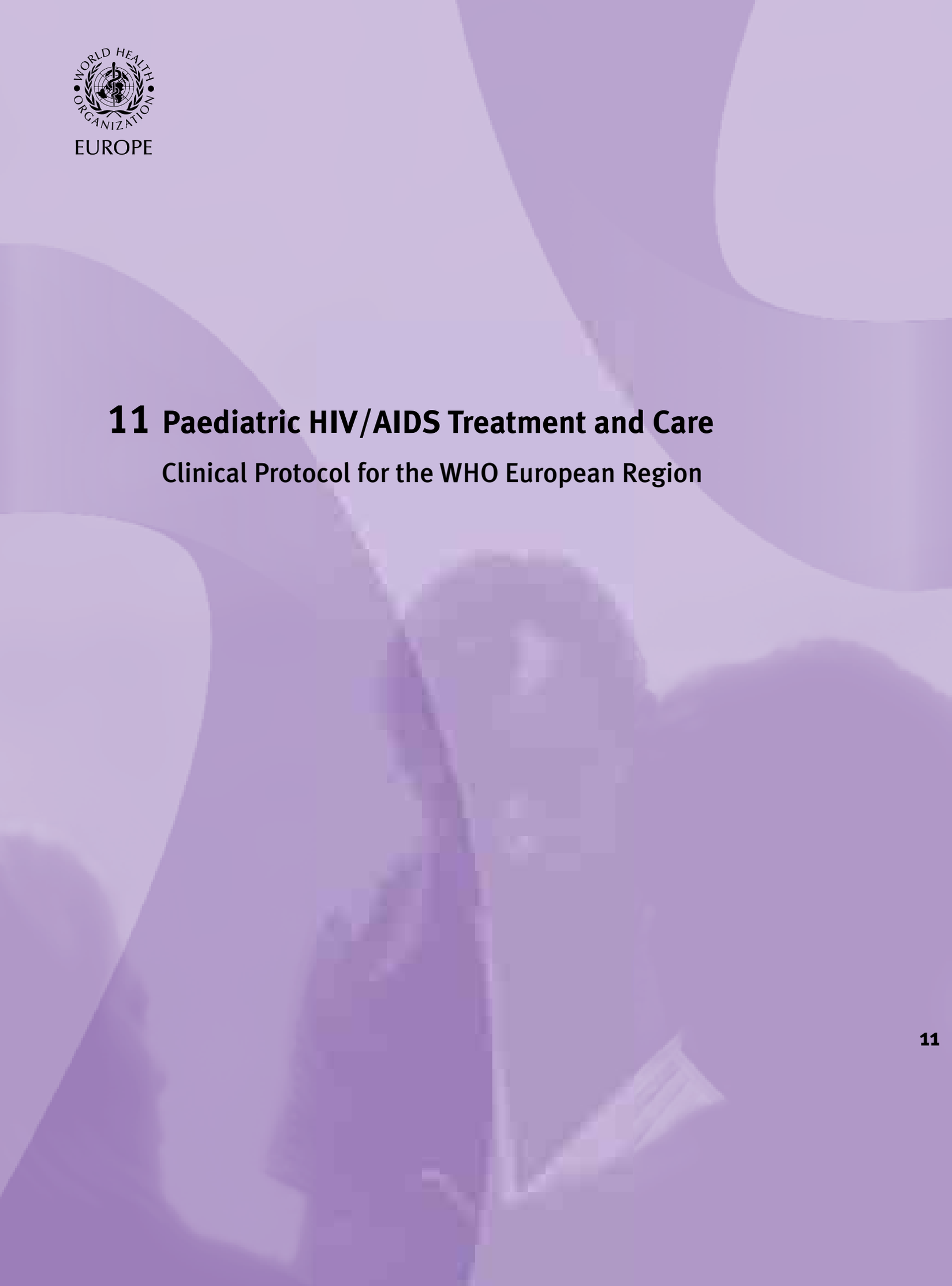
EUROPE

11 Paediatric HIV/AIDS Treatment and Care

Clinical Protocol for the WHO European Region



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I. Introduction

The increasing number of reported paediatric AIDS cases in European countries *(1)* demands urgent action to improve survival and quality of life for the affected children.

The core component of treatment and care of infants and children infected with HIV is provision of antiretroviral treatment (ART). Optimal ART increases the length and quality of their lives.

The goals of paediatric ART are the same as for adults and adolescents, the prolongation of life and improvement of its quality (see Protocol 1 *Patient evaluation and antiretroviral treatment for adults and adolescents)*.

Policy for ART in paediatric HIV/AIDS cases should be based on the following principles.

- Antiretroviral (ARV) treatment should be available as part of a comprehensive package of paediatric HIV care.
- It should be consistent with Protocol 10 *Prevention of HIV transmission from HIV-infected mothers to their infants.*
- Paediatricians should provide routine care and collaborate closely with paediatric HIV specialists to monitor HIV progression and the need for ART.
- A continuum of care should be assured during childhood, during transition to adolescence and adulthood and in line with future treatment and care for adolescents and adults (see Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents).*

II. Laboratory diagnosis of HIV

1. Diagnosis of children ‹18 months of age

In children <18 months, virological assays are recommended for detecting plasma HIV DNA *(2)*, plasma HIV RNA *(3–7)* and immune complex-dissociated (ICD) p24 antigen *(8–10)*. Virological tests have recently become technically easier, less expensive and more reliable.

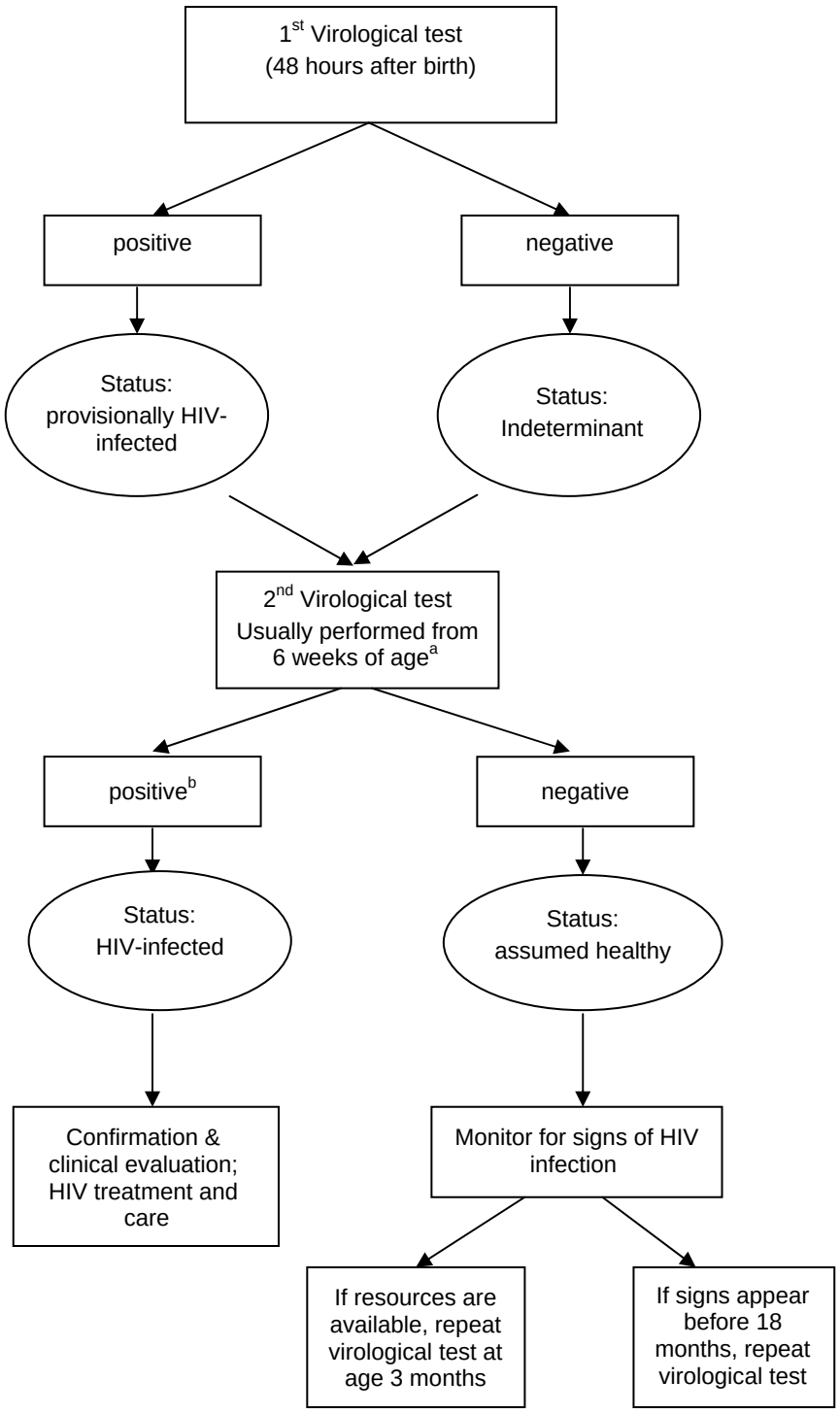
1.1. Diagnosis in non-breastfeeding infants

See the algorithm in Fig. 1 below.

- The probability of HIV diagnosis by DNA assay increases with age; 38% of infected children have positive DNA PCR tests by the age of 48 hours. By age 28 days, DNA PCR has 98% sensitivity *(11)* and 99% specificity in identifying HIV pro-viral DNA *(12)*.
- Infants with a positive virological test at age 48 hours may have an intrauterine infection.
- Infants with a negative virological test during the first week of life and subsequent positive tests have an intrapartum infection *(13)*.
- HIV infection can be diagnosed by HIV DNA or RNA detection in most infected non-breastfeeding infants by age 1 month and in virtually all infected infants by age 6 months.
- Blood samples from the umbilical cord should not be used for diagnostic evaluations because of potential contamination from maternal blood.
- A first virological test should be performed on infants about 48 hours after delivery, before mother and infant are discharged.[1] A positive virological test (usually DNA) means that the infant is "provisionally HIV-infected"; a negative result at this stage suggests an indeterminant status.
- The second virological test should be done at around 6 weeks of age. This is the key test for infants who tested negative with the first virological test. If this test is now positive, usually testing algorithms require confirmation by a repeat test on a separate specimen for confirmation.
- A second positive virological result indicates that the infant is HIV-infected and should be clinically evaluated to develop a management strategy, see section III below.
- If a second virological test is negative the infant is assumed to be uninfected, however, regular monthly monitoring for signs of HIV infection should be conducted and if resources are available, a third virological test may be offered at age of 3 months.

[1] In settings with limited resources or access to virological tests it may be more efficient and cost effective to conduct initial virological testing at 6 weeks or age, as HIV infection status can be reliably determined in almost all children at this stage (follow algorithm 1 from where 2nd test begins).

Fig 1. HIV virological diagnosis in non-breastfed infants born to HIV-infected mothers



[a] This may be the first diagnostic algorithm if testing at the age of 48 hours is not available.
[b] Usual confirmatory test should be followed on a new specimen.

1.2. Diagnosis in breastfeeding infants

- WHO EURO does not recommend breastfeeding for infants born to HIV-infected mothers.
- If alternative feeding is not available and an infant is breastfeeding, virological assays can be performed any time. If the result is negative then it should be conducted at least six weeks after complete cessation of breastfeeding, to confirm that the infant is not HIV-infected.

1.3. Diagnosis in infants exposed to ARV prophylaxis

- ARV prophylaxis to avoid mother-to-child transmission (MTCT) does not affect HIV DNA test results. HIV DNA remains detectable in the peripheral blood mononuclear cells of an HIV-infected child.
- The sensitivity of HIV RNA may be affected by ARV prophylaxis. Therefore, if the HIV RNA assay was negative while the infant was receiving prophylaxis, it should be repeated at least two weeks after prophylaxis has been completed.

1.4. Diagnosis in infants born to mothers on ART

- Infants of mothers who are on ART or have a low or undetectable viral load at delivery and do not breastfeed can be considered at low risk for acquiring infection *(14)*.
- Given the relatively high ARV levels found in breastfeeding infants, it is not known whether maternal ART during breastfeeding affects RNA detection in the infant.
- DNA detection is unaffected by maternal ART.

2. Diagnosis in children ≥ 18 months old

- By the age of 12 months, most uninfected HIV-exposed children will have lost maternal antibodies. HIV antibody testing with a positive result in a child at this age usually indicates HIV infection (96% specificity) *(15)*.
- Definitive HIV diagnosis in children ≥18 months old (whether HIV exposure is known or unknown) can be performed with antibody tests (ELISA or rapid test), while Western Blot has been used in the past, confirmation of HIV status is more reliably established with virological testing.
- Some clinical conditions are very unusual in the absence of HIV infection (*Pneumocystis* pneumonia, oesophageal candidiasis, lymphocytic interstitial pneumonitis (LIP), Kaposi sarcoma and cryptococcal meningitis). Diagnosis of such conditions and other stage 3 and 4 clinical (see Annex 1) diagnoses suggests HIV infection and indicates the need for an HIV antibody test.

III. Clinical management of HIV-infected children

1. Clinical and laboratory evaluations of HIV-infected children

All infants and children who are diagnosed with HIV infection should undergo clinical and laboratory evaluations to determine the stage of HIV clinical disease and immunodeficiency, eligibility for ART and other morbidities or issues to be addressed. This baseline assessment will also provide an opportunity to initiate cotrimoxazole preventive therapy and should serve as an opening to offer counselling and support to infected children and their parents/caregivers.

Clinical and laboratory evaluation of children with HIV should include the following:

- current clinical signs and symptoms to establish clinical stage (see Annex 1);
- exposure to and risk for coinfections (tuberculosis (TB), hepatitis B, hepatitis C);
- identification of comorbidities and medications taken to treat them;
- history of previous exposure to ARVs, including drugs used for prevention of mother-to-child transmission (PMTCT); and
- laboratory tests:
  - complete blood count;
  - CD4 cell count (absolute and percentage for children <6 years old);
  - liver enzymes (ALT and AST);
  - additional tests: bilirubin, creatinine, urinalysis, glucose;
  - testing for TB, hepatitis B and C (if at risk);
  - pregnancy tests for adolescent girls.

Other evaluations to be undertaken during the visit:

- anthropometrical measurements: weight, height/length and head circumference;
- nutritional assessment, including:
  - types of foods consumed and estimated amounts;
  - appetite and length of eating time;
  - problems associated with food intake;
  - identification of caregiver who feeds the child.
- social assessment:
  - general household hygiene and access to safe water;
  - availability of a secure refrigerator for medication storage;
  - the ability of family members and other caregivers to monitor adherence;

  and
- psychological status of both caregiver and child and a cognitive assessment of the child.

2. Nutritional support

Nutritional support should include early efforts to ensure adequate nutrient intake, based on locally available and affordable foods and the provision of micronutrients equivalent to the recommended daily allowance (RDA) *(16, 17)*.

- Increasing the energy intake of asymptomatic infants and children by 10% of the RDA for their age and sex is recommended.
- The energy intake of infants and children who are symptomatic or recovering from acute infections should be increased by 20–30% of the RDA *(18)*.
- Such requirements are minimal and may need to be augmented for children with nutritional deficiencies *(19)*.

- It is not necessary to increase protein intake beyond that required for a normally balanced diet (12–15% of the total energy intake) *(18)*.
- Vitamin A supplements should be given according to the WHO recommended high-dose prevention schedule for children at high risk[2] for deficiency *(20–22)*.
- Clinical observations indicated that infants with AIDS defining clinical disease commonly have temporary lactose intolerance and cow's milk protein (CMP) intolerance. Experts usually recommend that if the child presents with severe diarrhoea, special milk formulae and lactose CMP free milk, if available, can alleviate the problem.

3. Counselling caregivers

Parents and/or other caregivers of HIV-infected children should be counselled on several matters prior to starting children on ART. Adherence to ART is the key to successful treatment. It predicts and influences the virological and clinical response to treatment *(23)*, and its importance must be communicated to caregivers. The aims of such counselling should include:

- establishing trust with the caregiver and setting mutually acceptable goals for care;
- obtaining explicit agreement of the child's need for treatment and treatment adherence;
- identifying and addressing any of the caregiver's psychological issues that may decrease adherence;
- identifying a back-up caregiver who can help with adherence support;
- educating the patient and/or caregiver about the critical importance of maintaining at least 95% adherence, the link between partial adherence and resistance, and the way that temporary non-adherence can permanently limit choices;
- providing information about possible side-effects of ARVs and their management;
- emphasizing the need for follow-up visits and scheduling them; and,
- psychological and social issues should be discussed with caregivers and appropriate referrals should be offered, including:
    - social and rights based services;
    - peer support groups for parents/caregivers and for children.

Proper nutrition is also a prime counselling issue, including the optimal use of local foods, appropriate nutrition supplements and the nutritional management of HIV-related conditions affecting the appetite and the ability to eat (see section III.2 above).

Parents should be aware of developmental milestones and stages of growth that infants and young children should be reaching and the importance for these to be observed and discussed with the physician (see sections III.5.6 and III.5.7).

Prevention of infections should also be addressed, including *Pneumocystis jirovecii* pneumonia (PCP) prophylaxis (see section IV.3 below) and routine immunizations (see Protocol 12, *Immunization of people living with HIV and people at risk for HIV infection*).

3.1. Considerations of adolescent needs

Once a child reaches adolescence there are other considerations that need to be taken into account and addressed during counselling to ensure that appropriate treatment and care continue to be provided. During this time they pass through physical, psychological and sexual maturation, all which have implications in the continuum of their treatment and care. The following issues now need to be dscussed with and understood by the adolescent:

- disclosure of the HIV status to the adolescent if it had not already been done, this should include basic information related to HIV/AIDS;
- prevention strategies in light of impending sexual activity and fertility, including information on sexual and reproductive health and PMTCT (refer to protocols 9, *Support for sexual and*

[2] Children with severe infections or severe protien-energy malnutrition.

reproductive health in people living with HIV, and 10, *Prevention of HIV transmission from HIV infected mothers to their infants*;
- prevention of opportunistic infections and the need to treat them in an expedient manner;
- transition from paediatric to adult care, and that there may now be a change in health care providers as well as in ARV regimens;
- the importance of continuing to adhere to treatment and consequences of non-adherence;
- toxicity and signs of it; and
- ways to address possible stigma and discrimination.

4. ART in infants and children

The critical issue in clinically managing HIV-infected children is when to initiate lifelong ART. The effectiveness of HAART in reducing HIV-related morbidity and mortality in infants and children is comparable to that observed in adults *(24)*. However, there are unique considerations for HIV-infected infants and children, including:
- exposure to ZDV and NVP *(25–27)* and other ARVs taken during pregnancy, which may result in ARV resistance;
- age-dependent differences in immunological markers (e.g. CD4 percentage is used for children, not CD4 count);
- age-dependent pharmacokinetical differences;
- difficulties adhering to long-term combination treatment;
- difficulties taking medication during sleeping hours or at school; and
- unwillingness of children and adolescents to take medication.

Children should be started on ART when they have either an AIDS-defining illness or severe immunological failure (see Table 1). The decision to start ART should be made according to both CD4 percentage and age. It is now possible to determine the exact risk of progression to AIDS or death over the next calendar year based on these factors (a risk calculator is available from the HIV Paediatric Prognostic Markers Collaborative Study *(28)*). Infants who are at high risk for clinical progression, particularly for HIV encephalopathy, should start ART with a higher CD4 percentage than older children. Initiation of ART in children with a confirmed HIV diagnosis should be based on the WHO guidelines for clinical staging of paediatric HIV/AIDS (see Annex 1), immunological criteria and the Paediatric European Network for Treatment of AIDS (PENTA) guidelines[3] *(29)*.

Table 1. Criteria for initiation of ART in infants and children

WHO clinical paediatric stage	Age-specific treatment recommendations	
	<12 months[a]	≥12 months
1	Treat all	CD4-guided treatment[b]
2	Treat all	CD4-guided treatment[b]
3	Treat all	CD4-guided treatment[b]
4[c]	Treat all	

[a] The recommendation to treat all children <12 months differs from WHO global guidelines. European paediatric HIV experts generally believe that all infants diagnosed with HIV infection in the first year life should be treated, however, additional research is in need to confirm this recommendation.
[b] For CD4 guidance, refer to Table 2.
[c] Stabilize any opportunistic infection prior to initiating of ARV treatment.
Source: adapted from global guidelines, WHO *(30)*.

[3] Wherever possible, children with HIV in Europe should be cared for in collaboration with a member of the PENTA network. Full contact details are at http://www.ctu.mrc.ac.uk/penta.

4.1. Immunological, age-specific criteria for initiation of ART

- Immunological markers supplement clinical assessment and should therefore be used in combination with clinical staging.
- The threshold CD4 levels for severe immunodeficiency, as indicated in Table 2 below, are derived from longitudinal data on HIV-infected infants and children and indicate the levels at which ART is required. In general CD4 percentage is a more accurate marker in children aged under 5 years and CD4 count is the better guide for children aged over 5 years.
- Where the CD4 percentage is not available, absolute CD4 count thresholds may be used
- For children over the age of 5, the same cut-off value as in adults – i.e. 200–350 cells/mm^3 – can be used. There is a marked increase in risk of AIDS when the CD4 count drops below 200, so this should be avoided.
- A drop below threshold values should be avoided, as it significantly increases the risk of disease progression and mortality. ART should be initiated by these cut-off levels, regardless of clinical stage.
- For children with pulmonary TB, the result of CD4 measurement and clinical status should guide whether ART is urgently required or can be delayed (refer to Protocol 4, *Management of tuberculosis and HIV coinfection)*. See Annex 2 for an overview of the proposed revision to the immunological classification.

Table 2. CD4 criteria for initiation of ART

Immunological marker	Recommended threshold levels for initiating ART			
	≤11 months	**12–35 months**	**36–59 months**	**≥5 years[a]**
CD4 % and/or CD4 count	≤25% (≤1500 cells/mm^3)	≤20% (≤750 cells/mm^3)	≤15% (≤350 cells/mm^3)	≤200 cells/mm^3 (≤15%)

[a] Starting at 5 years of age CD4 cell count is a more accurate indication for initiation of treatment.
Source: adapted from WHO *(30)*.

HIV progression is more rapid in children than in adults. The predictive value of specific HIV RNA levels for disease progression is difficult to interpret, particularly for infants, so an assessment of viral load (VL) is not considered necessary before starting treatment. However, VL remains a useful measurement of treatment response and should be performed before starting ART and at one month and three months of treatment, if possible. The aim of treatment is to achieve an undetectable VL level (now usually defined as <50 copies HIV/ml plasma), which stops viral replication and reduces the chances of resistance to the ART combination being used.

The risk of progression to AIDS or death within 12 months based on age, CD4% or CD4 count or viral load may be a useful as complementary information to clinical and laboratory indicators when making a decision to initiate treatment. This may be calculated by using the risk calculator that can be accessed at http://www.ctu.mrc.ac.uk/penta/hppmcs *(31)*.

4.2. First-line HAART regimens

The choice of first-line ARV regimens for infants and children follows the same principles as for adults, with several additional considerations:

- the patient's age
- the suitability of drug formulations
- the side-effect profile
- the possibility of maintaining future treatment options
- anticipated patient adherence
- coexisting conditions (coinfections, malnutrition, metabolic abnormalities)
- risk of pregnancy in adolescent girls
- potential drug interactions.

In the absence of resistance assays, children who receive ARV prophylaxis should follow the standard first line ART regimens indicated in Table 3.

Table 3. First-line ART for infants and children

Age	ARV drug classes	ART regimens
<3 years (or <10 kg)	2 NRTIs + 1 NNRTI	ABC (or ZDV) + 3TC[a] + NVP[b]
≥3 years	2 NRTIs + 1 NNRTI	ABC (or ZDV) + 3TC[a] + EFV[b, c]

[a] The ABC + 3TC combination is very effective for ART-naive children. PENTA 5 follow up data clearly confirms the superiority of this regimen (http://www.ctu.mrc.ac.uk/penta/trials.htm *(32, 33)*. d4T should be avoided due to the increased risk of lipodystrophy *(34, 35)*.

[b] EFV is not currently recommended for children <3 years of age or <10 kg, and should not be given to post-pubertal girls who are either in the first trimester of pregnancy or are sexually active and not receiving adequate contraception. EFV is preferred over NVP in children older than three years.

[c] NVP should be avoided in post-pubertal girls (considered adults for treatment purposes) with baseline CD4 absolute cell counts >250 cells/mm^3.

4.3. HAART regimens in special circumstances

The triple-NRTI regimen can be considered an alternative option that simplifies initial treatment in special circumstances. The potency of this regimen with high viral load, which is common in infants infected in utero is a matter of concern, as has been demonstrated in adult studies *(36–38)*, and therefore its use is currently recommended to be considered for specific situations including to:

- pregnant adolescents with CD4 counts >250 cells/mm^3, for whom NVP and EFV are contraindicated; and
- adolescents with anticipated or documented poor adherence (if regimen is available as a fixed-dose combination (FDC)).

Table 4. Alternative ART

ARV drug class	ART regimen
3 NRTIs	ZDV + 3TC + ABC

4.4. ART in infants exposed to ARVs

There is a possibility of infants and children developing resistance to certain ARVs in utero, intrapartum or postpartum (during breastfeeding).

A resistant virus can be transmitted by:

- ARV-naive mothers who were infected with resistant HIV viruses;
- mothers exposed to ARVs before becoming pregnant; or
- mothers exposed to ARVs during pregnancy, whether for their own health or for MTCT prophylaxis.

The frequency of such transmission has not been well documented; consequently, the recommended ART regimens remain the same as for infants not exposed to ARVs.

4.4.1. Exposure through PMTCT

- If NVP or 3TC has been used for PMTCT, either alone or in a two-drug regimen, a single point mutation can result that may be associated with resistance to these ARVs *(39, 40)*. Further research is needed.
- Children who have previously received single-dose NVP or 3TC as part of PMTCT or other ARVs should not be denied access to life-sustaining ART.
- It is not yet clear whether triple-NRTI regimens offer benefits in such situations.
- The standard 2 NRTIs + 1 NNRTI first-line regimen is recommended *(30)*.

4.4.2. Continuing exposure due to maternal ART during breastfeeding

- Although some ARVs (NVP, ZDV and 3TC) are known to be present in breast milk, the concentration and quantity ingested by infants is less than therapeutic levels *(41, 42)*.
- If a breastfeeding infant is ill enough to require ART, the administration of ARVs at standard paediatric doses should be initiated, regardless of whether the mother is receiving ART.
- The standard 2 NRTIs + 1 NNRTI first-line regimen is recommended.

4.5. ARV dosage and age-dose adjustment

Every three months, the ARV drug dosage should be checked and adjusted according to the child's weight; otherwise, there is a risk of underdosing and developing resistance. Doses are calculated either on a milligram per kilogram body weight or milligram per square meter body surface basis. Standardization is important, so that non-expert personnel can safely dispense and/or check correct dosages for children. It is sensible clinical practice to round up doses into easier doses for the parents. It is better to overdose by up to 10% as the child rapidly grows. For ARV dosages please refer to Annex 3 *(30)*.

4.6. Adherence

Adherence is the key to achieving an effective clinical, immunological and virological response to ART, and it should be no less than 95% of the prescribed dosage *(23, 43, 44)*. An initial intervention strategy to improve adherence is described in section III.3 above on counselling of caregivers, and adherence monitoring is described in section III.5.5 below.

Medication strategies to improve adherence include:

- choosing the simplest regimen, with a lower dosing frequency and number of pills;
- prescribing carefully to avoid drug interactions;
- simplifying food requirements for administration of medication;
- informing patients and caregivers of possible side-effects, and anticipating and treating side-effects; and
- using the best-tasting liquid medication if possible, and introducing tablets as soon as feasible or if liquid medication is not available.

4.7. ART failure

Poor adherence, inadequate ARV dosage or potency *(23, 43, 45, 46)* and pharmacokinetic problems *(47)* can all contribute to treatment failure. Children should have been taking their first-line regimen for at least 24 weeks and adherence deemed adequate before treatment failure is suspected. The clinical criteria for treatment failure should be supported with immunological (CD4) criteria.

4.7.1. Immunological failure

In treatment failure, children on ART persist at or below the age-related CD4 threshold for initiating treatment (see Table 2 above). Failure is characterized by an initial immune recovery after initiation of ART, followed by a drop in CD4 measurements to values at or below their age-related threshold for initiation of treatment. Previous CD4 values are thus needed to define treatment failure using immunological criteria.

4.7.2. Virological failure

The definition of virological treatment failure is more complex, and consensus on it has not yet been reached. The overall aim of treatment is to reduce VL to levels below the lowest detection threshold (<50 copies/ml) and to maintain it as long as possible. A large number of children on treatment, however, have a detectable VL between 1000 and 50,000 copies/ml, but continue to have excellent clinical response and maintain high CD4% values. Since no clear single virological threshold can be recognized to prompt switching to second-line ART, the final decision should be taken based upon consideration of the clinical and immunological status of the child.

4.7.3. Clinical failure

The following are considered indicative of treatment failure:

- development of new or recurring Stage 3 or 4 events (see Annex 1) at least 24 weeks after initiation of a first-line regimen;
- lack of or decline in growth rate in children who show an initial response to treatment, despite adequate nutritional support and without other explanation;
- loss of neuro-developmental milestones (presence of two or more of the following: impairment in brain growth, decline in cognitive function and clinical motor dysfunction *(48)*); and
- new opportunistic infections, new malignancies, recurrence of refractory oral candidiasis or recurrence of oesophageal candidiasis.

Clinical disease progression should be differentiated from immune reconstitution inflammatory syndrome (IRIS), please see section III.5.3.

4.8. Second-line ART regimens

The entire regimen should be changed from a first-line to a second-line combination only in the event of immunological or clinical failure after 24 weeks of treatment. The new second-line regimen should include at least three new drugs, one or more of them from a new class, in order to increase the likelihood of treatment success and minimize the risk of cross- resistance, and it should be based upon drugs that retain activity against the patient's viral strain (see Table 5).

The advantages of PI-based regimens include proven clinical efficacy and well-described toxicities. Because of the diminished potential of almost any second-line nucleoside component, a low-dosed RTV-enhanced PI (PI/r) component is recommended.

TABLE 5. SECOND-LINE ART FOR INFANTS AND CHILDREN

First-line ART regimen at failure	Preferred second-line ART regimen		
	NRTI/NNRTI components		PI component[a]
2 NRTIs[a] + 1 NNRTI Containing ABC + 3TC + (+NVP or EFV)	ZDV + ddI[b]	+	LPV/r[d] or SQV/r[e] or NFV[f]
ABC + 3TC	ZDV + ddI[b]		
Triple NRTI (ZDV + 3TC + ABC)	ddI[b] + EFV[c] or NVP		

[a]Continuation of 3TC in the second line may be considered.
[b]Should not be taken on an empty stomach.
[c]EFV is not recommended for children <3 years of age or <10 kg, nor should it be given to sexually active girls who are not using adequate contraception.
[d]LPV/r is available as solid or liquid.
[e]SQV/r should not be used in children weighing <25 kg.
[f]Unboosted NFV may be used where no cold chain is in place, and should be taken with food (if other PIs are not available).

4.9. Strategies in the event of second-line treatment failure

Multidrug resistance in children who have received multiple antiretroviral regimens is an increasing problem in paediatric treatment in developed countries. Limited data are available for making recommendations about treatment options in these cases. Such decisions are complex and require consultation with an HIV specialist; refer the child and the caregiver to the tertiary-level hospital as indicated.

Possible strategies include:

- addition or substitution of new drugs (such as enfurvirtide/T20)
- strategic recycling of drugs
- structured treatment interruptions
- continuation of current treatment until additional drugs become available.

5. Monitoring children with HIV

Children with HIV should be monitored regularly in order to adjust case management strategy and treatment plans. Such monitoring should cover the health conditions of those not eligible for ART as well as those who are under treatment.

5.1. Routine monitoring of patients before ART

The main reasons for monitoring HIV-infected children are to identify the proper time for initiation of ART, to prepare the patient and caregiver for ART and to prevent, detect and treat common HIV complications.

- Clinical evaluation of infants and children not yet eligible for ART should be performed every 3–6 months.
- The same parameters that were used in the baseline evaluation should continue to be monitored. All children should be plotted on a growth chart, as growth failure is one of the commonest AIDS-defining symptoms in paediatric HIV.
- Clinical evaluation and CD4 measurements can be performed more frequently as the clinical or immunological threshold for initiating ART approaches (see Table 2).
- Evaluation and nutritional support should be provided during each contact with children and caregivers, preferably every month.

5.2. Routine monitoring of patients on HAART

Children's responses to ART should be monitored regularly, including clinical, laboratory and adherence monitoring.

5.2.1. Clinical monitoring

Clinical monitoring should be performed every three months, focusing on important signs of ART response, including:

- growth, especially in children who have been failing to grow;
- neurological symptoms and development in children who have encephalopathy or have been late in reaching developmental milestones; and
- type and frequency of opportunistic infections (bacterial infections, thrush, etc.).

5.2.2. Laboratory monitoring

- CD4 values should be measured every three months, or more often if clinically indicated.
- Laboratory monitoring of ARV toxicity and comorbidities should largely be directed by clinical symptoms.

5.3. Immune reconstitution inflammatory syndrome

IRIS has been observed in adults and less frequently in children starting ART, particularly those with very low CD4 values *(49–54)*. Symptoms are similar to those seen in opportunistic infections. They usually occur within the first three months after the start of potent ART *(55)*, concurrent with a rapid rise in CD4 values. It is also possible that immunological reconstitution may lead to the development of atypical presentations of some opportunistic infections.

5.4. Monitoring ARV toxicity

Distinguishing complications of HIV disease from toxicity secondary to ARVs is sometimes difficult. Alternative explanations for apparent ARV toxicity can include a concurrent infection (such as viral hepatitis infection in a child with hepatitis symptoms), or a reaction to a concurrent non-

ARV drug (such as isoniazid-induced hepatitis in a child on TB treatment or cotrimoxazole-induced rash in a child receiving preventive therapy). Such non-ARV-related adverse events do not necessitate a change in ARVs. Drug-related adverse events may be acute (occurring soon after the drug is administered), subacute (occurring within one or two days) or late (occurring after prolonged administration).[4]

Most toxicities are less common in children than in adults (for example, NVP-related symptomatic hepatotoxicity is rare in children). Adverse events can vary in severity from mild to severe and life-threatening. Take the following steps when managing ARV toxicity:

- Determine the seriousness of the toxicity.
- Establish whether toxicity is due to an ARV or a concurrent non-ARV medication.
- Consider other disease processes (for example, viral hepatitis in ARV patients with jaundice), since not all problems that arise during treatment are due to ARVs.
- Manage the adverse event according to its severity.
    - In case of severe life-threatening reactions, immediately discontinue *all* ARVs, manage the medical event and then reintroduce the same ARVs in a modified regimen, substituting for the offending drug when the patient stabilized. Such reactions are very rare and are usually only seen with fulminant hyperlactaemia.
    - In case of severe reactions, substitute for the offending drug without stopping ART. Severe reactions are also rare, and they most commonly occur when a child develops lipoatrophy or neuropathy from prolonged d4T use.
    - In case of moderate reactions, consider continuation of ART as long as feasible; if the patient does not improve on symptomatic treatment, consider single drug substitutions.
    - Mild reactions may be bothersome but do not require changes in treatment.
- For mild and moderate reactions, stress the importance of maintaining adherence despite toxicity.
- To reiterate, if life-threatening toxicity develops, *all* ARVs should be stopped until the patient's condition is stabilized.

Several distinct types of adverse effects common with certain ARVs or drug classes have been identified, including:

- adverse haematological events (anaemia, neutropenia and, more rarely, thrombocytopenia) from drug-induced bone-marrow suppression, most commonly due to ZDV treatment;
- mitochondrial dysfunction, primarily seen with the NRTI drugs, including lactic acidosis, hepatic toxicity, pancreatitis and peripheral neuropathy;[5]
- lipodystrophy and metabolic abnormalities, primarily seen with d4T and ritonavir-boosted PIs, as well as with certain other NRTIs;[6] and
- allergic reactions such as skin rashes and hypersensitivity reactions, more common with the NNRTIs but also seen with certain NRTIs, such as ABC.

[4] Brief details of toxicity for specific drugs can be found on the Children's HIV Association web site (http://www.bhiva.org/chiva) under the relevant name.
[5] NRTIs differ in their ability to affect mitochondrial function, with d4T having greater toxicity than ZDV, and 3TC or ABC having less.
[6] Abnormalities include fat maldistribution, particularly peripheral lipoatrophy associated with d4T and ZDV, and body habitus changes; hyperlipidaemia; hyperglycaemia, insulin resistance and diabetes mellitus; and osteopenia, osteoporosis and osteonecrosis.

5.4.1. Clinical signs of ARV toxicity and its management

Table 6. Signs of ARV toxicity and its management

Clinical manifestations	Laboratory abnormalities	Toxicity management
Acute serious adverse reactions		
Acute symptomatic hepatitis (NNRTIs – particularly NVP, more rarely EFV – NRTIs and PIs)		
Jaundice Liver enlargement Gastrointestinal symptoms Fatigue, anorexia Hypersensitivity (rash, fever, systemic symptoms), usually within 6–8 weeks Lactic acidosis (see below) if secondary to an NRTI	Elevated aminotransferase levels Elevated bilirubin	Discontinue all ARVs until symptoms resolve. Monitor aminotransferase and bilirubin levels. If the patient is on NVP, it should be discontinued and not re-administered. Once symptoms resolve, either: • change to an alternative ARV (required for NVP regimens); or • restart the ART regimen with close observation; if symptoms recur, substitute an alternative ARV (see Table 7).
Acute pancreatitis (NRTIs, particularly d4T and ddI, more rarely 3TC)		
Severe nausea and vomiting Severe abdominal pain Lactic acidosis (see below)	Elevated pancreatic amylase Elevated lipase	Discontinue all ARVs until symptoms resolve. Monitor serum pancreatic amylase and lipase. Once symptoms resolve, restart ART with an alternative NRTI, preferably without pancreatic toxicity (see Table 7).
Hypersensitivity reaction (ABC, NVP)		
ABC: acute onset of respiratory and gastrointestinal symptoms, including fever, fatigue, myalgia, nausea, vomiting, diarrhoea, abdominal pain, pharyngitis, cough, dyspnoea; rash (usually mild); progressive worsening of symptoms soon after receiving ABC dose, usually within 6–8 weeks NVP: systemic symptoms of fever, myalgia, arthralgia, hepatitis, with or without rash[c]	Elevated aminotransferase levels Elevated eosinophil count	Immediately discontinue all ARVs until symptoms resolve. NVP and ABC should *not* be re-administered to the patient in future. Once symptoms resolve, restart ART with an alternative ARV for ABC or NVP (see Table 7).
Lactic acidosis (NRTIs, particularly d4T)		
Generalized fatigue and weakness Gastrointestinal symptoms (nausea, vomiting, diarrhoea, abdominal pain, hepatomegaly, anorexia and/or sudden unexplained weight loss) Hepatitis or pancreatitis (see above) Respiratory features (tachypnoea and dyspnoea) Neurological symptoms (including motor weakness)	Increased anion gap Lactic acidosis (symptoms may continue or worsen despite discontinuing ART) Elevated aminotransferase levels Elevated CPK Elevated LDH	Discontinue all ARVs until symptoms resolve. Once symptoms resolve, restart ART with an alternative NRTI that has lower mitochondrial toxicity risk (e.g. ABC or ZDV) (see Table 7).

Clinical manifestations	Laboratory abnormalities	Toxicity management
Severe rash/Stevens–Johnson syndrome (NNRTIs, particularly NVP, less commonly EFV)		
Rash during first 6–8 weeks *Mild-to-moderate rash*: erythematous, maculopapular, confluent, most often on the body and arms; no systemic symptoms *Severe rash*: extensive rash with moist desquamation, angio-oedema or serum sickness-like reaction; or a rash with constitutional findings such as fever, oral lesions, blistering, facial oedema, conjunctivitis Life-threatening Stevens–Johnson syndrome or toxic epidermal necrolysis	Elevated aminotransferase levels	For mild or moderate rash, continue ART without interruption but under close observation. For severe or life-threatening rash, discontinue all ARVs until symptoms resolve. NVP should *not* be readministered to the patient. Once symptoms resolve, restart ART with an alternative ARV for NVP (see Table 7 below). (Note: most experts would not change to another NNRTI if the patient experienced severe or life-threatening Stevens–Johnson syndrome from NVP.)
Severe life-threatening anaemia (ZDV)		
Severe pallor, tachycardia Significant fatigue Congestive heart failure	Low haemoglobin	If refractory to symptomatic treatment (e.g. transfusion), discontinue ZDV only and substitute another NRTI (see Table 7 below).
Severe neutropenia (ZDV)		
Sepsis/infection	Low neutrophil count	If refractory to symptomatic treatment (e.g. transfusion), discontinue ZDV only and substitute another NRTI (see Table 7 below).
Chronic late serious adverse reactions		
Lipodystrophy/metabolic syndrome (d4T, PIs)		
Fat accumulation and/or loss in distinct regions of the body: • increased fat around the abdomen, buffalo hump, breast hypertrophy; and • fat loss from limbs, buttocks and face Insulin resistance, including diabetes mellitus Potential risk for later coronary artery disease	Hypertriglyceridaemia Hypercholesterolaemia Low HDL levels Hyperglycaemia	Do not prescribe d4T. Substitution of an NNRTI for a PI may decrease serum lipid abnormalities.
Severe peripheral neuropathy (d4T, ddI; more rarely 3TC)		
Pain, tingling, numbness of hands or feet; refusal to walk Distal sensory loss Mild muscle weakness and areflexia	None	Stop only the suspected NRTI and substitute an NRTI not associated with neurotoxicity (see Table 7). Symptoms may take several weeks to resolve.

Source: WHO *(30)*

5.4.2. ARV substitution in first-line regimens due to toxicity

Given the limited number of ARV options, drug substitutions should be limited to situations where toxicity is severe or life-threatening (see Table 6). Substitution with PIs because of toxicity should be avoided if possible.

Table 7. ARV substitution options in first-line ART

First-line ARV	Most frequent significant toxicities	Suggested first-line ARV drug substitution
ABC	Hypersensitivity reaction	ZDV
ZDV	Severe anaemia or neutropenia[a]	ABC
	Lactic acidosis	ABC
	Severe gastrointestinal intolerance[b]	ABC
EFV	Persistent and severe central nervous system toxicity[c]	NVP
	Teratogenicity (avoid in adolescent girls in first-trimester pregnancy or who have childbearing potential but do not receive adequate contraception)	
NVP	Acute symptomatic hepatitis[d]	EFV[e]
	Hypersensitivity reaction	NRTI substitution preferred, giving a triple NRTI (*Note*: may be less potent); or PI substitution (*Note*: premature start of second-line ARV)
	Severe or life-thr eatening rash (Stevens–Johnson syndrome)[f]	

[a] Defined as a severe, possibly life-threatening haematological abnormality that is refractory to supportive therapy.
[b] Defined as a severe, refractory gastrointestinal intolerance that prevents ingestion of the ARV regimen.
[c] Defined as severe central nervous system toxicity such as persistent hallucinations or psychosis.
[d] Symptomatic NVP-associated hepatic toxicity is very rare in HIV-infected children prior to adolescence.
[e] EFV is not currently recommended for children <3 years of age or <10 kg, and should not be given to post-pubertal adolescent girls who are either in the first trimester of pregnancy or are sexually active without adequate contraception.
[f] Severe rash is defined either as an extensive rash with desquamation, angio-oedema or serum sickness-like reactions, or a rash with constitutional findings such as fever, oral lesions, blistering, facial oedema or conjunctivitis. Stevens–Johnson syndrome can be life-threatening. For life-threatening rash, most clinicians would not substitute EFV due to the possibility of NNRTI-class toxicity.

5.5. Monitoring adherence

As there is evidence that adherence to HAART predicts the virological and clinical response to treatment *(23, 43, 44)*, monitoring it is essential. Monitoring adherence should be seen as a team responsibility of the patient, caregiver and health care workers. Intervention strategies include:

- It is important to monitor and assess adherence at each visit, for example by using a simple questionnaire, and between visits by telephone or letter as needed
- using pill boxes, reminders, alarms, pagers or timers
- using patient education aids, including pictures and calendars
- patient support groups or one-on-one counselling
- directly observed treatment (DOT)
- adherence checklist for caregivers
- discussing potential adherence constraints with caregivers

When children are 8–10 years old at diagnosis, adherence may improve in contrast to younger children. The age, maturity and social circumstances of the children should be taken into consideration, and communication should occur in a language and at a level they can understand.

Children's support groups can be helpful, in which children come to the hospital and play (educational) games together. They learn they are not the only ones with HIV, while their caregivers also have the opportunity to talk with each other.

5.6. Nutritional and growth monitoring

Systematic evaluation of nutritional status and related symptoms is critical to early identification of malnutrition and poor growth, and it should be part of routine clinical monitoring of HIV-infected infants and children.

- For infants, nutritional evaluation should occur monthly and other children every three months, and includes:
  - mode of feeding[7]
  - frequency, duration or quantity taken
  - adequacy of supply
  - bowel and urine habits
  - reported problems *(56).*
- Children should be measured and weighed at each visit assessment:
  - use the same scale at each visit
  - measure length of babies supine
  - measure length of children >2 years standing
  - measure head circumference to obtain greatest
  - gender and age specificity should be taken into consideration
  - plot growth parameters on chart.
- If the child requires particular attention due to growth problems or special nutritional require ments it should be performed more often *(56).*

5.7. Developmental assessment

It is important to assess and continue to monitor the development of cognitive, motor, language and social skills of infants and young children as a significant proportion of them show early and marked delays in these areas that may be important early indicators of HIV disease progression *(57, 58).*

- A developmental assessment should be conducted at each visit.
- The assessment should include cognitive, motor, language and social skills.
- Discuss the infant's milestones and verify that the child is developing appropriately for age.
- Use the developmental chick list or observe the infant during the examination (see Annex 4) *(56).*

The primary aim is early detection of developmental weaknesses in order to facilitate intervention to prevent and/or reduce the impact of severe problems.

[7] The WHO Regional Office for Europe recommends infant formulae feeding; when this is not available exclusive breast-feeding is an alternative.

IV. Prevention and management of major opportunistic infections

The optimal management of children with HIV infection requires attending to more than just ART. Children with very low CD4 counts for their age are the most at risk for OIs. When considering prophylactic treatment in a newly presenting and severely immunosuppressed child, the first priority is to start effective ART to restore the immune response. For children who have failed multiple ART regimes and have very low CD4 counts, whether or not they are currently on ART, appropriate OI prophylaxis is extremely important.[8]

1. Tuberculosis

Tuberculosis (TB) represents a significant threat to child health, and HIV infection increases susceptibility to infection with *M. tuberculosis* and the risk of rapid progression to TB disease. Please refer to Protocol 4, *Management of tuberculosis and HIV coinfection*, for recommendations regarding identification of TB/HIV in infants and children, and clinical management of TB/HIV in children.

2. Disseminated mycobaceteriosis other than TB (DMOT)

DMOT is associated with severe immunosuppression and a CD4 count <50 cells/mm^3. Ninety per cent of cases are due to *Mycobacterium avium* complex (MAC). Median survival for children is six months from diagnosis. Such cases should be discussed with an HIV paediatrician.

2.1. Prophylaxis

DMOT can be prevented by giving all children with a CD4 count <50 azithromycin 20 mg/kg as a single weekly dose (to a maximum of 600 mg).

2.2. Diagnosis

Clinical features usually include prolonged fever, bone marrow suppression, weight loss and chronic gastrointestinal symptoms. In patients with DMOT, MAC may be isolated from the lungs, or acid-fast bacilli (AFB) may be detected in the stools or bone marrow. Radiological presentation can occur as enlarged hilar lymph nodes.

2.3. Treatment

Treatment involves a complex multidrug regime of ciprofloxacin, rifabutin and clarithromycin and is valid for all ages. Rifabutin is not available in a liquid formulation, but a suspension (10 mg/ml in cherry or simple syrup) can be formulated from the contents of capsules (60).

If the clinical presentation is suspected then mycobacterial blood cultures should be taken using the special bottles available from microbiology. Mycobacterial stool cultures should also be taken. Treatment for DMOT is shown in Table 8.

Table 8. Treatment of DMOT

Antimicrobial Agent	Dose	Frequency	Route	Duration
ciprofloxacin	30 mg/kg	BID (twice daily) (max dose 750 mg)	PO (orally)	6 months
+				
rifabutin	10–20 mg/kg	OD (once daily) (max dose 300 mg/day)	PO	
+				
clarithromycin*	7.5 mg/kg	BID (max dose 500 mg)	PO	

* If clarithromycin is not available, it can be substituted with ethambutol, 15 mg/kg OD, PO.

[8] Much of this section is based on or taken directly from *Treating Opportunistic Infections In HIV-Infected Children Guidelines for the Children's HIV Association* (CHIVA) *(59)*, with the permission of the authors and CHIVA. More details of the prevention and management of opportunistic infections in infants and children can be found on the Children's HIV Association website (http://www.bhiva.org/chiva/protocols/supportdocs/CHIVA-presubmissionAug06.pdf).

Be aware of possible complex drug interactions, especially with rifabutin. For possible drug interactions and management strategies please refer to www.druginteraction.org.

3. *Pneumocystis jirovecii* pneumonia

PCP is one of the most common categories of HIV-associated OIs, occurring in about 40–50% of children reported to have HIV infection. It has also been identified as the leading cause of death in infants with HIV infection and accounts for 50–60% of AIDS diagnoses in infants *(61, 62)*. PCP is most common in children under one year old (72% of children presenting with PCP) *(63)*, for whom chemoprophylaxis of PCP is recommended.

3.1. Prophylaxis

Prophylaxis with cotrimoxazole (trimethoprim-sulfamethoxazole, or TMP-SMZ) (see Table 9) is recommended for:

- all HIV-exposed infants, starting at 4–6 weeks of age and continuing until HIV infection can be excluded by virological testing (younger than 18 months of age in non-breastfeeding infants) or serological testing (18 months and older); and
- all children under one year old with documented HIV infection, regardless of symptoms or CD4 percentage.

Once initiated, prophylaxis should be continued until age 5, when discontinuing may be considered in accordance with the recommendations for adults and adolescents.

Table 9. Cotrimoxazole (TMP-SMZ) formulations and dosage for HIV-infected

Recommended once-daily dosage[a]	**Suspension** (5 ml syrup, 40/200 mg)	**Paediatric tablet** (20/100 mg)	**Single-strength adult tablet** (80/400 mg)	**Double-strength adult tablet** (160/800 mg)
<6 months 20/100 mg	2.5 ml	1 tablet	¼ tablet, possibly mixed with feeding[b]	–
6 months–5 years 40/200 mg	5 ml[c]	2 tablets	½ tablet	–
6–14 years 80/400 mg	10 ml[c]	4 tablets	1 tablet	½ tablet
>14 years 160/800 mg	–	–	2 tablets	1 tablet

[a] Some countries may use weight bands to determine dosage. The following table is from the CHAP trial:

Age	**Weight**
<6 months	<5 kg
6 months–5 years	5–15 kg
6–14 years	15–30 kg
>14 years	>30 kg

[b] Splitting tablets into quarters is not considered best practice. It should be done only if syrups are not available.
[c] Children of these ages (6 months–14 years) may be able to swallow crushed tablets.
Source: adapted from WHO *(64, 65)*.

After successfully treating an acute episode of PCP, it is necessary to continue secondary prophylaxis with cotrimoxazole on a long-term basis to prevent recurrence. It may be discontinued when the patient's CD4 count remains stable for at least three months.

3.2. Diagnosis

The clinical features of PCP are tachypnoea, dyspnoea, cough, hypoxia and low-grade fever. The onset may be insidious over one or two weeks with slowly increasing tachypnoea. Coughing is not usually prominent until the full clinical picture develops with severe dyspnoea. Physical findings are usually limited to fine crepitations. Fever is often low grade. A rapidly progressive course of disease leading to respiratory failure in a few days has also been described. The classic chest X-ray may be normal or hyperinflated early in the disease, but there is usually rapid development of complete opacification with air bronchograms. The alveolar infiltrates progress peripherally with late apical sparing and small pleural effusions reported. Occasionally bullae, cysts or pneumothorax may be seen.

In infants, bronchoscopy with bronchoalveolar lavage (BAL) is now the optimal method for diagnosing PCP. BAL can be done using an 8F nasogastric feeding tube in intubated children who may not tolerate bronchoscopy. If BAL cannot be performed immediately, then start cotrimoxazole treatment first (positive results can be obtained up to 48 hours after starting treatment). The microbiology laboratory should be informed prior to BAL, as it is very important to make a definitive diagnosis even after commencing treatment.

3.3. Treatment

See Table 9 above for the recommended initial treatment of PCP.

- After the acute pneumonitis has resolved, children with mild-to-moderate disease who do not have malabsorption or diarrhoea can receive treatment with the dose of TMP-SMZ 60 mg/kg every 12 hours, IV, once the child is on oral feeding (around the second week of treatment) administer treatment PO for a total of a 21-day course.
- If there is failure to respond to cotrimoxazole, or an allergic reaction, second-line treatment should be undertaken (see Table 10).
- In case of failure to respond to cotrimoxazole, repeated BAL or lung biopsy should be considered.
- Cytomegalovirus (CMV) is frequently found in BAL with PCP infection, but ganciclovir should only be used for children with PCP and CMV if they are not responding to standard PCP therapy.
- In case of a moderate and severe PCP, oral prednisolone might be an option: 2mg/kg 1 week, 1 mg/kg 1 week, 0.5mg/kg 1 week.

TABLE 10. SECOND-LINE TREATMENT

Antimicrobial agent[a]	Dose	Frequency	Route	Duration
pentamidine isethionate	4 mg/kg/day	OD	Pentamidine isethionate slow infusion IV for 14–21 days	14–21 days
or:				
dapsone	2 mg/kg (max. 100 mg)	OD	PO	21 days

[a] Atovoquone or clindamycin might also be a choice, however only limited data exists regarding its use in children.

4. Bacterial infections (non-mycobacterial)

Serious bacterial infections are very common among HIV-positive children. The frequency of bacterial infection increases with HIV disease progression and immunosuppression. The commonest organisms are *encapsulated Streptococcus pneumoniae and Haemophilus influenzae. Staphylococcus* aureus and gram-negative infections, especially *Pseudomonas aeruginosa*, are seen more commonly in children with severe HIV infection *(63)*.

4.1. Diagnosis

The clinical presentation of acute bacterial pneumonia in children with early HIV infection is similar to that in non-infected children: the commonest clinically diagnosed infection is acute pneumonia and primary septicaemia. The clinical signs may be less obvious in children with HIV. It is always important to obtain blood cultures. Ear infections and throat infections are very common. Sinusitis should be particularly sought for, either by clinical signs or sinus X-rays.

4.2. Treatment

A child with clinical evidence of an acute lower respiratory tract infection (fever, cough, raised respiratory rate, chest signs or CXR changes) should be treated promptly and empirically with broad-spectrum antibiotics (oral co-amoxiclav or IV ceftriaxone). The choice of oral or intravenous antibiotics depends on the patient's clinical condition. If there is a poor response to treatment add azithromycin (10 mg/kg OD for 5 days) and consider BAL. Generally, treatment regimes should be long (10–14 days).

5. Toxoplasmosis

Toxoplasma encephalitis should be considered in all HIV-infected children with new neurologic findings. Although focal findings are more typical, the initial presentation can be variable and reflect diffuse central nervous system (CNS) disease.

5.1. Prophylaxis

PCP prophylaxis also provides prophylaxis against toxoplasmosis. Atovoquone may also provide protection. Severely immunosuppressed children (with CD4 cell count <100/mm^3) who are not receiving TMP-SMZ or atovoquone and are found to be seropositive for *Toxoplasma* should be administered prophylaxis for both PCP and toxoplasmosis (i.e. dapsone plus pyrimethamine) (see Table 11).

Indication for prophylaxis prevention in Table 11 is IgG antibody-positive for *Toxoplasma* and severe immunosuppression (CD4 <15%).

Table 11. Prophylaxis to prevent first episode of toxoplasmosis

Antimicrobial agent	Dose	Frequency	Route	Duration
First line treatment				
cotrimoxazole	960 mg/m^2	OD	PO	Until CD4 >200 mm^3
Alternative				
dapsone	2 mg/kg (max 25 mg)	OD	PO	Until CD4 >200 mm^3
+				
pyrimethamine	1 mg/kg	OD	PO	
+				
folic acid	5 mg	Every 3 days	PO	
Or				
atovoquone	age 1–3 months 30 mg/kg	OD	PO	Until CD4 >200 mm^3
	age 4–24 months 45 mg/kg	OD	PO	
	age >24 months 30 mg/kg	OD	PO	

5.2. Diagnosis

A presumptive diagnosis of *Toxoplasma* encephalitis is based on clinical symptoms, serologic evidence of infection, and the presence of a space-occupying lesion on imaging studies. Clinical symptoms include motor and speech disturbances, often accompanied by headache, altered mental status, and fever. Children can also present with seizures, cranial nerve abnormalities, visual field defects, sensory disturbances, cerebellar dysfunction, meningismus and movement disorders *(66)*. Manifestations of extracerebral toxoplasmosis in HIV-infected children include ocular toxoplasmosis, which occurs most often in association with *Toxoplasma* encephalitis necessitating neurologic examination. Patients with chorioretinitis present with blurred vision, pain or photophobia *(67)*.

Children who are infected latently with *Toxoplasma gondii* have variable IgG titres and rarely possess IgM antibody. Although seroconversion and fourfold increase in IgG antibody titers may occur, the ability to diagnose active disease is commonly impaired by immunosuppression. IgM antibodies typically disappear a few months after infection but can remain elevated for more than 1 year confounding the differentiation of acute and remote infection *(68)*.

Additional investigations to support the diagnosis of *Toxoplasma* encephalitis include (where available) CT scanning of the brain that might indicate multiple, bilateral, hypodense, focal ring-enhancing lesions especially in the basal ganglia and cerebral corticomedullary junction in 70-80% of patients *(69)*. Magnetic resonance imaging is more sensitive and will confirm basal ganglia lesions in most patients *(70)*. Although toxoplasmic encephalitis can occasionally cause a single brain lesion on MRI, such a finding suggests an alternative diagnosis (primarily CNS lymphoma and tuberculoma) *(71)*.

Definitive diagnosis of *Toxoplasma* encephalitis requires histologic confirmation by brain biopsy, and can be considered when early neurologic deterioration is present despite empiric treatment or in children who fail to respond to anti-*Toxoplasma* therapy after 10–14 days. If lumbar puncture is not contraindicated, PCR of CSF should also be considered. Ocular toxoplasmosis is diagnosed on the basis of observation of characteristic retinal lesions in conjunction with serum specific antibodies.

5.3. Treatment

Acute induction therapy should be followed by chronic suppressive therapy (see Table 12).

Table 12. Treatment of acquired toxoplasmosis: acute induction therapy

Antimicrobial agenta	Dose	Frequency	Route	Duration
pyrimethamine *then*	2 mg/kg/day (max: 50 mg)	OD	PO	3 days
pyrimethamine +	1 mg/kg (max: 25 mg)	OD	PO	At least 6 weeks
sulphadiazine +	25-50 mg/kg (max:1.0-1.5 g/dose)	QID (four times daily)	PO	
Folic acid	10-25 mg	OD	PO	

6. Fungal infections

6.1. Candidiasis

6.1.0.1. Prophylaxis

Immune reconstitution with ART accompanied by a reduction in plasma HIV viraemia is the best intervention to reduce the rate of candida colonization and clinical disease *(72, 73)*. Other useful interventions include good oral hygiene, avoidance of unnecessary antibiotics and steroids, and specific antifungal medications. Continuous prophylactic anticandida therapy is rarely indicated, and may result in the emergence of resistant and refractory infections *(74)*. Universal primary antifungal prophylaxis is therefore not currently recommended and the indications for secondary prophylaxis should be individualized.

6.1.1. Oropharyngeal candidiasis (OPC)

6.1.1.1. Diagnosis

OPC has variable clinical manifestations: pseudomembranous (thrush), erythematous (atrophic), hyperplastic (hypertrophic) and angular cheilitis. Thrush is the most classic form of oral candidiasis, appearing as creamy white curd-like patches with inflamed underlying mucosae that are exposed after removal of the exudates. It can be found on the oropharyngeal mucosae, palate and tonsils. Erythematous OPC manifests as flat erythematous lesions on the mucosal surface. Hyperplastic candidiasis is composed of raised white plaques appearing on the lower surface of the tongue, palate and buccal mucosa and cannot be removed. Angular cheilitis occurs as red, fissured lesions in the corners of the mouth.

Diagnosis of oral candidiasis can be made by a KOH preparation and culture with microscopic demonstration of budding yeast cells in wet mounts or biopsy specimens. For recurrent or refractory OPC, cultures with in vitro susceptibility testing can be used to guide antifungal treatment *(75)*.

6.1.1.2. Treatment

Table 13. Treatment options for children with oropharyngeal candidiasis

Antimicrobial agenta	Dose	Frequency	Route	Duration
First line treatment				
Fluconazole	3–6 mg/kg (max: 400 mg/day)	OD	PO	7–14 days
Alternative				
Itraconazole cyclodextrin oral solution *Or* Amphotericin B oral suspension	2.5 mg/kg (max: 200 mg/day) 1 ml (100 mg/ml)	BID QID	PO PO	7–14 days 14 days

6.1.2. Oesophageal candidiasis

6.1.2.1. Diagnosis

This condition can present with odynophagia, dysphagia or retrosternal pain, which can be severe enough to cause dehydration and weight loss in children. Although oropharyngeal candidiasis is common, evidence of it may be absent among children with oesophageal candidiasis, particularly those receiving HAART. Unlike infected adults, a substantial number of children with the condition may experience nausea and vomiting.

Oesophageal candidiasis has a classic cobblestone appearance on barium swallow. In refractory symptomatic cases, endoscopy should be performed to rule out other causes of refractory oesophagitis (HSV, CMV, MAC and azole-resistant *Candida* species). Endoscopies may show anything from a few small white raised plaques to elevated confluent plaques with hyperaemia and extensive ulceration.

6.1.2.2. Treatment

Table 14. Treatment options for children with oesophageal candidiasis

Antimicrobial agenta	Dose	Frequency	Route	Duration
First line treatment				
Fluconazole *then* Fluconazole	6 mg/kg/day 3–6 mg/kg/day (max: 400 mg/day)	OD	PO PO	Day 1 14– 21 days
Alternative				
Itraconazole cyclodextrin oral solution *Or* Amphotericin B	paediatric dosage: 2.5 mg/kg or 5.0 mg/kg 0.3–0.5 mg/kg/day	BID OD OD	PO PO IV	At least 14–21 days At least 7 days

6.1.3. Candidaemia

6.1.3.1. Diagnosis

A new-onset fever in an HIV-infected child with advanced disease and a central venous catheter is the most common clinical manifestation of candidaemia. Systemic fungaemia can lead to endogenous endophthalmitis, and ocular examination by an ophthalmologist may be warranted among children with candidaemia. Diagnosis is best made with blood cultures using lysis-centrifugation techniques *(76)* or automated broth-based systems *(77)*. When fungaemia is present, retinal examination for endophthalmitis, abdominal CAT or ultrasound for hepatic or renal involvement, and bone scans for clinically suspected osteomyelitis may be appropriate.

6.1.3.2. Treatment

Primary prophylaxis of candidiasis in HIV-infected infants/children is not indicated.

Table 15. Treatment options for children with invasive candidiasis

Antimicrobial agenta	Dose	Frequency	Route	Duration
First line treatment				
Fluconazole If failure to respond: Amphotericin B	10 mg/kg/day 250 mcg increased by 250 mcg to 1 mg/kg	OD OD or alternate day	IV IV	21 days 14 days
Alternative				
Amphotericin B lipid complex (Abelcet)	3 mg/kg	OD given over two hours	IV	2–3 weeks

7. Viral infections

7.1. Cytomegalovirus (CMV)

7.1.1. Prophylaxis

Severely immunocompromised children with HIV/CMV coinfection should have a dilated retinal examination performed every 4–6 months. Prophylaxis for children has not been well established and used.

Prophylaxis with oral ganciclovir or valganciclovir can be considered for HIV-infected adolescents who are CMV-seropositive with CD4 cells count of <50 cells/mm3 (see Table 16) but must be balanced with the risks of (val)ganciclovir-induced neutropenia, anaemia, conflicting reports of efficacy, lack of proven survival benefit, risk for emergence of ganciclovir-resistant CMV, and cost. Neither aciclovir nor valaciclovir should be used for CMV infection.

Table 16. Prophylaxis for severely immunosuppressed adolescents *(78)*

Antimicrobial agent	Dose[a]	Frequency	Route	Duration
Valganciclovir	900 mg	BID	PO	21 days
Maintenance phase Ganciclovir	900 mg	OD	PO	3–6 months

[a] There are presently no paediatric doses available

There are no data to guide decisions concerning discontinuation of secondary prophylaxis (chronic maintenance therapy) in children with treated CMV disease, but it is reasonable to consider stopping when there are sustained T-cell responses to ART.

7.1.2. Diagnosis

In HIV-infected children, CMV infection may be difficult to differentiate from active CMV disease. Because of transplacental transfer of antibodies from mother to child, a positive CMV antibody assay in an infant under 12 months old is indicative of maternal infection but not necessarily infection of the infant. In a child older than 12 months, a positive CMV antibody assay indicates previous infection with CMV but not necessarily active disease. At any age, a positive CMV culture is indicative of infection, but not necessarily of disease. CMV disease is rare in HIV-infected children, but it does occur in children with severe immunosuppression, in whom the common clinical manifestations include CMV retinitis (with white fluffy exudates), hepatitis and colitis.

CMV can be isolated in cell cultures from peripheral blood leukocytes, body fluids and body tissues. Using centrifuge-assisted shell vial culture amplification techniques, CMV can be detected within 16–40 hours of culture inoculation. A positive blood buffy-coat culture establishes a diagnosis of CMV viraemia and increases the likelihood that CMV disease or symptoms are caused by CMV, because children with positive blood cultures are at higher risk for developing end-organ disease.

Different methods have been used to detect CMV antigen or DNA directly and identify patients at risk for development of CMV disease, including detection of pp65 antigenaemia, qualitative and quantitative PCR and DNA hybridization. The DNA assays are more sensitive than buffy-coat or urine cultures for detecting CMV and can be used to identify patients at higher risk for developing clinically recognizable disease. CMV DNA detection in CSF by DNA PCR is highly sensitive for CMV disease. Quantitative DNA PCR can be used as a marker of risk for disease and to monitor response to therapy *(77)*.

7.1.3. Treatment

Table 17. Treatment of CMV infection

Antimicrobial agenta	Dose	Frequency	Route	Duration
First line treatment				
Induction phase Ganciclovir	5 mg/kg	every 12 hours	IV	7 days
Maintenance phase Ganciclovir	5 mg/kg	OD	IV	2–3 weeks

7.2. Varicella-zoster virus

7.2.1. Prophylaxis

Immunosuppressed HIV-infected children who are susceptible to varicella-zoster virus[9] (VZV) should avoid exposure to people with chicken pox or shingles. For the prophylaxis of chicken pox, HIV-infected patients susceptible to VZV should be administered varicella-zoster immunoglobulin (VZIg) as soon as possible, ideally within 96 hours after any close contact with chicken pox or shingles.

There are no data on the effectiveness of aciclovir for preventing chicken pox in HIV-infected children or adults.

7.2.2. Diagnosis

The diagnosis of VZV infection is often suspected from the clinical presentation A generalized severe pruritic vesicular rash and fever is diagnostic. Lesions appear first and are most numerous on the trunk, neck, and face. The vesicles contain fluid, rest on an erythematous base and ulcerate and dry to form crusts and scabs. Lesions during chronic VZV infection are varicelliform at onset but may evolve into non-healing, necrotic and crusted ulcers that become hyperkeratotic *(79)*.

The classical clinical presentation of zoster (a painful localized cutaneous vesicular eruption along one or more contiguous dermatomes) is diagnostic. Lesions evolve over 1 to 2 days to form vesicles, pustules, and crusts. In HIV-infected patients, zoster may be bullous, haemorrhagic, necrotic, and particularly painful. Blisters and crusts usually last 2–3 weeks, although necrotic lesions may last up to 6 weeks and heal with severe scarring. Zoster in HIV-infected children may also present as an atypical rash that extends beyond dermatomal boundaries or is bilaterally distributed or generalized or as multiple episodes of a disseminated rash more similar in appearance to chickenpox than zoster *(80)*.

Varicella pneumonitis in HIV-infected children is associated with severe pulmonary manifestations resulting in hypoxaemia and diffuse reticulo-nodular densities on radiography. Encephalitis occurs more frequently with zoster in the ophthalmic distribution, and cerebellar findings are typical; prominent symptoms include ataxia, tremors, and dizziness. Cerebral involvement results in fever, headache, vomiting and lethargy *(81)*.

Direct immunofluorescence expressed on the surface of infected cells from scrapings obtained from the base of skin, conjunctiva, or mucosal lesions allow VZV antigen detection, and is the diagnostic procedure of choice. Direct and indirect immunofluorescence or immunoperoxidase methods can also detect antigen in VZV-infected cells in tissue sections of lung, liver, brain, or other organs.

[9] Susceptible patients are those who have no history of chicken pox or shingles or who have no detectable VZV antibody.

7.2.3. Treatment

Table 18. Treatment of varicella-zoster infection

Infection	Antimicrobial agent[a]	Dose	Frequency	Route	Duration
Varicella	*Children with moderate or sever immune suppression, high fever or necrotic lesions*				
	Acyclovir	10–20 mg/kg	TID (three times daily)	IV	7 days after no new lesions
	Children with mild immune suppression and mild oral disease:				
	Acyclovir	20 mg/kg (max: 200 mg/dose)	QID	PO	7 days after no new lesions
Zoster	***Children with severe immune suppression, trigeminal nerve involvement or extensive multidermatomal zoster IV***				
	Aciclovir	10–20 mg/kg	TID	IV	7–10 days
	Children with mild immune suppression and mild oral disease				
	Aciclovir	20 mg/kg (max: 200 mg/dose)	QID	PO	7–10 days
For patients not responding to acyclovir[a]					
	Foscarnet	40–60 mg/kg	TID	IV	7–10 days

[a] Valaciclovir is approved for use in adult and adolescents with zoster at a dose of 1 gram PO BID 7–10 days; data on dosing in children is limited.

7.3. Herpes simplex virus (HSV)

7.3.1. Prophylaxis

HIV-infected children with severe oral recurrences (more than 3–6 severe episodes a year) or previous disseminated disease may benefit from prophylaxis with oral acyclovir *(82)*.

7.3.2. Diagnosis

Neonatal HSV can appear as disseminated multi-organ disease (occurring in approximately 25% of neonates with HSV infection), localized disease of the CNS (approximately 35% of infected neonates) or localized disease of the skin, eyes and mouth (approximately 40% of infected neonates) *(83)*. Vesicular rash is present in approximately 80% of children with localized skin, eye or mouth disease, but only in approximately 60% of children with CNS or disseminated disease *(84, 85)*.

Outside of the neonatal period, the most common appearance of HSV infection in children is orolabial disease. Fever, irritability, tender submandibular lymphadenopathy and superficial, painful ulcers in the gingival and oral mucosae and perioral area characterize primary HSV gingivostomatitis. HIV-infected children who experience primary infection when they are immunocompromised can have severe local lesions or, more rarely, disseminated HSV with visceral involvement and generalized skin lesions with primary infection. Other sites of involvement among severely immunocompromised HIV-infected children include the oesophagus, CNS and genitals and disseminated disease in the liver, adrenals, lungs, kidneys, spleen and brain.

Among children with suspected HSV encephalitis, detection of HSV DNA by PCR is the diagnostic test of choice *(86)*. CSF cultures for HSV are usually negative. Definitive diagnosis of HSV oesophagitis requires endoscopy with biopsy (histological evidence of multinucleated giant cells with intranuclear viral inclusion) and culture.

7.3.3. Treatment

Table 19. Treatment of HSV disease

Condition	Antimicrobial agenta	Dose	Frequency	Route	Duration
Skin, eye and mouth disease	Acyclovir	20 mg/kg	TID	IV	14 days (63)
Disseminated HSV disease or encephalitis		20 mg/kg or 500 mg/m^2	TID	IV	21days
Symptomatic HSV gingivostomatitis		5–10 mg/kg *Or* 20 mg/kg	TID TID	IV PO	7–14 days 7–14 days
Alciclovir-resistant HSV infection					
	Foscarnet	120 mg/kg/day	2–3 divided doses over 1–2 hours (administer slowly over 2 hours or no faster than 1 mg/kg/min.)	IV	Until the infection resolves

Aciclovir therapy should not be discontinued in neonates with CNS disease unless a repeat CSF HSV DNA PCR assay is negative at day 19–21 of treatment.

Because episodes of HSV disease can be treated successfully, chronic therapy with aciclovir is not required after lesions resolve. However, people with frequent or severe recurrences can be administered daily suppressive treatment with oral aciclovir or valaciclovir.

V. Paediatric HIV pain management

1. Background

Pain in children with HIV AIDS is a multifactor, biologically complex problem associated with diminished quality of life and increased mortality *(87)*. Pain elimination, pain amelioration and (when appropriate) palliative administration of analgesics and sedatives are essential aspects of the care of every HIV-infected child.

Despite advances in the treatment and control of HIV infection in children, pain may still complicate medical management and diminish quality of life for some children with advanced disease. Because pain in this population is often complex, optimal management will best be achieved through the coordinated collaboration of several specialists, including anaesthesiologists, pain specialists, social workers, nursing staff and others.

Patients with pain are more than five times more likely to die than those who do not report pain. Pain is also associated with lower CD4 cell percentages and more severe immunosuppression *(88)*.

2. Pain management strategies

Pain management in HIV-infected children should combine pharmacological and non-pharmacological therapies. The latter include:

- relaxation techniques and behaviour modification;
- environmental management: play, music, scheduled medical and nursing interventions, and structured time for sleep and rest;
- gentle handling and supportive positioning;
- nutritional support, adequate hydration and electrolyte replacement;
- optimized tissue perfusion and oxygenation;
- transcutaneous electrical nerve stimulation (TENS), gentle massage, whirlpool baths and physical therapy; and
- electrical or needle stimulation of acupuncture meridians by HIV-knowledgeable practitioners *(88, 89)*.

VI. Suggested minimum data to be collected at the clinical level

The suggested minimum data to be collected is important in the development of key indicators on access to diagnosis and treatment and their success. Such indicators assist managers in decision making on ways to strengthen and expand these services to all who need them.

The following data should be collected at each clinical facility on a regular basis (e.g. monthly, quarterly or semi-annually):

- number of infants <18 months of age born to HIV-infected mothers;
- number of infants <18 months of age born to HIV-infected mothers and have had PCR testing;
- number of HIV diagnosed infected infants <18 months of age;
- number of infants ≥18 months of age born to HIV-infected mothers
- number of infants ≥18 months of age born to HIV-infected mothers and have had only serological HIV testing;
- number of HIV-infected infants ≥18 months of age diagnosed only serologically;
- number of HIV-infected children (<15 years old) seen for care who are eligible for HAART;
- number of HIV-infected children(<15 years old) seen for care and receiving first-line HAART regimen;
- number of HIV-infected children(<15 years old) on HAART changing from first-line HAART to second-line HAART;
- number of HIV-infected children(<15 years old) interrupting HAART, including the reasons (e.g. death, toxicity/side effects, loss to follow-up, ARVs not available, etc.);
- number of HIV-infected children who died while on HAART, including cause of death (e.g.HIV/AIDS related mortality or non-HIV/AIDS related mortality such as accident, etc.);
- number of HIV-infected children who died within first 12 months of initiating HAART;
- number of death among all HIV infected children including cause of death (e.g. HIV/AIDS related mortality or non-HIV/AIDS related mortality such as accident, etc).

Annex 1. Revised WHO clinical staging of HIV/AIDS for infants and children

Revised WHO clinical staging of HIV/AIDS
for infants and children
(Interim European Region version for people <15 years old
with confirmed laboratory evidence of HIV infection –
HIV antibody test if ≥18 months old, virological or p24 antigen test if <18 months)

Clinical Stage 1
- Asymptomatic
- Persistent generalized lymphadenopathy (PGL)

Clinical Stage 2
- Hepatosplenomegaly
- Papular pruritic eruptions
- Extensive molluscum contagiosum
- Fungal nail infections
- Recurrent oral ulcerations
- Lineal gingival erythema (LGE)
- Angular cheilitis
- Parotid enlargement
- Herpes zoster
- Asymptomatic lymphocytic interstitial pneumonitis (LIP)
- Recurrent or chronic respiratory tract infections (otitis media, otorrhoea, sinusitis)

Clinical Stage 3
- Moderate unexplained malnutrition not adequately responding to standard therapy
- Unexplained persistent diarrhoea (14 days or more)
- Unexplained persistent fever (intermittent or constant, for longer than one month)
- Oral candidiasis (excluding first two months of life)
- Oral hairy leukoplakia
- Acute necrotizing ulcerative gingivitis or periodontitis
- Lineal gingival hyperplasia
- Severe recurrent presumed bacterial pneumonia
- Extensive and confluent warts
- Giant disfiguring molluscum
- Chronic HIV-associated lung disease, including bronchiectasis
- Symptomatic lymphocytic interstitial pneumonitis (LIP)
- Unexplained anaemia (<8 g/dl) and/or neutropenia (<500/mm^3)
- Unexplained thrombocytopenia (<50 000/mm^3) for more than one month

Clinical Stage 4
- Unexplained severe wasting or severe malnutrition not adequately responding to standard therapy
- Recurrent severe presumed bacterial infections (e.g. empyema, pyomyositis, bone or joint infection or meningitis, but not pneumonia)
- Chronic herpes simplex infection (orolabial or cutaneous and of more than one month's duration)
- Extrapulmonary TB
- Kaposi sarcoma
- Oesophageal candidiasis
- CNS toxoplasmosis (after the neonatal period)
- HIV encephalopathy
- CMV infection (CMV retinitis or infection of organs other than liver, spleen or lymph nodes; onset at age one month or more)
- Extrapulmonary *Cryptococcus*, including meningitis
- Any disseminated endemic mycosis (e.g. extrapulmonary histoplasmosis, coccidiomycosis, penicilliosis)
- Cryptosporidiosis
- Isosporiasis

continued on next page

- Disseminated non-tuberculous mycobacteria infection
- Candida of trachea, bronchi or lungs
- Visceral herpes simplex infection
- Acquired HIV-associated rectal fistula
- Cerebral or B-cell non-Hodgkin lymphoma
- Progressive multifocal leukoencephalopathy (PML)
- HIV-associated cardiomyopathy or HIV-associated nephropathy[a]
- Leiomyosarcoma and other HIV-related solid tumours

[a] WHO is seeking further information and evidence relating to the occurrence and definitions of these conditions.
Source: WHO Regional Office for Europe *(90)*.

Annex 2. WHO classification of HIV-associated immunodeficiency in infants and children

Table 20. Classification of HIV-associated immunodeficiency

Classification of HIV-associated immunodeficiency	Age-related CD4 values			
	≤11 months (%)	12–35 months (%)	36–59 months (%)	≥5 years[a] (cells/mm^3)
Not significant	>35	>30	>25	>500
Mild	30–35	25–30	20–25	350–499
Advanced	25–29	20–24	15–19	200–349
Severe	<25	<20	<15	<200 or <15%

[a] Including adolescents and adults.
Source: WHO *(30).*

Annex 3. ARV dosage ranges

Table 21. ARV DOSAGE RANGES

Surface area (m^2)		Weight range (kg)		Abacavir			Didanosine (twice daily)			Efavirenz		Lamivudine			Nelfinavir		
				Formulation	DOSE (ml or tablets)		Formulation	Dose (ml or tablets)		Formulation	Dose (capsules, tablets)	Formulation	Dose (ml, tablets)		Formulation	Dose (tablets)	
Bottom	Top	Bottom	Top		AM	PM		AM	PM	Age 3 years and above. Dose given ONCE daily			AM	PM		AM	PM
0.30	0.34	5.0	5.9	20 mg/ml syrup	2 ml	2 ml	10 mg/ml suspension	4 ml	4 ml			10 mg/ml solution	3 ml	3 ml	250 mg tablets	2	2
							or										
							25 mg chew tablets	2	2								
0.34	0.38	6.0	6.9	20 mg/ml syrup	3 ml	3 ml	10 mg/ml suspension	5 ml	5 ml			10 mg/ml solution	3 ml	3 ml	250 mg tablets	2	2
							or										
							25 mg chew tablets	2	2								
0.38	0.40	7.0	7.9	20 mg/ml syrup	4 ml	4 ml	10 mg/ml suspension	6 ml	6 ml			10 mg/ml solution	4 ml	4 ml	250 mg tablets	3	2
							or										
							25 mg chew tablets	2	2								
0.40	0.43	8.0	8.9	20 mg/ml syrup	4 ml	4 ml	10 mg/ml suspension	6 ml	6 ml			10 mg/ml solution	4 ml	4 ml	250 mg tablets	3	3
							or										
							25 mg chew tablets	2	2								
0.43	0.45	9.0	9.9	20 mg/ml syrup	4 ml	4 ml	10 mg/ml suspension	6 ml	6 ml			10 mg/ml solution	4 ml	4 ml	250 mg tablets	3	3
							or										
							25 mg chew tablets	2	2								
0.45	0.49	10	10.9	20 mg/ml syrup	5 ml	5 ml	10 mg/ml suspension	6 ml	6 ml	200 mg capsule	1	10 mg/ml solution	5 ml	5 ml	250 mg tablets	3	3
							or										
							25 mg chew tablets	3	2								
0.49	0.53	11	11.9	20 mg/ml syrup	5 ml	5 ml	10 mg/ml suspension	7 ml	7 ml	200 mg capsule	1	10 mg/ml solution	5 ml	5 ml	250 mg tablets	3	3
				or			or										
				300 mg tablets	0.5	0.5	25 mg chew tablets	3	3								
0.53	0.58	12	13.9	20 mg/ml syrup	6 ml	6 ml	10 mg/ml suspension	7 ml	7 ml	200 mg capsule	1	150 mg tablet	0.5	0.5	250 mg tablets	4	4
				or			or										
				300 mg tablets	0.5	0.5	25 mg chew tablets	3	3								
0.58	0.70	14	16.9	300 mg tablets	0.5	0.5	10 mg/ml suspension	8 ml	8 ml	200 mg capsule + 50 mg capsule	1 + 1	150 mg tablet	0.5	0.5	250 mg tablets	4	4
							or										
							25 mg chew tablets	4	3								
0.70	0.80	17	19.9	300 mg tablets	0.5	0.5	10 mg/ml suspension	9 ml	9 ml	200 mg capsule + 50 mg capsule	1 + 1	150 mg tablet	0.5	0.5	250 mg tablets	5	5
							or								or		
							25 mg chew tablets	4	4						625 mg tablets	2	2
0.80	0.95	20	24.9	300 mg tablets	1	0.5	25 mg chew tablets	5	5	200 mg capsule + 100 mg capsule	1 + 1	150 mg tablet	1	0.5	250 mg tablets	5	5
															or		
															625 mg tablets	2	2
0.95	1.10	25	29.9	300 mg tablets	1	1	25 mg chew tablets	5	5	200 mg capsule + 100 mg capsule + 50 mg capsule	1 + 1 + 1	150 mg tablet	1	1	250 mg tablets	5	5
															or		
															625 mg tablets	2	2
1.10	1.20	30	34.9	300 mg tablets	1	1	25 mg chew tablets	5	5	200 mg capsule	2	150 mg tablet	1	1	250 mg tablets	5	5
															or		
															625 mg tablets	2	2
		35	39.9				25 mg chew tablets	5	5	200 mg capsule	2				250 mg tablets	5	5
															or		
															625 mg tablets	2	2
		40	and over							200 mg capsule	3						
										or							
										600 mg tablet	1						

				Nevirapine (maintenance)			Stavudine			Zidovudine			Lopinavir/ritonavir		
Surface area (m^2)		Weight range (kg)		Formulation	DOSE (ml or tablets)		Formulation	Dose (ml or tablets)		Formulation	Dose (ml or capsules)		Formulation	Dose (ml, capsules or tablets)	
Bottom	Top	Bottom	Top		AM	PM		AM	PM		AM	PM		AM	PM
0.30	0.34	5.0	5.9	10 mg/ml syrup	6 ml	6 ml	1 mg/ml syrup	6 ml	6 ml	10 mg/ml syrup	6 ml	6 ml	80 mg lop/20mg rit per ml solution	1 ml	1 ml
0.34	0.38	6.0	6.9	10 mg/ml syrup	7 ml	7 ml	20 mg capsule	0.5	0.5	10 mg/ml syrup	7 ml	7 ml	80 mg lop/20mg rit per ml solution	1.5 ml	1.5 ml
0.38	0.40	7.0	7.9	10 mg/ml syrup	8 ml	8 ml	20 mg capsule	0.5	0.5	10 mg/ml syrup	8 ml	8 ml	80 mg lop/20mg rit per ml solution	1.5 ml	1.5 ml
													or		
													133 mg lop/33 mg rit per capsule	1	1
0.40	0.43	8.0	8.9	10 mg/ml syrup	9 ml	9 ml	20 mg capsule	0.5	0.5	10 mg/ml syrup	9 ml	9 ml	80 mg lop/20mg rit per ml solution	2 ml	2 ml
										or			or		
										100 mg capsules	1	1	133 mg lop/33 mg rit per capsule	1	1
0.43	0.45	9.0	9.9	10 mg/ml syrup	9 ml	9 ml	20 mg capsule	0.5	0.5	10 mg/ml syrup	9 ml	9 ml	80 mg lop/20mg rit per ml solution	2 ml	2 ml
				or						or			or		
				200 mg tablets						100 mg capsules	1	1	133 mg lop/33 mg rit per capsule	1	1
0.45	0.49	10	10.9	10 mg/ml syrup	10 ml	10 ml	15 mg capsule	1	1	10 mg/ml syrup	10 ml	10 ml	80 mg lop/20mg rit per ml solution	2 ml	2 ml
				or						or			or		
				200 mg tablets	0.5	0.5				100 mg capsules	1	1	133 mg lop/33 mg rit per capsule	1	1
0.49	0.53	11	11.9	10 mg/ml syrup	10 ml	10 ml	15 mg capsule	1	1	10 mg/ml syrup	10 ml	10 ml	80 mg lop/20mg rit per ml solution	2 ml	2 ml
				or						or			or		
				200 mg tablets	0.5	0.5				100 mg capsules	1	1	133 mg lop/33 mg rit per capsule	1	1
0.53	0.58	12	13.9	10 mg/ml syrup	11 ml	11 ml	15 mg capsule	1	1	100 mg capsules	1	1	80 mg lop/20mg rit per ml solution	2 ml	2 ml
				or									or		
				200 mg tablets	0.5	0.5							133 mg lop/33 mg rit per capsule	2	1
													or		
													200 mg lop/50 mg rit per tablet	1	1
0.58	0.70	14	16.9	200 mg tablets	1	0.5	20 mg capsule	1	1	100 mg capsules	2	1	80 mg lop/20mg rit per ml solution	2 ml	2 ml
										or			or		
										300 mg tablets	0.5	0.5	133 mg lop/33 mg rit per capsule	2	1
													or		
													200 mg lop/50 mg rit per tablet	1	1
0.70	0.80	17	19.9	200 mg tablets	1	0.5	20 mg capsule	1	1	100 mg capsules	2	1	80 mg lop/20mg rit per ml solution	2.5 ml	2.5 ml
										or			or		
										300 mg tablets	0.5	0.5	133 mg lop/33 mg rit per capsule	2	1
													or		
													200 mg lop/50 mg rit per tablet	1	1
0.80	0.95	20	24.9	200 mg tablets	1	0.5	20 mg capsule	1	1	100 mg capsules	2	2	80 mg lop/20mg rit per ml solution	3 ml	3 ml
										or			or		
										300 mg tablets	0.5	0.5	133 mg lop/33 mg rit per capsule	2	2
													or		
													200 mg lop/50 mg rit per tablet	1	1
0.95	1.10	25	29.9	200 mg tablets	1	1	30 mg capsule	1	1	100 mg capsules	2	2	80 mg lop/20mg rit per ml solution	3.5 ml	3.5 ml
										or			or		
										300 mg tablets	1	0.5	133 mg lop/33 mg rit per capsule	2	2
													or		
													200 mg lop/50 mg rit per tablet	2	1
1.10	1.20	30	34.9	200 mg tablets	1	1	30 mg capsule	1	1	100 mg capsules	3	3	80 mg lop/20mg rit per ml solution	4 ml	4 ml
										or			or		
										300 mg tablets	1	1	133 mg lop/33 mg rit per capsule	3	3
													or		
													200 mg lop/50 mg rit per tablet	2	2
		35	39.9										80 mg lop/20mg rit per ml solution	5 ml	5 ml
													or		
													133 mg lop/33 mg rit per capsule	3	3
													or		
													200 mg lop/50 mg rit per tablet	2	2
		40	and over										80 mg lop/20mg rit per ml solution	5 ml	5 ml
													or		
													133 mg lop/33 mg rit per capsule	3	3
													or		
													200 mg lop/50 mg rit per tablet	2	2

Source: WHO *(27)*.

Annex 4. Developmental assessment checklist

Table 22. Developmental assessment checklist

Age	Developmental milestones	Date Accomplished
1 month	Raises head Crawling movement Alerts to sound	
2 months	Holds head at midline Lifts chest off table Smiles socially	
4 months	Rolls front to back Laughs	
6 months	Sits unsupported Babbles	
9 months	Pulls to stand Says “mama”	
12 months	Walks alone Uses a couple of words together	
18 months	Can remove some clothing Scribbles Uses 6 or more words together Runs	
24 months	Can wash hands Jumps up Combines words	
36 months	Begins to dress (puts on shirt) Understandable speech Able to balance on one foot	
48 months	Dresses alone Draws a person Uses complex speech Hops	

Source: Adapted from Abrams, El-Sadr, Rabkin *(56)*.

References

1. European Centre for the Epidemiological Monitoring of AIDS (EuroHIV). *HIV/AIDS surveillance in Europe: end-year report 2004.* Saint-Maurice, Institut de Veille Sanitaire, 2005 (No. 71; http://www.eurohiv.org/reports/index_reports_eng.htm, accessed 24 July 2006).
2. Fischer A et al. Simple DNA extraction method for dried blood spots and comparison of two PCR assays for diagnosis of vertical human immunodeficiency virus type 1 transmission in Rwanda. *Journal of Clinical Microbiology,* 2004, 42(1):16–20.
3. Nesheim S et al. Quantitative RNA testing for diagnosis of HIV-infected infants. *Journal of Acquired Immune Deficiency Syndromes,* 2003, 32(2):192–195.
4. Rouet F et al. Pediatric viral human immunodeficiency virus type 1 RNA levels, timing of infection, and disease progression in African HIV-1-infected children. *Pediatrics,* 2003, 112(4):e289.
5. Pineau F et al. Reliable diagnosis of neonatal HIV-1 infection by real time PCR in Congo. *11th Conference on Retroviruses and Opportunistic Infections, San Francisco, 2004* (Abstract No. 900).
6. Rouet F et al. Transfer and evaluation of an automated, low-cost real-time reverse transcription-PCR test for diagnosis and monitoring of human immunodeficiency virus type 1 infection in a West African resource-limited setting. *Journal of Clinical Microbiology,* 2005, 43(6):2709–2717.
7. Rouzioux C et al. Is early diagnosis of HIV infection feasible in resource-limited settings? *12th Conference on Retroviruses and Opportunistic Infections, Boston, 2005* (Abstract No. 107).
8. Schupbach J et al. HIV-1 p24 antigen is a significant inverse correlate of CD4 T-cell change in patients with suppressed viremia under long-term antiretroviral therapy. *Journal of Acquired Immune Deficiency Syndromes,* 2003, 33(3):292–299.
9. Sherman GG, Stevens G, Stevens WS. Affordable diagnosis of human immunodeficiency virus infection in infants by p24 antigen detection. *The Pediatric Infectious Disease Journal,* 2004, 23(2):173–176.
10. Zijenah LS et al. Signal-boosted qualitative ultrasensitive p24 antigen assay for diagnosis of subtype C HIV-1 infection in infants under the age of 2 years. *Journal of Acquired Immune Deficiency Syndromes,* 2005, 39(4):391–394.
11. Sherman GG et al. Polymerase chain reaction for diagnosis of human immunodeficiency virus infection in infancy in low resource settings. *Pediatric Infectious Disease Journal*. 2005; 24(11):993-7.
12. Dunn DT et al. The sensitivity of HIV-1 DNA polymerase chain reaction in the neonatal period and the relative contributions of intra-uterine and intra-partum transmission. *AIDS*, 1995, 9(9):F7–11.
13. Bryson YJ et al. Proposed definitions for in utero versus intrapartum transmission of HIV-1. *The New England Journal of Medicine*, 1992, 327(17):1246–1247.
14. Benjamin DK Jr. Integration of statistical theory and practical clinical expertise. Polymerase chain reaction testing of the HIV-exposed infant. *Minerva Pediatrica*, 2002, 54(2):105–111.
15. Moodley D et al. Predicting perinatal human immunodeficiency virus infection by antibody patterns. *The Pediatric Infectious Disease Journal*, 1995, 14(10):850–852.
16. *Management of a child with a serious infection or malnutrition: guidelines for the care at the first-referral level in developing countries*. Geneva, World Health Organization, 2000.
17. *Management of serious malnutrition: a manual for physicians and other senior health workers*. Geneva, World Health Organization, 1998.
18. *Nutrient requirements for people living with HIV: report of a technical consultation.* Geneva, World Health Organization, 2003.
19. Miller TL. Nutritional aspects of HIV-infected children receiving highly active antiretroviral therapy. *AIDS*, 2003, 17(Suppl. 1):S130–S140.
20. *Vitamin A supplements: a guide to their use in the treatment and prevention of vitamin A deficiency and xerophthalmia*, 2nd ed. Geneva, World Health Organization, 1997.
21. Coutsoudis A et al. The effects of vitamin A supplementation on the morbidity of children born to HIV-infected women. *American Journal of Public Health*, 1995, 85(8):1076–1081.
22. Sfawzi WW et al. A randomized trial of vitamin A supplements in relation to mortality among human immunodeficiency virus-infected and uninfected children in Tanzania. *The Pediatric Infectious Disease Journal*, 1999, 18(2):127–133.

23. Van Dyke RB et al. Reported adherence as a determinant of response to HAART in children who have HIV-infection. *Pediatrics*, 2002, 109:e61.
24. De Martino M et al. Reduction in mortality with availability of antiretroviral therapy for children with perinatal HIV-1 infection. Italian Register for HIV Infection in Children and the Italian National AIDS Registry. *JAMA*, 2000, 284:190–197.
25. Phase IIB trial to evaluate the efficacy of oral nevirpaine and the efficacy of oral AZT in infants born to HIV-infected mothers in Uganda for prevention of vertical HIV transmission (Version 2.0). (HIVNET 012) HIVNET/HPTN Group, 14 May 2003, Seattle, Washington, USA (http://www.hptn.org/Web%20Documents/HIVNET_Protocols/HIVNET_012.pdf
26. Short-term risk of disease progression in HIV-1-infected children receiving to antiretroviral therapy or zidovudine monotherapy: a meta-analysis. HIV Paediatric Prognostic Markers Collaborative Study *Lancet* 2003; 362:1605-11.
27. Use of total lymphocyte count for informing when to start antiretroviral therapy in HIV-infected children: a meta-analysis of longitudinal data. HIV Paediatric Prognostic Markers Collaborative Study. *Lancet* 2005; 366:1868-74.
28. HIV Paediatric Prognostic Markers Collaborative Study [web site]. London, Medical Research Council Clinical Trials Unit, 2006 (http://www.hppmcs.org, accessed 8 June 2006).
29. Sharland M et al. PENTA guidelines for the use of antiretroviral therapy. *HIV Medicine*, British HIV Association, 5(S2):61–86, 2004 (http://www.ctu.mrc.ac.uk/penta/guidelin.pdf, accessed 30 May 2006).
30. *Antiretroviral therapy of HIV infection in infants and children in resource-limited settings, towards universal access: recommendation of a public health approach:* 2006. Geneva, World Health Organization, 2006 (http://www.who.int/hiv/pub/guidelines/WHOpaediatric.pdf, accessed 19 February 2007).
31. HIV Paediatric Prognostic Markers Collaborative Study; risk calculator [web site]. London, Medical Research Council Clinical Trials Unit, 2006 (http://www.ctu.mrc.ac.uk/penta/hppmcs/calcProb.htm, accessed 28 December 2006).
32. Penta 5, PENTA Trials [web site]. London, Paediatric European Network for the treatment of AIDS (PENTA), 2006 (http://www.ctu.mrc.ac.uk/penta/trials.htm, accessed 23 February 2007).
33. Gibb DM, et al. Evolution of antiretroviral phenotypic and genotypic drug resistance in antiretroviral naïve HIV-1 infected children treated with abacavir/lamivudine, zidovudine/lamivudine or abacavir/zidovudine, with or without nelfinavir (the PENTA 5 trial). *Antiviral Therapy* 2002*;* 7(4): 293-303 (http://www.ctu.mrc.ac.uk/penta/p5avt02.pdf accessed on 23 February 2007).
34. Ramos JT et al. Prevalence of lipodystrophy and hyperlipidemia in a large cohort of HIV-infected children, *12th Conference on Retroviruses and Opportunistic Infections* Boston 2005; (Abstract No. 775) (http://www.aegis.org/conferences/croi/2005/775.html, accessed on 28 December 2006)
35. BHIVA Writing Committee, Gazzard B et al. Draft BHIVA guidelines for the treatment of HIV-infected adults with antiretroviral therapy (2006) for consultation. (http://www.bhiva.org/guidelines/2006/hiv/hivfs06.html, accessed on 28 December 2006).
36. Handforth J, Sharland M. Triple nucleoside reverse transcriptase inhibitor therapy in children. *Paediatric Drugs*, 2004, 6(3):147–159.
37. Gulick RM et al. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. *The New England Journal of Medicine*, 2004, 350(18):1850–1861.
38. Staszewski S et al. Abacavir-lamivudine-zidovudine vs. indinavir-lamivudine-zidovudine in antiretroviral-naive HIV-infected adults: a randomized equivalence trial. *JAMA*, 2001, 285(9):1155–1163.
39. Eshleman SH et al. Selection and fading of resistance mutations in women and infants receiving nevirapine to prevent HIV-1 vertical transmission (HIVNET 012). *AIDS*, 2001, 15(15):1951–1957.
40. Mandelbrot L et al. Lamivudine-zidovudine combination for prevention of maternal-infant transmission of HIV-1. *JAMA*, 2001, 285(16):2083–2093.
41. Bulterys M et al. Combination antiretroviral therapy in African nursing mothers and drug exposure in their infants: new pharmacokinetic and virologic findings. *Journal of Infectious Diseases*, 2005, 192(5):709–712.
42. Shapiro RL et al. Antiretroviral concentrations in breast-feeding infants of women in Botswana receiving antiretroviral treatment. *Journal of Infectious Diseases*, 2005, 192(5):720–727.

43. Watson DC, Farley JJ. Efficacy of, and adherence to, highly active antiretroviral therapy in children infected with human immunodeficiency virus type 1. *The Pediatric Infectious Disease Journal*, 1999, 18(8):682–689.
44. Farley J et al. Assessment of adherence to antiviral therapy in HIV-infected children using the Medication Event Monitoring System, pharmacy refill, provider assessment, caregiver self-report and appointment keeping. *Journal of Acquired Immune Deficiency Syndromes*, 2003, 33(2):211–218.
45. Gibb DM et al. Adherence to prescribed antiretroviral therapy in human immunodeficiency virus-infected children in the PENTA 5 trial. *The Pediatric Infectious Disease Journal*, 2003, 22(1):56–62.
46. Saitoh A et al. An MDR1-3435 variant is associated with higher plasma nelfinavir levels and more rapid virologic response in HIV-1 infected children. *AIDS*, 2005, 19(4):371–380.
47. Machado DM et al. Analysis of HIV-type 1 protease and reverse transcriptase in Brazilian children failing highly active antiretroviral therapy (HAART). *Revista do Instituto de Medicina Tropical de São Paulo*, 2005, 47(1):1–5.
48. Lindsey JC et al. Treatment-mediated changes in human immunodeficiency virus (HIV) type 1 RNA and CD4 cell counts as predictors of weight growth failure, cognitive decline, and survival in HIV-infected children. *Journal of Infectious Diseases*, 2000, 182(5):1385–1393.
49. Hirsch HH et al. Immune reconstitution in HIV-infected patients. *Clinical Infectious Diseases*, 2004, 38(8):1159–1166.
50. Jevtovic DJ et al. The prevalence and risk of immune restoration disease in HIV-infected patients treated with highly active antiretroviral therapy. *HIV Medicine*, 2005, 6(2):140–143.
51. Shelburne SA et al. Incidence and risk factors for immune reconstitution inflammatory syndrome during highly active antiretroviral therapy. *AIDS*, 2005, 19(4):399–406.
52. Puthanakit T. Immune reconstitution syndrome after highly active antiretroviral therapy in human immunodeficiency virus-infected Thai children. *Pediatric Infectious Diseases Journal*, 2006, 25(1):53–58.
53. Tangsinmankong N et al. *Varicella zoster* as a manifestation of immune restoration disease in HIV-infected children. *Journal of Allergy and Clinical Immunology*, 2004, 113(4):742–746.
54. Nuttall JJ et al. Progressive multifocal leukoencephalopathy after initiation of highly active antiretroviral therapy in a child with advanced human immunodeficiency virus infection: a case of immune reconstitution inflammatory syndrome. *The Pediatric Infectious Disease Journal*, 2004, 23(7):683–685.
55. Shelburne SA, Montes M, Hamill RJ. Immune reconstitution inflammatory syndrome: more answers, more questions. *The Journal of Antimicrobial Chemotherapy*, 2005, 57(2):167–170.
56. Abrams E, El-Sadr W, Rabkin M. The Pediatric Clinical Manual. *The International Center for AIDS Programs*. New York, Columbia University Mailman School of Public Health, 2004 (http://www.columbia-icap.org/clinicalunit/pdf/cm/Pediatric_Clinical_Manual.pdf, accessed 28 December 2006).
57. Chase C et al. Early Cognitive and motor development among infants born to women infected with human immunodeficiency virus. *Pediatrics* 2000, 106(2):e25.
58. The European Collaborative Study. Height, weight, and growth in children born to mothers with HIV-1 infection in Europe. *Pediatrics* 2003, 111(1): e52-e60.
59. Chakraborty R, Shingadia D. *Treating Opportunistic Infections In HIV-Infected Children Guidelines for the Children's HIV Association* (CHIVA) [web site]. London, Children's HIV Association (CHIVA), September 2006, accessed 23 February 2007).
60. Dunn A-M, Tizer K, Cervia JS. Rifabutin-associated uveitis in a pediatric patient. *The Pediatric Infectious Disease Journal*, 1995, 14:246–247.
61. Chintu C et al. Cotrimoxazole as prophylaxis against opportunistic infections as HIV-infected Zambian children (CHAP): a double-blind randomised placebo-controlled trial. *The Lancet*, 2004, 364:1865–18671.
62. Graham SM et al. Clinical presentation and outcome of *Pneumocystis carinii* pneumonia in Malawian children. *The Lancet*, 2000, 355:369–373.
63. Riordan A. *The child with HIV and respiratory illness.* London, British HIV Association, 2005 (http://www.bhiva.org/chiva/protocols/respiratory.html, accessed 22 May 2006).

64. *Report of a WHO expert consultation on cotrimoxazole prophylaxis in HIV infection.* Geneva, World Health Organization, 2005 (WHO Technical Report Series; http://www.who.int/hiv/pub/meetingreports/ctxprophylaxismeeting.pdf, accessed 24 May 2006).
65. *Guidelines for cotrimoxazole prophylaxis for HIV-related infections in children, adolescents and adults in resource limited settings: recommendations for a public health approach.* Geneva, World Health Organization.
66. Renold C et al. Toxoplasma encephalitis in patients with the acquired immunodeficiency syndrome. *Medicine,*1992; 71 (4): 224-39.
67. Mitchell CD et al. Congenital toxoplasmosis occurring in infants perinatally infected with human immunodeficiency virus 1. *Pediatric Infectious Disease Journal,* 1990; 9: 512–8.
68. Montoya JG, Remington JS. Toxoplasma gondii. In: Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases. Philadelphia: Churchill Livingstone, 2000; 2858-2888.
69. Post MJ et al. Cranial CT in acquired immunodeficiency syndrome: spectrum of diseases and optimal contrast enhancement technique. *American Journal of Roentgenol* 1985; 145(5): 929-40.
70. Levy RM et al. The efficacy and clinical impact of brain imaging in neurologically symptomatic AIDS patients: a prospective CT/MRI study. *Journal of Acquired Immune Deficiency Syndrome,* 1990 3(5): 461-71.
71. Ciricillo SF, Rosenblum ML. Imaging of solitary lesions in AIDS. J Neurosurg 1991; 74(6): 1029.
72. Martins MD, Lozano-Chiu M, Rex JH. Declining rates of oropharyngeal candidiasis and carriage of Candida albicans associated with trends toward reduced rates of carriage of fluconazole-resistant C. albicans in human immunodeficiency virus-infected patients. *Clinical Infectious Diseases,* 1998; 27(5):1291-4
73. Gottfredsson M et al. Association of plasma levels of human immunodeficiency virus type 1 RNA and oropharyngeal Candida colonization. *Journal of Infectious Diseases,* 1999; 180 (2): 534-7.
74. Fichtenbaum CJ et al. Refractory mucosal candidiasis in advanced human immunodeficiency virus infection. *Clinical Infectious Diseases,* 2000; 30(5):749-56
75. Muller FM, Groll AH, Walsh TJ. Current approaches to diagnosis and treatment of fungal infections in children infected with human immuno deficiency virus. *European Journal of Pediatrics,* 1999, 158:187–199.
76. Walsh TJ et al. Fungemia in children infected with the human immunodeficiency virus: new epidemiologic patterns, emerging pathogens and improved outcome with antifungal therapy. *Clinical Infectious Diseases,* 1995, 20:900–906.
77. Nigro G et al. Rapid progression of HIV disease in children with cytomegalovirus anaemia. *AIDS,* 1996, 10:1127–1133.
78. Martin DF et al. A controlled trial of valganciclovir as induction therapy for cytomegalovirus retinitis. *The New England Journal of Medicine,* 2002, 346:1119–1126.
79. Leibovitz E et al. Chronic varicella-zoster in a child infected with human immunodeficiency virus: case report and review of the literature. *Cutis,* 1992; 49:27–31.
80. von Seidlein L et al.. Frequent recurrence and persistence of varicella-zoster virus infections in children infected with human immunodeficiency virus type 1. *Journal of Pediatrics,* 1996; 128(1): 52-7.
81. Silliman CC et al. Unsuspected varicella-zoster virus encephalitis in a child with acquired immunodeficiency syndrome. *Journal of Pediatrics,* 1993; 123:418–22.
82. CDC. Guidelines for the prevention of opportunistic infections among HIV-infected persons—recommendations of the U.S. Public Health Service and the Infectious Disease Society of America. *Morbidity and mortality weekly report,* 2002; 51(No. RR-8). MMWR. Available at: http://AIDSInfo.nih.gov.
83. Whitley R, Kimberlin D, Roizman B. *Herpes simplex* viruses. *Clinical Infectious of Diseases,* 1998, 26:541–553.
84. Kimberlin DW et al. Natural history of neonatal *Herpes simplex* virus infections in the acyclovir era. *Pediatrics,* 2001, 108:223–229.
85. Kimberlin DW et al. Application of the polymerase chain reaction to the diagnosis and management of neonatal *Herpes simplex* virus disease. *Journal of Infectious Diseases,* 1996, 174:1162–1167.

86. Hilgartner MW et al. The effect of plasma human immunodeficiency virus RNA and CD4+ T lymphocytes on growth and measurements of hemophilic boys and adolescents. *Pediatrics*, 2001, 107(4): E56.
87. Gaughan DM et al. Avascular necrosis of the hip (Leggs-Calve-Perthes Disease) in HIV-infected children in long-term follow-up: PACTG study 219. *8th Conference on Retroviruses and Opportunistic Infections, Chicago, 4–8 February 2001* (Abstract 638; http://www.retroconference.org/2001/abstracts/abstracts/abstracts/638.htm, accessed 13 June 2006).
88. Schwartz L, Houck CS. Pain management for children with HIV. In: Nedeljkovic, SS, ed. *Pain management, anesthesia, and HIV/AIDS*. New York, Elsevier Science Health, 2002.
89. *Guidelines for the use of antiretroviral agents in pediatric HIV infection.* Boston, Butterworth Heinemann, 2005 (http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf, accessed 18 June 2006).
90. *Report of the technical consultation on clinical staging of HIV/AIDS and HIV/AIDS case definition for surveillance*. Copenhagen, WHO Regional Office for Europe, 2005 (http://www.euro.who.int/document/E87956.pdf, accessed 19 December 2006).