to attend a clinic for vaccine.
- Pre-exposure vaccination should be encouraged, especially for children and if RIG is not available locally.
- Post-exposure prophylaxis is urgent.
- If rabies vaccine is unaffordable or in short supply use robust economical ID regimens that are suitable for use globally.

This scheme is a modification of WHO recommendations.

<table>
<thead>
<tr>
<th>Type of exposure</th>
<th>Criteria Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>No exposure*</td>
<td>Touching animals, or being licked on intact skin No treatment</td>
</tr>
<tr>
<td>Minor exposure, WHO Category II</td>
<td>Nibbling (tooth contact) with uncovered skin, or minor scratches or abrasions without bleeding Start vaccine immediately</td>
</tr>
<tr>
<td>Major exposure, WHO Category III</td>
<td>Single or multiple bites or scratches that break the skin, or licking on broken skin, or licking or saliva on mucosae, or physical contact with bats Immediate rabies immunoglobulin and vaccine</td>
</tr>
<tr>
<td>Severe exposure, WHO Category III</td>
<td>Bites on the head, neck or hands, or multiple bites Immediate rabies immunoglobulin is mandatory with vaccine</td>
</tr>
</tbody>
</table>

For all cases:
- Stop treatment if the dog or cat remains healthy for 10 days.
- Stop treatment if the animal’s brain is shown to be negative for rabies by appropriate investigation.

*The confusing term ‘WHO Category I’ should be avoided, as misunderstanding leads to unnecessary treatment.

Pre-exposure:

<table>
<thead>
<tr>
<th>Vaccine regimen and route</th>
<th>Days of injection (number of sites injected denoted by superscript number)</th>
<th>Visits to clinic</th>
<th>Total vaccine used (ampoules)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>ID 0.1 mL†</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Post-exposure (+ RIG day 0):</td>
<td>0</td>
<td>3</td>
<td>1 (or &lt; 1)*</td>
</tr>
<tr>
<td>IM four-site†</td>
<td>04</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Post-exposure booster if previous vaccine course:</td>
<td>04</td>
<td>1</td>
<td>1 (or &lt; 1)*</td>
</tr>
</tbody>
</table>

IM, intramuscular; ID, intradermal.

* 0.1 mL/site, whole ampoule used for 0.5 mL vaccines. For 1 mL ampoules share between two, or alternatively use the whole dose to avoid wastage.

† Intradermal doses are 0.1 mL/site for PVRV vaccine (0.5 mL/ampoule) or the equivalent dose, 0.2 mL/site of injection, for PCECV vaccine (1.0 mL/ampoule).

‡ Intradermal doses are all 0.1 mL/site of injection.
Introduction

Viral haemorrhagic fevers (VHFs) are a group of severe infections caused by viruses that normally affect animals. Human infection is characterised by high fever and, in a proportion of cases, haemorrhage. Animal hosts such as rodents are usually asymptomatic and are often infected with virus from birth, excreting it in urine or body fluids throughout life.

In primary cases, transmission to humans occurs by a variety of routes, such as food contaminated with urine (e.g. Lassa, Junin, Machupo and Hantaan fevers) via arthropod vectors such as ticks (e.g. Crimean-Congo and Omsk fevers) or mosquitoes (e.g. Rift Valley fever). The hosts for Ebola and Marburg haemorrhagic fevers are not yet known.

Humans with disease are usually highly infectious. Most VHFs cause severe disease with a high mortality, especially following human-to-human spread (secondary cases). Some (e.g. Lassa fever) may also cause asymptomatic or mild illness.

Symptomatic disease is commonly mistaken for other febrile illnesses, typically malaria, typhoid fever or Shigella dysentery, which fail to respond to treatment. Individual VHFs are geographically restricted in distribution. As with all geographical illnesses, clinicians only need to know of those present in the local area. VHFs are fortunately rare.

Lassa fever

- Distribution: West Africa (Nigeria, Sierra Leone, Liberia and Guinea).
- Host: Mastomys rat (habitat is rural).
- Transmission:
  - Primary: mainly from contact with host (rat) urine. Food may be contaminated.
  - Secondary: transmission from patient to carer, or to hospital and laboratory staff is common, particularly from haemorrhagic cases. Maternal illness is particularly severe, with a high risk of vertical transmission to the baby (which is invariably fatal).

Prevalence

This disease is relatively common. Most primary human infections are not severe, and many are subclinical. Childhood seroprevalence in Sierra Leone can be as high as 20% in some rural villages. Outbreaks may occur in displaced communities or when humans enter host habitat.

Clinical features

- High fever (>39°C) with cough and vomiting in 65% of hospital cases.
- Abdominal pain and diarrhoea are common (around 35% of cases).
- In children, wheeze and pleural effusions are more frequent than in adults.
- Sore throat and pharyngeal ulcers occur less frequently in children than in adults, but are highly suggestive of Lassa fever.
- In children, oedema (especially of the face) and overt bleeding are seen in 10% of cases, and in a febrile child from an appropriate area should suggest Lassa fever.
- At the epicentre of the transmission area, Lassa fever is a common cause of a febrile child with convulsions.

Diagnosis of Lassa fever

Clinical case diagnosis

- An unexplained febrile illness compatible with Lassa fever, in a child from an area of known transmission, with no response of either fever or illness to an antimalarial drug plus a broad-spectrum antibiotic (e.g. chloramphenicol).
- Note that malaria parasitaemia in an area of endemic malaria transmission is not sufficient to exclude other causes of fever (e.g. VHF) as the cause of a febrile illness, as many adults and older children may have coincidental asymptomatic malaria parasitaemia as the cause of a febrile illness.

Supportive indirect laboratory tests

- Raised liver transaminases (AST/SGOT) (in adults this reflects a poorer prognosis).
- Low initial white blood cell counts, but often a normal platelet count.

Confirmation of diagnosis

- Positive specific IgM serology (on admission only 50% of cases are positive).
- Rising IgG titres to Lassa on acute and convalescent serum.
- Isolation of virus: this is rarely appropriate and, due to the high risks of laboratory infection, samples should not be taken without senior expert advice.
- Samples must be marked as high infection risk, ideally with standard yellow hazard tape, and sent in two sealed plastic bags. Samples should only be taken if laboratory staff are aware of the potential risks, and are able to take the necessary precautions to handle such specimens safely. The laboratory should be informed that the specimen has been sent.

Management

- Appropriate symptomatic management of fever, distress and pain.
- Fluid and nutritional requirements.
- Supportive care includes oxygen (if hypoxic) and initial IV volume replacement if the patient is hypovolaemic (see Section 5.5).
- Blood transfusion may be required for a falling PCV or haemorrhage. Fresh-frozen plasma (FFP) may not be of benefit, as inhibitors of clotting factors may cause bleeding.
- Early ribavirin can improve the prognosis in severe disease, but is very expensive.
Infection control
See below and Section 1.2.

Ebola
● Distribution: Central Africa (Sudan, Democratic Republic of the Congo, Gabon, Cote d’Ivoire, Uganda) and West Africa (Guinea, Liberia and Sierra Leone).
● Host: the main animal reservoir is unknown.
● Transmission:
  – Primary: infection occurs mainly in adults trekking in tropical Central African forests. Transmission from primates to humans has been recorded.
  – Secondary: patients with advanced disease are viraemic and highly infectious. Once in a human host, transmission to carers, hospital and laboratory staff is frequent (30% of doctors developed Ebola during an outbreak in Kikwit, Democratic Republic of the Congo). However, once effective infection control measures have been implemented, secondary cases are rare.

The disease is invariably severe, with a high death rate, but only 20% of cases in the Democratic Republic of the Congo outbreak were under 15 years of age. Children are at low risk in the community, and boys have half the incidence of girls, possibly because they are less involved in the care of sick adults.

Invariably, in children, there is a history of contact with a primary case, and an outbreak of an illness that could be Ebola is present in the hospital and/or community. Post-mortem transmission does occur, possibly through skin contact.

Prevalence
Prevalence is low: the disease occurs sporadically in well-localised outbreaks.

Clinical disease (data for adults)
● Fever is invariably present, and diarrhoea occurs in 85% of cases. This is bloody in 20% of cases, and can be confused with Shigella dysentery.
● Vomiting and abdominal pain are common (75% of cases).
● Headaches, myalgia or arthralgias are reported in 50% of cases.
● Sore throat occurs in 50% of cases, and is a distinguishing feature, as is conjunctival injection (45%).
● A maculopapular rash, although poorly visible on black African skin, is common.
● Cough occurs in 10% of cases.
● Bleeding is seen in 40% of cases, and is usually either gastrointestinal, oral, at injection sites or as skin petechiae. This is a major diagnostic sign.
● Hospital mortality is around 80%. Recovery starts 2 weeks into the illness.

Diagnosis of Ebola
Clinical diagnosis
● Suspected clinical case (during epidemic): any febrile illness associated with haemorrhage. No contact history is required.
● Probable case (during epidemic): a febrile illness occurring within 3 weeks of contact with a case of Ebola or a febrile illness in which three or more of the above clinical features are present.
● Possible clinical case (non-epidemic): an unexplained severe febrile illness, particularly with haemorrhage, in an area of Ebola transmission, with no response to an antimalarial drug plus a broad-spectrum antibiotic (e.g. chloramphenicol).

Indirect laboratory tests supportive of diagnosis
● Raised liver transaminases (AST/SGOT).
● Low or normal initial white blood cell count.

Confirmation of diagnosis
Early serological tests were difficult to interpret, but newer specific IgM ELISAs may allow diagnosis of acute cases on a single positive test. However, IgM is not always positive at presentation.

Specific IgG (by ELISA) rises too slowly to be used as a test of acute infection, but may be useful in epidemiological surveys.
● Isolation of the virus is not appropriate outside a specialised laboratory.
● A post-mortem skin biopsy (in formalin at room temperature) is not infectious, and can allow a diagnosis to be made using immunohistochemistry.

Samples need to be marked as high infection risk, ideally with standard yellow hazard tape, and sent in two sealed plastic bags. Samples should only be taken where laboratory staff are aware of the potential risks and can take the necessary precautions to handle such specimens safely. The laboratory should be informed that the specimen has been sent.

Infection control
See below and Section 1.2.

Notification
Consider formal identification of a possible outbreak of Ebola if there is a new illness of high mortality in adults in a recognised area of transmission, particularly if hospital-acquired secondary cases have occurred.

Management
● Apart from supportive care, particularly with regard to adequate fluid and nutritional intake, there are no specific treatments that modify the course of the illness.
● Antimalarial and antibiotic therapy should be given routinely, directed at treating possible alternative diagnoses (e.g. shigellosis, typhoid).

Infection control of VHF
At increased risk are laboratory staff, midwives, and those staff and family members who are handling body fluids and excreta. High-risk patient groups are those with active haemorrhage, those who are confused and agitated, and pregnant mothers.

Barrier nursing
● Secondary spread is usually by contact with blood, urine-infected secretions, used needles or stool, but
some viruses (e.g. Ebola) have also been found on patients’ skin.

- There is little clinical evidence of respiratory aerosol spread for the VHF outbreaks, although virus may be present in the nose and oropharynx.
- Surgical and obstetric procedures carry a particularly high risk of infection for staff.
- Transmission is substantially reduced by strict adherence to barrier nursing, disinfection of excreta, and clear labelling of ‘at risk’ specimens.
  - Only essential specimens should be taken.
  - The laboratory should be aware of and prepared to receive specimens.
  - Family contact should be restricted to the minimum required for care.
  - Soap and water should be available for hand washing before and after patient contact.
  - For all carers, including family members, careful barrier nursing with gloves and plastic aprons is mandatory, and stocks of these must be readily to hand.
  - Hospital staff and carers are advised to wear double gloves, plastic aprons, gowns (with boots), a head covering, HEPA-type face masks and goggles or eye shields. However, in a tropical setting these can only be tolerated for a few hours at a time, so arrange work to account for this.
  - If outer gloves are not changed between patients, gloved hands should be washed in 1:10 bleach.
  - Appropriate disposal of excreta and clinical waste is essential, so incinerate burnable clinical waste daily, and flush excreta down a dedicated toilet, having added 1:10 household bleach (0.5% chlorine) first.
  - Consider using seropositive staff to nurse these patients.

(a) Disinfect bedpans and urine bottles with 1:10 bleach.
(b) Disinfect beds and equipment with 1:100 bleach.
(c) Disinfect the dead with 1:100 bleach before burying in a sealed plastic bag.

Consider using seropositive staff to nurse these patients. The identification and involvement of these staff has been successful in some outbreaks. They must follow the ward infection control measures. Remember that convalescent patients may continue to excrete virus for many months (in Lassa and Ebola).

- Hospital staff and carers are advised to wear double gloves, plastic aprons, gowns (with boots), a head covering, HEPA-type face masks and goggles or eye shields. However, in a tropical setting these can only be tolerated for a few hours at a time, so arrange work to account for this.
- If outer gloves are not changed between patients, gloved hands should be washed in 1:10 bleach.
- Appropriate disposal of excreta and clinical waste is essential, so incinerate burnable clinical waste daily, and flush excreta down a dedicated toilet, having added 1:10 household bleach (0.5% chlorine) first.

Differential diagnosis of VHFIs
- The important differential diagnoses are, depending on geography, falciparum malaria, typhoid, meningococcaemia, Shigella or non-specific bloody dysentery, severe sepsis, leptospirosis, plague, yellow fever and dengue.
- It is crucial to exclude other treatable disease in patients presenting with symptoms suggestive of a VHF, and to initiate therapy directed at these.
- All patients should therefore receive a broad-spectrum antibiotic (e.g. chloramphenicol), and in some areas an antimalarial drug.
- In an endemic area, or during a known outbreak, the clinical diagnosis of a VHF is relatively straightforward. Difficulty arises when sporadic or new cases occur.
- A history of contact with a case in the previous 3 weeks and a history of recent travel to a transmission area should be sought. As no VHF has an incubation period longer than 3 weeks, travellers or contacts of known or suspected cases who are well after this period are unlikely to be infected.

Further reading
- The following very practical resources are for those who require additional VHF control information.
6.2.J Yellow fever

**BOX 6.2.J.1 Minimum standards**
- Immunisation.
- Intensive supportive care.
- Blood transfusion.
- Vector control.
- Internationally notifiable.

**Introduction**
Yellow fever is a flavivirus infection spread by the bite of Aedes and other mosquitoes.

**Epidemiology**
- Yellow fever is currently confined to tropical Africa and parts of South America, especially around the Amazon basin. It does not occur in Asia.
- A reservoir of infection exists in jungle primates, and mosquitoes which bite the animals in the tree canopy.
- Three transmission cycles are recognised:
  - sylvatic (jungle), in which a reservoir is maintained among jungle primates by mosquitoes, with humans being infected incidentally
  - intermediate (savannah), the commonest cycle occurring in Africa, in which semi-domestic mosquitoes may cause small epidemics in rural villages
  - urban, in which infected humans introduce infection to urban areas, where the day-biting Aedes aegypti flourishes and may cause major epidemics in unvaccinated populations.

**Pathophysiology**
Symptoms are due to toxic effects on the liver, kidneys and sometimes other organs, such as the heart and brain. Asymptomatic infections may also occur.

**Clinical features**
- The incubation period is 3–6 days.
- Many patients have an initial febrile illness, with chills and muscle pains, from which they recover.
- Others, after an illness of about 5 days, have a brief period of apparent improvement followed by deterioration and the following complications:
  - vomiting: first bilious and then black (‘coffee grounds’)
  - jaundice, liver failure and hypoglycaemia
  - bleeding of the gums, nose and stomach
  - proteinuria, oliguria and renal failure
  - delirium and coma.
- Mortality among complicated cases is 20–50%.

**Laboratory diagnosis**
- Leukopenia, thrombocytopenia, initial haemoconcentration and then haemodilution.
- Raised transaminases and bilirubin levels.
- Abnormal clotting.
- Proteinuria and impaired renal function.
- Rapid detection methods for yellow fever virus include PCR and antigen detection.
- The serum IgM-ELISA assay is 95% sensitive if performed within 7–10 days of clinical onset.
- A probable case is defined as positive IgM-ELISA taken within days 3–10 of symptoms.
- A confirmed case is defined as a clinically compatible case plus a fourfold rise in antibody titre in a patient with no history of recent yellow fever vaccination and having excluded cross-reactivity with other flaviviruses.
- Post-mortem liver biopsy specimens show mid-zone necrosis of hepatic lobules, often with eosinophilic Councilman bodies. Antigen may also be detected in tissue.

**Management**
- Universal cross-infection precautions, careful nursing and symptom control.
- Nurse suspected patients under permethrin-treated bed nets, as blood may remain infective for mosquitoes up to 5 days after onset.
- Supportive management, fluids, blood transfusion, fresh-frozen plasma, inotropes, dialysis, and ventilation if required.
- No specific antiviral treatment is available. Caution in prescribing and beware risk of bleeding, hepatic and renal impairment. H2-receptor antagonists may reduce risk of gastric bleeding.
- Suspected cases of yellow fever must be notified within 24 hours to national public health authorities, which in turn notify the WHO.

**Prevention**
- Elimination of the breeding sites of Aedes aegypti mosquitoes around human dwellings.
- Immunisation of the local population with live attenuated 17D yellow fever vaccine. Immunisation becomes effective after 10 days. Vaccine may be given to children aged 6 months or older unless there are specific contraindications (e.g., if they are immunocompromised).