MANAGEMENT OF HIV INFECTION AND ANTIRETROVIRAL THERAPY IN INFANTS AND CHILDREN

A Clinical Manual

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Regional Office for South-East Asia

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Management of HIV Infection and Antiretroviral Therapy in Infants and Children

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ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
AFB	acid-fast bacillus
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransaminase
ARV	antiretroviral (drug)
ART	antiretroviral therapy
AST	aspartate aminotransferase
AZT	azidothymidine (also named zidovudine)
BAL	bronchoalveolar lavage
CD4	CD4+ T-lymphocyte
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
d4T	stavudine
ddI	didanosine
DNA	deoxyribonucleic acid
EFV	efavirenz
FBC	full blood cell count
FDC	fixed-dose combination
FTC	emtricitabine
Hb	haemoglobin
HCW	health-care worker
HIV	human immunodeficiency virus
HSV	herpes simplex virus
IDV	indinavir
IMCI	Integrated Management of Childhood Illnesses
INH	isoniazid
IPT	isoniazid preventive therapy
IRIS	immune reconstitution inflammatory syndrome
LDH	lactate dehydrogenase

LDL	low-density lipoprotein
LIP	lymphocytic interstitial pneumonia
LPV	lopinavir
LPV/r	lopinavir/ritonavir
MAC	*Mycobacterium avium* complex
MTCT	mother-to-child transmission (of HIV)
NFV	nelfinavir
NRTI	nucleoside reverse transcriptase inhibitor
NNRTI	non-nucleoside reverse transcriptase inhibitor
NVP	nevirapine
OHP	oral hairy leukoplakia
OI	opportunistic infection
PCP	*Pneumocystis jiroveci* pneumonia (previously *Pneumocystis carinii* pneumonia)
PCR	polymerase chain reaction
PI	protease inhibitor
PGL	persistent generalized lymphadenopathy
PML	progressive multifocal leukoencephalopathy
PMTCT	prevention of mother-to-child transmission (of HIV)
RTV	ritonavir
SD	standard deviation
SQV	saquinavir
STI	sexually transmitted infection
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
TLC	total lymphocyte count
TMP–SMX	trimethoprim–sulfamethoxazole
TST	tuberculin skin test
ULN	upper limit of normal
UNICEF	United Nations Children's Fund
Up24 Ag	ultra-sensitive p24 antigen
VZV	Varicella zoster virus
WBC	white blood cell
WHO	World Health Organization
ZDV	zidovudine

CONTENTS

Annexes

1 Introduction

Successful scaling-up of antiretroviral therapy (ART) requires rational use of antiretroviral (ARV) drugs. These simplified and standardized guidelines on the appropriate and rational use of ART in resource-limited settings for South and South-East Asia are intended as a resource for

- physicians and other health-care providers caring for children with known exposure to the human immunodeficiency virus (HIV), HIV-infected children and sick children with unknown HIV exposure but suspected to have HIV infection;
- national AIDS programme managers, maternal and child health programme managers, and other health planners as a reference for developing national guidelines on the management of HIV infection and ART in infants and children, and
- NGOs and other civil society organizations supporting people living with and affected by HIV.

These guidelines are based on the discussions held with health-care workers, researchers and programme managers from South-East Asia during a regional consultation organized by the World Health Organization Regional Office for South-East Asia (WHO SEARO) and the United Nations Children's Fund Regional Office for South Asia (UNICEF ROSA) in New Delhi during 2006. This consultation meeting reviewed the new data, experiences of scaling-up of paediatric ART in the Region and made recommendations for adaptation to the needs in the Region of the global WHO guidelines on *Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access.* To facilitate use at the country level the consultation recommended simplification of the global guidelines.

This publication is being released along with the following publications from WHO SEARO:

- *Antiretrovirals for HIV: a compilation of facts and product information*
- *Antiretroviral therapy of HIV infection in adults and adolescents: a clinical manual*

These guidelines have been developed in recognition of the need for physicians, programme planners, other health-care workers and people living with HIV to have one simple, user-friendly reference manual for national adaptation. It covers the diagnosis of HIV infection in infants and children, followed by patient evaluation, prevention and management of opportunistic infections (OIs), pre-enrolment information and counselling process for ART, and ensuring treatment adherence. The guidelines are meant to be complementary to the global guidelines as mentioned above. For further details readers are referred to these.

As the field of HIV/AIDS and, in particular, ART is changing rapidly, the guidelines will require updating at regular intervals as new significant data emerge.

2 Assessment and management: first visit in paediatric or general outpatient clinic

Child with known HIV exposure [a]

- Assess the likelihood of acquiring HIV infection by checking for:
  - maternal HIV disease status; [b]
  - maternal and infant's exposure to ARVs; [c,d]
  - mode of delivery, and breastfeeding.[e]

- Take the history and perform physical examination. Evaluate if the child has signs and symptoms of HIV infection or OI.
- Provide appropriate investigation/ treatment for OI. (*see* pp. 88–96)

- Assess whether there is a need for ART. Referral to a paediatrician experienced with ART should be considered if available.
- All HIV-exposed babies should receive co-trimoxazole. Identify whether there is a need for children >1 year to continue co-trimoxazole. (*see* pp. 15–16)

- Perform HIV diagnostic testing.
- Methods used depend on the child's age (*see* pp. 5–11).

Sick child with unknown HIV exposure but suspected to have HIV infection

- Identify if there are any risk factors for HIV:
  - maternal HIV disease status; [b]
  - blood transfusion;
  - injecting drug use, or
  - sexual exposure.

- Take the history and perform physical examination. Identify if the child has signs and symptoms of HIV infection or OI.
- Provide appropriate investigation/ treatment for OI. (*see* pp. 88–96)

- Identify risk factors and/or signs/ symptoms consistent with HIV infection or HIV-related OIs.
- Offer diagnostic testing and counselling for HIV.
- Use methods appropriate for the child's age (*see* pp. 5–11).
- In cases where the maternal HIV status cannot be confirmed and virological testing is not available to diagnose HIV infection in a child <18 months, HIV antibody testing should be performed.

Notes

[a] All HIV-exposed children should be evaluated by a physician and/or, if available, by a paediatrician as above.

[b] Advanced clinical HIV disease or low CD4 count in the mother are risk factors for HIV transmission from mother to infant during pregnancy, delivery and breastfeeding.

[c] Successful long-term treatment with ART of mothers reduces the risk of HIV transmission.

[d] Use of ARV drugs for the prevention of mother-to-child transmission (PMTCT) using azidothymidine (AZT) monotherapy alone, AZT monotherapy + nevirapine (NVP) single dose, NVP single dose alone are associated with transmission rates of approximately 5–10%, 3–5%, 10–20%, respectively, in nonbreastfeeding mothers. The transmission rate is approximately 2% in mothers receiving combination ART. [1]

[e] HIV transmission can occur via breastfeeding. A child remains at risk for acquiring HIV infection as long as he/she is breastfed.

[1] *Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants in resource-limited settings: towards universal access. Recommendations for a public health approach.* Geneva, World Health Organization, 2006.

3 Diagnosis of HIV infection in children[2]

3.1 Excluding HIV infection in infants and children

- The definitive diagnosis of HIV infection at any age requires diagnostic testing to confirm the presence of HIV.
- Antibody testing identifies HIV antibody generated as part of the immune response to HIV infection. In children ≥18 months of age, antibody testing should be done in the same manner as in adults.

- As maternal HIV antibody transferred passively during pregnancy can persist for as long as 18 months in children born to HIV-infected mothers,[3,4] the interpretation of positive HIV antibody test results is more difficult in children below this age.
- HIV-exposed infants who have a positive HIV antibody test result at ages 9 to <18 months are considered at high risk of having HIV infection but a definitive diagnosis of HIV infection using antibody testing can only be done at ≥18 months of age.
- To diagnose HIV infection definitively in children aged <18 months, assays that detect the virus or its components (i.e. virological tests) are required. A range of laboratory-based techniques is available. These techniques are discussed in detail in the next section. Children who have a positive virological test result at any age are considered HIV-infected.
- Children who are breastfed have an ongoing risk for acquiring HIV infection; therefore, HIV infection can be excluded only after breastfeeding is stopped for >6 weeks.

[2] Adapted from *Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access*. Geneva, WHO, 2006.

[3] Chantry CJ, Cooper ER, Pelton SI, Zorilla C, Hillyer GV, Diaz C. Seroreversion in human immunodeficiency virus-exposed but uninfected infants. *Pediatr Infect Dis J* 1995, 14:382–7.

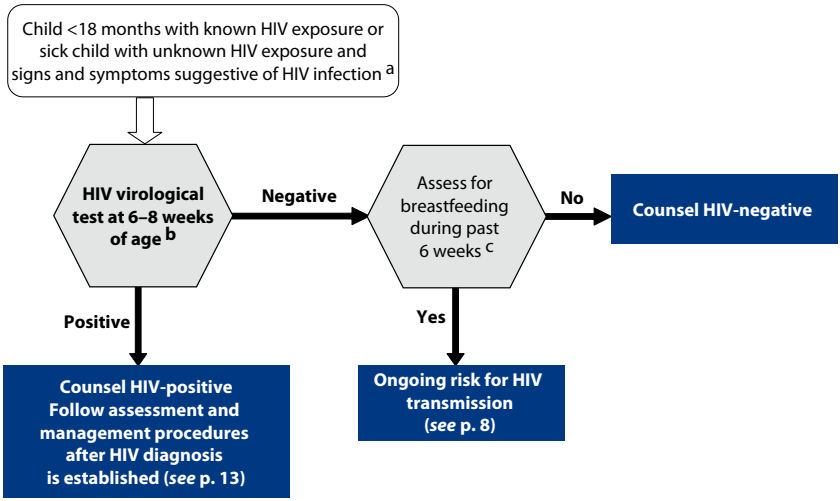
[4] Rakusan TA, Parrott RH, Sever JL. Limitations in the laboratory diagnosis of vertically acquired HIV infection. *J Acquir Immune Defic Syndr* 1991, 4:116–21.

There are two ways to exclude HIV infection in infants and children:

1. **HIV virological test**
   - A negative virological test result in an infant 6 weeks of age or more who has never breastfed
   - A negative virolocial test result in an infant who has completely stopped breastfeeding for at least 6 weeks
2. **HIV antibody test**
   - A child has a negative HIV antibody test result at ≥18 months of age if not breastfeeding and has completely stopped breastfeeding for >6 weeks.
   - A child who has a negative HIV antibody test result at ≥9 months of age and has completely stopped breastfeeding for at least 6 weeks is HIV-uninfected.
   - HIV antibody testing can be done as early as 9–12 months of age. By then, 74% and 96% of HIV-uninfected children will test negative for HIV antibody at 9 and 12 months of age, respectively.

3.2 Diagnosing HIV infection in infants and children less than 18 months of age

3.2.1 Diagnosing HIV infection in infants and children less than 18 months of age with unknown HIV exposure



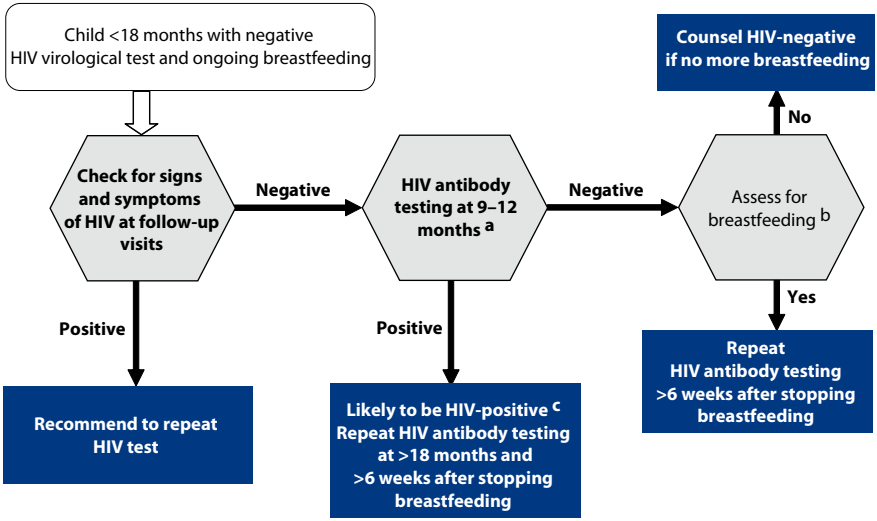
Notes

[a] If HIV exposure is not certain, consider testing the mother first before doing a virological test on the child. If the mother tests negative for HIV, explore other risk factors for HIV transmission.

[b] Children who are breastfed have an ongoing risk of acquiring HIV infection; therefore, HIV infection at this age can be excluded only after completely stopping breastfeeding for >6 weeks.

[c] Virological testing includes detection of HIV DNA or HIV RNA (viral load) or ultra-sensitive p24 antigen (Up24 Ag). Virological testing can be used to confirm the diagnosis of HIV infection at any age. Children <18 months of age can have maternal HIV antibodies, making it difficult to interpret HIV-positive antibody test results; therefore, only virological testing is recommended for confirming the diagnosis in this age group. Ideally, a second virological test on a separate specimen should be done to confirm an initial positive test result.

3.2.2 Diagnosing HIV infection in infants and children less than 18 months of age with ongoing breastfeeding



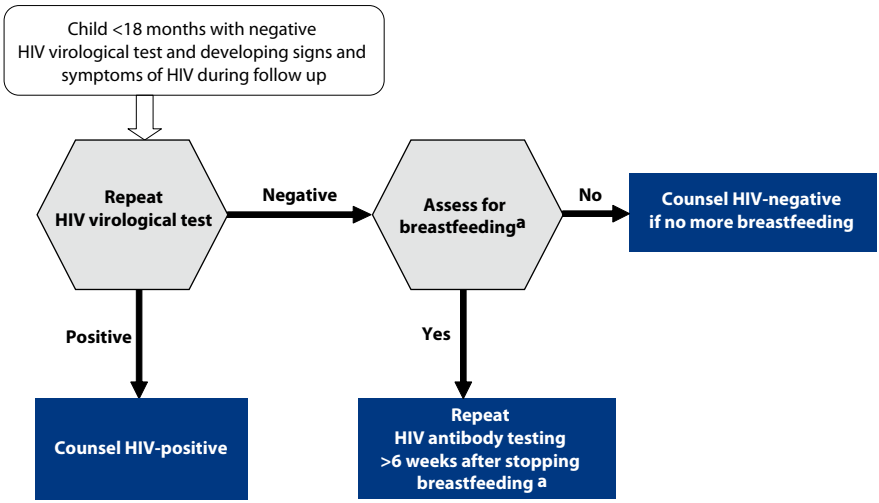
Notes

[a] HIV antibody testing can be used to exclude HIV infection in children from 9–12 months of age. At 9 months of age, approximately 74% of uninfected children and by 12 months, 96% of uninfected children have negative antibody test results, respectively.

[b] Children who are breastfed have an ongoing risk of acquiring HIV infection; therefore, HIV infection can be excluded only after stopping breastfeeding for >6 weeks.

[c] Parents should be counselled that the child is likely to be HIV-infected. However, the chance that the child may be HIV-negative is 4–26% depending on the child's age at testing. Therefore, confirmatory HIV antibody testing is needed at 18 months of age.

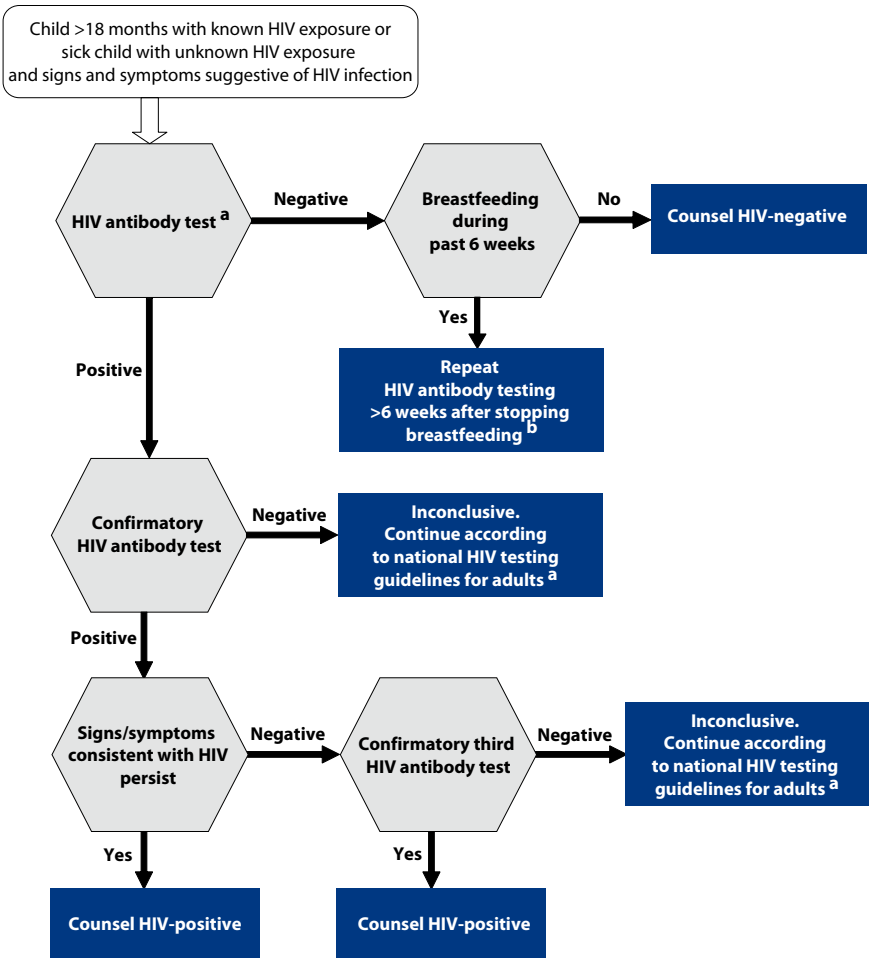
3.2.3 Diagnosing HIV infection in infants and children less than 18 months of age with an initial negative HIV virological test and presenting with signs/symptoms of HIV at follow-up visit



Note

[a] Children who are breastfed have an ongoing risk of acquiring HIV infection; therefore, HIV infection can be excluded only after stopping breastfeeding for >6 weeks.

3.3 Diagnosing HIV infection in infants and children aged 18 months or more[1]



Notes

[a] HIV testing procedures should follow each country's national HIV testing guidelines and algorithms.

One positive HIV antibody test (rapid test or ELISA) should be confirmed by a second HIV antibody test (rapid test or ELISA) using an assay relying on a different antigen

or with different operating characteristics. In the selection of HIV antibody tests for diagnosis, the first test should have the highest sensitivity, whereas the second and third tests should have a similar or higher specificity than the first. Tests currently recommended by WHO have both high sensitivity and specificity.

National HIV testing algorithms may require a third confirmatory test in low HIV-prevalence settings.

A definitive diagnosis of HIV infection in children aged ≥ 18 months (with known or unknown HIV exposure) can be made with antibody testing, following standard testing algorithms used for adults. For further information consult *HIV assays: operational characteristics. Report 14. Simple/rapid tests.* Geneva, WHO, 2004.

Virological testing according to national algorithms can be used to diagnose HIV infection at any age.

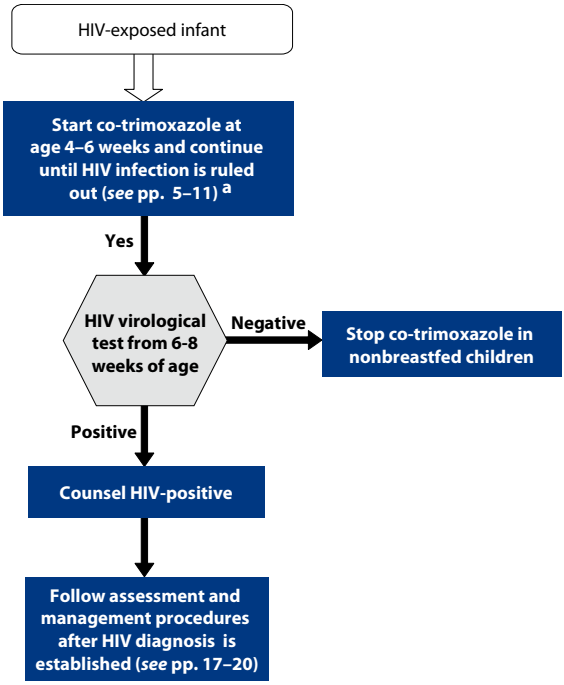
[b] Children who are breastfed have an ongoing risk of acquiring HIV infection; therefore, HIV infection can be excluded only after stopping breastfeeding for > 6 weeks.

4 ASSESSMENT AND MANAGEMENT OF HIV-EXPOSED CHILDREN LESS THAN 18 MONTHS OF AGE

- Assess the growth and nutritional status, and need for intervention.
- Provide co-trimoxazole prophylaxis for prevention of *Pneumocystis jiroveci* pneumonia (PCP), as well as malaria, bacterial diarrhoeal disease and pneumonias (*see* pp. 15–16 and 86–96).
- Assess for signs and symptoms suggestive of HIV infection/disease. If these are consistent with severe HIV disease, consider starting ART (*see* pp. 19–20).
- Assess for signs and symptoms of OIs, diagnose the condition and provide treatment if these are suspected (*see* pp. 78–79).
- Assess the family situation and provide guidance, support and treatment to family members with or at risk for HIV infection.
- Offer HIV antibody testing starting from 9 to 12 months of age. HIV infection can be excluded if HIV antibody is negative provided that breastfeeding has completely stopped for >6 weeks. Antibody test results are negative in 74% of uninfected children at 9 months, and 96% of uninfected children by 12 months.
- Diagnosis of HIV infection in children <18 months in resource-limited settings is at times not possible due to the lack of availability of and accessibility to HIV DNA, HIV RNA PCR and/or Up24 Ag testing.

5 CO-TRIMOXAZOLE PROPHYLAXIS FOR *Pneumocystis jiroveci* PNEUMONIA

Starting co-trimoxazole in an infant born to an HIV-positive mother



Note

[a] The dosage regimen for co-trimoxazole is given on pp. 114–116.

Patients and families should understand that co-trimoxazole does not treat and cure HIV infection. Co-trimoxazole protects from infections with a high mortality which are more common or more likely to occur in HIV-exposed infants and immunocompromised children. It is essential to take co-trimoxazole regularly. Co-trimoxazole does not replace the need for ART.

Initiation of co-trimoxazole prophylaxis in children

Table 1: Situation			
HIV-exposed infants and children	**Confirmed HIV-infected infants and children**		
	< 1 year	1–5 years	≥ 6 years
CTX prophylaxis is universally indicated, starting at 4–6 weeks after birth and maintained until cessation of risk of HIV transmission and exclusion of HIV infection	CTX prophylaxis indicated regardless of CD4% or clinical status	WHO stages 2, 3 and 4 regardless of CD4% [b] **or** Any WHO stage and CD4 < 25% [a]	Any WHO clinical stage and CD4 < 350 [a] **or** WHO stage 3 or 4 and any CD4 level [b]
Universal option: This strategy may be considered in settings such as in TB programmes with a high prevalence of HIV and limited health infrastructure.			

CTX co-trimoxazole

Notes

[a] In resource-limited settings, co-trimoxazole may be started when the CD4 count has dropped to < 25% at age < 5 years or is < 350 cells/mm^3 at ≥ 6 years.The aim is to reduce the morbidity and mortality associated with malaria, bacterial diarrhoeal diseases and pneumonia, in addition to the prevention of PCP and toxoplasmosis.

In other settings where the use of co-trimoxazole is limited to preventing PCP, co-trimoxazole may be started when the CD4 count has dropped to < 20% at age ≤ 5 years or is < 200 cells/mm^3 at ≥ 6 years.

[b] Asymptomatic children in WHO clinical stage I do not require co-trimoxazole prophylaxis. However, it is strongly recommended to measure the CD4 count as asymptomatic children may also have laboratory signs of immunodeficiency.

6 ASSESSMENT AND MANAGEMENT AFTER HIV INFECTION IS CONFIRMED

- Assess the growth and nutritional status, and need for intervention.
- Assess the immunization status and provide appropriate immunizations.
- Assess for signs and symptoms of OIs (*see* pp.86–96) and history of exposure to TB. If an OI is suspected, diagnosis and treatment of the OI takes priority over initiation of ART.

- Assign the WHO clinical stage. (*see* pp. 19–20).
- Ensure that the child is on co-trimoxazole. (*see* pp. 15–16).
- Identify concomitant medications that may produce drug interactions with ART.
- Stage HIV disease using immunological criteria (*see* WHO stage from "not significant" to "severe immune suppression"; pp.19–20).
  - Perform a CD4 count (CD4% is preferred in children <5 years and CD4 count is preferred in children ≥ 5 years).
  - To calculate the CD4% and count, a full blood cell count (FBC) needs to be performed as well (ideally automated).
- TLC is an option that may be used for starting ART where CD4 assessment is not available (*see* p. 20).

- Assess whether the child fulfils the criteria for starting ART (*see* pp. 21–23). Starting ART is not an emergency but once started the treatment must be given on time every day. Non-adherence to treatment is the main reason for treatment failure.
- Assess the family situation including, but not limited to, the number of persons with or at risk for HIV infection and their current health/treatment status.
  - Identify the primary caregiver for the child and his/her ability and willingness to adhere to follow-up schedules and treatment for HIV, especially ART.
  - Identify other caregivers who may be responsible for administering ART.
  - Assess family members' understanding of HIV disease and its treatment.
  - Assess the disclosure status of HIV diagnosis within the family (whether the child knows his/her diagnosis, whether anyone else knows, and if the child knows the parent[s]' HIV status).
  - Assess the financial status of the family, including their ability to pay for transportation to the clinic, afford adequate food/nutritional supplements for the child, pay for any treatment needed and whether they have a refrigerator for keeping ARVs that need to be stored at a low temperature, if required.

7 HIV STAGING IN CHILDREN USING CLINICAL AND IMMUNOLOGICAL CRITERIA

7.1 Using clinical criteria

Table 2: WHO classification of HIV-associated clinical disease

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

Details of the WHO clinical staging are given on pp. 78–84.

- Clinical staging can be used to predict mortality in HIV-infected children not yet on ART.
- The WHO clinical stage can be used as an indication for when to start co-trimoxazole and when to start ART, particularly in situations where CD4 assessment is not available (*see* pp. 15–16 and pp. 21–23).

7.2 Using immunological criteria

7.2.1 Using CD4 count

Table 3: WHO classification of HIV-associated immunodeficiency using CD4 count

Classification of HIV-associated immunodeficiency	Age-related CD4 values			
	≤11 months (CD4%)	12–35 months (CD4%)	36–59 months (CD4%)	≥5 years (cells/mm^3 or CD4%)
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%

- CD4 (absolute count or %) is the best measurement to assess immune deficiency.
- The CD4 count should be used in conjunction with clinical assessment; however, CD4 count allows early detection of worsening of HIV disease, as the CD4 count usually falls before clinical progression takes place.
- CD4 monitoring can aid in the decision to initiate ART or switch to another ARV drug.
- Younger children normally have higher CD4 counts than older children and adults.
- CD4% is the preferred measurement in children <5 years old, as it varies less in them than in older children.
- At ≥5 years of age, either CD4% or absolute CD4 count can be used but CD4 count is preferred.
- The threshold CD4 levels for severe immunodeficiency in children ≥1 year of age correspond with a 12-month mortality risk of ≤5%. In children <1 year of age, especially those <6 months, the CD4 count is less predictive of mortality and there is a high risk for death even if the CD4% is high.

7.2.2 Using total lymphocyte count (TLC)

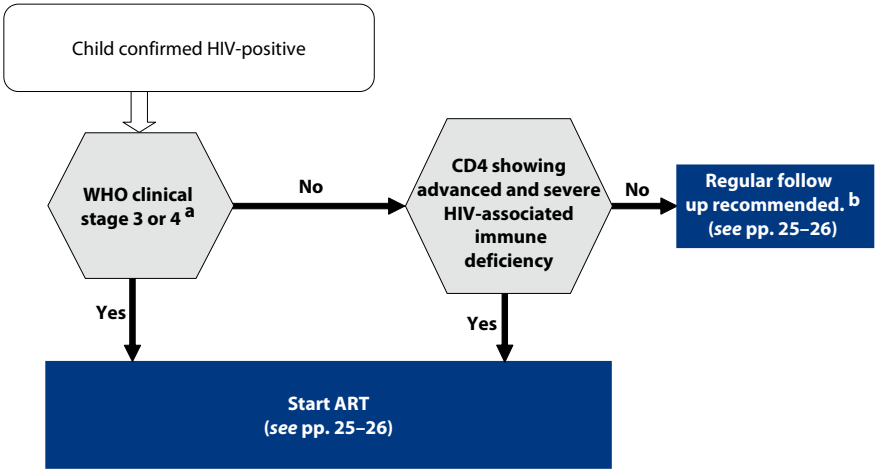
Table 4: Diagnosing severe immunodeficiency using TLC (optional if CD4 is not available)

Classification of HIV-associated immunodeficiency	Age-related TLC values (cells/mm^3)			
	<11 months	12–35 months	36–59 months	≥5 years
TLC	<4000	<3000	<2500	<2000
CD4 count	<1500	<750	<350	<200

- The TLC is an option that is used only if CD4 measurement is not available in children with WHO clinical stage 2 disease. It cannot be used in asymptomatic children. The TLC is also not useful for monitoring ART.
- Calculation of TLC = % lymphocytes x total white blood cell (WBC) count. Annex C (*see* p. 85) shows the 12-month mortality risk at selected thresholds for CD4%, absolute CD4 cell count and TLC.

8 STARTING ART USING CLINICAL AND IMMUNOLOGICAL CRITERIA

8.1 Starting ART using clinical criteria



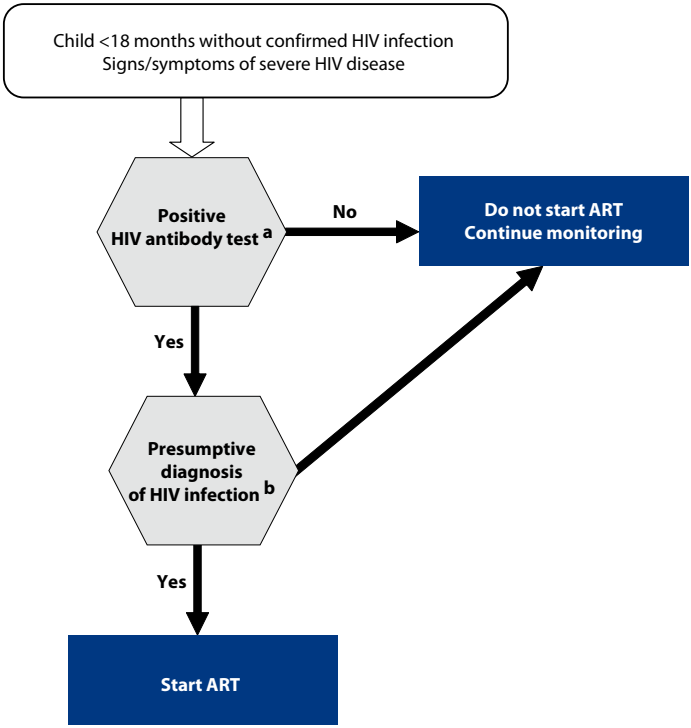
Notes

[a] The risk of mortality is increased if the child is in WHO clinical stage 3 or 4. Therefore, it is recommended that any child presenting in WHO clinical stage 3 and 4 should start ART. Children presenting in WHO clinical stages 1 and 2 can be monitored regularly for the correct time to start co-trimoxazole and ART (*see* pp. 25–26).

Children < 12 months of age and especially < 6 months of age have the highest risk of HIV disease progression and death, even with a high CD4 count and ART. In children > 12 months of age with TB, particularly pulmonary and lymph node TB, oral hairy leukoplakia (OHL) and symptomatic lymphocytic interstitial pneumonia (LIP) , the CD4 count should be used to determine the need for and timing of initiation of ART. CD4 counts can fluctuate and values can vary with intercurrent illness, physiological changes or test variability. If possible, two values should be obtained for making a decision regarding ART failure.

[b] Children who are not yet eligible for initiation of ART should be monitored by clinical evaluation and CD4 counts every 3–6 months with more frequent follow up in infants and younger children, and in children approaching the clinical and CD4 threshold for starting ART. TLC monitoring is not recommended. In situations where the child is in WHO clinical stage 2 and the CD4 count is not available, it is recommended to use TLC for decision-making (*see also* p. 17).

8.2 Starting ART in children less than 18 months without a confirmed diagnosis of HIV infection



Notes[5]

[a] In children with a presumptive diagnosis of severe HIV immunodeficiency it is not possible to perform clinical staging.

[b] At least one of the following:

- PCP, cryptococcal meningitis, oesophageal candidiasis
- Toxoplasmosis
- Severe unexplained malnutrition

[5] As per the definition given in the Integrated Management of Childhood Illnesses (IMCI)

or

Symptomatic with at least two of the following:

- Oral thrush
- Severe pneumonia
- Severe sepsis
- Recent HIV-related maternal death or advanced HIV disease in the mother
- CD4% < 20%

Creamy-white to yellow soft, small plaques on red or normal-coloured mucosa which can often be scraped off (pseudomembranous), or red patches that are usually painful or tender on the tongue, palate or lining of the mouth; not responding to topical antifungal treatment.

Cough or difficult breathing in a child with indrawing of the chest, stridor or any of the IMCI general danger signs, i.e. lethargic or unconscious, not able to drink or breastfeed, vomiting, and presence or history of convulsions during the current illness; responding to antibiotics.

Fever or low body temperature in an infant with any severe sign such as fast breathing, indrawing of the chest, bulging fontanelle, lethargy, reduced movement, not feeding or sucking breast milk, convulsions, etc.

9 MONITORING OF HIV-INFECTED CHILDREN NOT ON ART

Regular follow up is recommended for:

- monitoring growth and development (including neurodevelopment) and providing other routine care;
- early detection of children requiring ART;
- management of HIV-related and other intercurrent illnesses;
- ensuring patient compliance with treatment including co-trimoxazole prophylaxis;
- monitoring treatment outcome and side-effects;
- counselling.

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

Table 5: Monitoring of HIV-infected children

Items	Baseline	Month 1	Month 2	Month 3	Month 6	Every 6 months
Clinical						
Clinical evaluation [a]	X	X	X	X	X	X
Weight, height	X	X	X	X	X	X
Nutritional status and needs	X	X	X	X	X	X
Co-trimoxazole need and adherence [b]	X	X	X	X	X	X
Counselling for prevention of STIs and pregnancy [c]	X				X	X
OI prevention and treatment needs [d]	X	X	X	X	X	X
Laboratory						
Hb and WBC count	X					X
ALT [e]	X					
CD4% or count [f]	X					X

STI sexually transmitted infection OI opportunistic infection
ALT alanine aminotransferase

Notes

[a] Includes history-taking, physical examination and assessment of neurodevelopment. Children < 12 months of age have a higher risk of HIV disease progression and should be followed more frequently than older children.

[b] *See* pp. 15–16 and p. 114 for co-trimoxazole prophylaxis.

[c] In teenage girls in the reproductive age group provide counselling on family planning and prevention of STIs. Counselling should also include prevention of transmission of HIV to others and the risk of transmitting HIV to their infants.

[d] Exposure to TB should be assessed (*see* pp. 57–64 and pp. 86–96 for more information on OIs).

[e] ALT at baseline is the minimum monitoring required for possible liver impairment. Children with a high ALT (> 5 times upper limit of normal [ULN]) should undergo a complete assessment of liver functions as well as for hepatitis B, hepatitis C or other hepatic disease. Other biochemical tests are performed if indicated by the symptoms.

[f] CD4% is used in children < 5 years of age. For children ≥ 5 years of age, CD4 count is mainly used. TLC can be used when CD4 assessment is not available to classify severe immunodeficiency, which is a criterion for starting ART (*see* pp. 19–20).

10 Recommended (first-line) ART regimens

10.1 Recommended first-line ART regimen

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

Based on availability and national ART guidelines, these are the three NRTI combinations to be considered:

Table 6: Step 1. Select 1 NRTI to be used in combination with 3TC [a]

NRTI	Pros	Cons
Zidovudine (AZT) [b] (preferred NRTI if Hb ≥7.5 g/dl)	– AZT causes less lipodystrophy and lactic acidosis than d4T. – AZT liquid formulation does not need refrigeration.	– AZT has more initial gastrointestinal (GI) side-effects. – A large volume of AZT liquid formulation is often poorly tolerated. – Severe anaemia and neutropenia can occur. FBC monitoring before and after treatment is recommended. – AZT liquid formulation comes in glass bottles and is sensitive to light.
Abacavir (ABC)	– ABC is less likely to cause lipodystrophy and lactic acidosis than AZT and d4T. – ABC has little haematological toxicity and is well tolerated. – ABC does not need refrigeration. – ABC has good efficacy.	– ABC is associated with potentially fatal hypersensitivity in 3% of children. – ABC is more expensive than AZT and d4T, and is not widely available in generic form.
Stavudine (d4T)	– d4T is usually very well tolerated. – d4T causes less GI side-effects and anaemia than AZT and ABC.	– d4T causes more lipodystrophy, lactic acidosis and peripheral neuropathy than AZT and ABC. – d4T liquid formulation needs refrigeration.

Notes

[a] Lamivudine (3TC) is used in all 3 combinations as it has an excellent record of efficacy, safety and tolerability. However, it has a low threshold for the development of drug resistance if full adherence is not ensured. 3TC and emtricitabine (FTC) are interchangeable.

[b] AZT is the drug of choice. However, should the child have an Hb <7.5 g/dl, ABC or d4T should be considered. Because of the risk of lipodystrophy with the long-term use of d4T, consider switching from d4T to AZT.

Table 7: Step 2. Choose 1 NNRTI

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

Notes

[a] Children who were exposed to NVP single dose as part of the PMTCT programme are at a higher risk for development of resistance to NNRTIs, but currently no data are available on whether the response to subsequent ART with NNRTI-based regimens is compromised. Therefore, at this time, 2 NRTIs + 1 NNRTI is the treatment of choice for these children.

[b] NNRTIs may lower the drug levels of estrogen-based contraceptives. A condom or diaphragm should always be used to prevent HIV transmission regardless of the HIV serostatus. Adolescent girls in the reproductive age group taking EFV should avoid pregnancy. Additional information is given on pp. 97–102.

10.2 Alternative first-line regimen if the child has co-infection with tuberculosis

Table 8: Children on rifampicin-containing anti-TB treatment and starting ART	
Course of action during rifampicin-based treatment	
Preferred regimen	**Alternative regimen**
2 NRTI + EFV (in children ≥3 years old)	AZT or d4T + 3TC + ABC 2 NRTI + NVP [a]
After completing rifampicin-based anti-TB treatment, consider switching treatment to a standard first-line regimen with 2 NRTI + NVP or continue EFV.	Continue treatment after completing rifampicin-based anti-TB treatment.
Course of action after completion of rifampicin-based treatment	
Preferred regimen	**Alternative regimen**
After completing rifampicin-based anti-TB treatment, consider switching treatment to standard first-line regimen with 2 NRTI + NVP or continue EFV.	Continue current ART regimens after completing rifampicin-based anti-TB treatment regardless of preferred or alternative regimens.

[a] In children, there is no information on the appropriate dosage of NVP and EFV when used with rifampicin. Standard dosage regimens of EFV can be used.

- If TB is diagnosed first, anti-TB treatment should be started and ART should be started 2–8 weeks after anti-TB treatment to ensure that the treatment is tolerated and to decrease the risk of inflammatory immune reconstitution syndrome (IRIS).
- AZT or d4T + 3TC + ABC have no drug interaction with rifampicin. However, this combination has been shown to be less potent in one study in adults than 2 NRTI + EFV. ABC is expensive and is therefore not readily available.

Table 9: Children on first-line ART and starting rifampicin-containing anti-TB treatment	
Current first-line regimen	**Preferred regimen**
2 NRTI + ABC	Continue the same regimen.
2 NRTI + EFV	Continue the same regimen.
2 NRTI + NVP	Switch to either 2 NRTI + ABC or 2 NRTI + EFV (if age >3 years and weight >10 kg).

- There is no drug interaction between NRTIs and rifampicin.
- Rifampicin lowers the drug level of NVP by 20–58% and that of EFV by 25%. In children, there is no information on the appropriate dosage of NVP and EFV when these are used with rifampicin.
- Apart from rifampicin, other anti-TB drugs do not interact with ARV drugs.
- Anti-TB drugs and NNRTIs (especially NVP) can have overlapping hepatotoxicity; therefore, close monitoring of liver functions is required.
- Rifampicin is the best bactericidal anti-TB drug and should be part of an anti-TB regimen, especially during the first 2 months of treatment. Changing from a rifampicin-based to a non-rifampicin-based regimen during the maintenance phase depends on the discretion of the treating physician and should follow the national TB treatment guidelines. However, non-rifampicin containing maintenance-phase anti-TB therapy has been shown to have lower efficacy.

11 Preparing to start ART

- Starting ART is not an emergency. But once ART is started the ARV drugs must be given on time every day. Non-adherence to treatment is the main reason for treatment failure.
- Starting ART when the child/caregiver is not ready can result in poor adherence to treatment and ART resistance.

Prepare the caregiver

The caregiver should be able to
- understand the natural history of HIV infection in children, and the benefits and side-effects of ART.
- understand the importance of taking ART on time every day and ensure adherence to treatment.
- assume the primary responsibility to directly observe the daily ARV intake of the child.
- assume the primary responsibility to ensure compliance in adolescents. Direct observation of drug intake may not be needed in adolescents. The caregiver may allow the adolescent to be responsible for taking ART.
- appropriately store ARV drugs.
- correctly demonstrate mixing/measuring of the selected ART regimen.
- afford ART and necessary laboratory monitoring as well as transportation to the hospitals in a sustainable manner (if self-paid).

Prepare the child

Children who know their HIV status (explanation is given by health-care worker according to the child's maturity level) should be able to
- understand the natural history of HIV infection, and the benefits and side-effects of ART.
- understand the importance of taking ART on time every day and adhere to treatment.

Children who do not know their HIV status should be explained why they need to take ART by using culturally- and age-appropriate explanations and by avoiding the words "HIV" or "AIDS". They should be
- ready and agree to take ART (depending on their level of maturity but mostly in children >6 years the health-care worker can explain according to the child's maturity level), and
- able to understand the importance of taking ART on time every day and of adherence to treatment.

Agree on the treatment plan

Caregiver/child and health-care personnel agree on an ART regimen and follow-up appointments that the caregiver/child can adhere to.

Assess treatment preparedness and factors that may affect adherence

- Assess the caregiver/child's understanding of the reason for taking ART, anticipated treatment response, side-effects of ART and how ART is taken (dose, time and food requirements).
- Assess the factors that may affect adherence and work with the caregiver/child in finding solutions for these anticipated problems.
- Assess the readiness for disclosure of HIV status. Disclosure is not a prerequisite for starting ART but is encouraged when the caregiver is ready and the child is felt to be mature enough and can keep secrets. Preparing for and performing disclosure is a process that takes time. The health-care personnel's role is to help prepare and support the caregiver and child.

12 Ensuring long-term adherence and good response to ART

A team effort by the health-care worker, the caregiver and child is required to ensure long-term adherence and good response to ART.

- It is important for health-care personnel to understand the child/caregiver's problems and provide positive reinforcement.
- Taking ART on time every day is not an easy task.
- Health-care workers should never reprimand the caregiver/child for non-adherence to treatment but instead work with them to solve the issues affecting adherence.

Reasons for non-adherence

(a) Missed doses

The health-care worker should ask about missed doses at every visit:

- Ask whether the child has missed any dose in the past 3 days and since the last visit.
- Ask when the child takes ART.
- Ask for reasons for non-adherence.
- Missed doses may occur
  - if the dosing time is inconvenient/does not fit in with caregiver/child's lifestyle
  - if the regimen is hard to take because of a high pill/liquid load and bad taste
  - if there are ART supply issues (lack of money, inadequate ART prescribed)
  - if the child refuses to take the medicines (especially an older child who is tired of taking medications or who does not know his/her HIV status).

(b) Incorrect dosing

- At every visit, the health-care worker should check
  - the dose of each ARV
  - the preparation of each ARV
  - the storage of each ARV

(c) Side-effects

- Severe side-effects should be taken seriously and treated promptly.
- Minor side-effects that are non-life threatening can be easily overlooked and may be the reason for non-adherence.
- Lipodystrophy can cause adolescents to discontinue ART.

(d) Others

- There are many possible reasons why a child does not adhere to treatment. Examples are a bad relationship between health-care personnel and the family, OIs/other conditions and their treatments which cause the child to feel ill, a large pill burden, and social issues such as change of caregiver, illness of primary caregiver, etc.

Proposed management

Management

- Find out why the ARV schedule cannot be adhered to:
  - — find out the time when doses are usually missed.
  - — check why doses are missed at that time.
  - — work with the family towards a suitable schedule.
  - — consider using tools such as a pill box and alarm clock.
- Find out why the ARV regimen is hard to take:
  - — work with the family in adjusting the regimen/formulation.
  - — consider training the patient to swallow pills to decrease the volume of liquid.
- Find out if the supply of ARV is interrupted and why:
  - — help the caregiver solve this problem.
- Find out why the child refuses to take ART:
  - — counselling, especially peer group counselling, can help reinforce adherence.
  - — if the child does not know his/her HIV status and questions the need to take ART, the health-care worker should work with the caregiver/child in preparing the child for disclosure of the HIV status.

Management

- Consider using tools such as a pill box.
- Use written/pictorial cards with details of regimens.
- Go over the dosage regimen and have the caregiver/child demonstrate preparation of ART.
- Adjust the dose according to the weight/height of the child.

Management

- Side-effects should be treated promptly regardless of their severity.
- The health-care worker needs to pay attention to minor side-effects and how the child feels.
- If relevant, consider switching to an ART regimen that causes less lipodystrophy.

Management

- The health-care worker needs to provide an environment that is supportive and friendly so that the caregiver/child can feel comfortable discussing reasons for non-adherence.
- Treatment of OI takes priority and stopping/modifying ART may be needed.
- Involving the community and support groups, and providing support outside the clinic environment such as home visits, may help.

Table 10: Monitoring after initiation of ART									
Items	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Every 2–3 months	Symptom-directed
Clinical									
Clinical evaluation	X	X	X	X	X	X	X	X	X
Weight, height	X	X	X	X	X	X	X	X	
Calculation of ART dose [a]	X	X	X	X	X	X	X	X	
Concomitant medications [b]	X	X	X	X	X	X	X	X	
Check adherence to ART [c]		X	X	X	X	X	X	X	
Laboratory									
Hb and WBC [d]	X								X
Full blood chemistry [e]									
Pregnancy test in adolescent girls [f]	X								X
CD4% or count [g]	X							X	X

Notes

[a] Children may have rapid weight and height gain after ART in addition to the expected normal growth; therefore, re-calculation of the dose of ART should be done at every visit. Giving doses of ART that are less than those recommended can lead to rapid development of resistance.

[b] Check for concomitant drug intake at every visit such as appropriate co-trimoxazole prophylaxis (if indicated) and other drugs. Check for potential drug interactions with ART (*see* pp. 103–105).

[c] Assessment for adherence to ART can be done by asking the child and parent/caregiver questions about missed doses and the times at which the child takes ART. Performing a pill count is time-consuming but may be a better measure of adherence, if done correctly.

[d] Hb and WBC monitoring may be considered in children on AZT at 1, 2 and 3 months.

[e] Full blood chemistry includes liver enzymes, renal function, glucose, lipids, amylase, lipase, serum electrolytes. Monitoring depends on the symptoms and regimens. Regular monitoring of liver function tests during the first 3 months of treatment should be considered for children on NVP-based regimens, especially in adolescent girls with CD4 cell counts >250 cells/mm^3 as well as infants and children co-infected with hepatitis B virus (HBV), hepatitis C virus (HCV), or with other hepatic diseases.

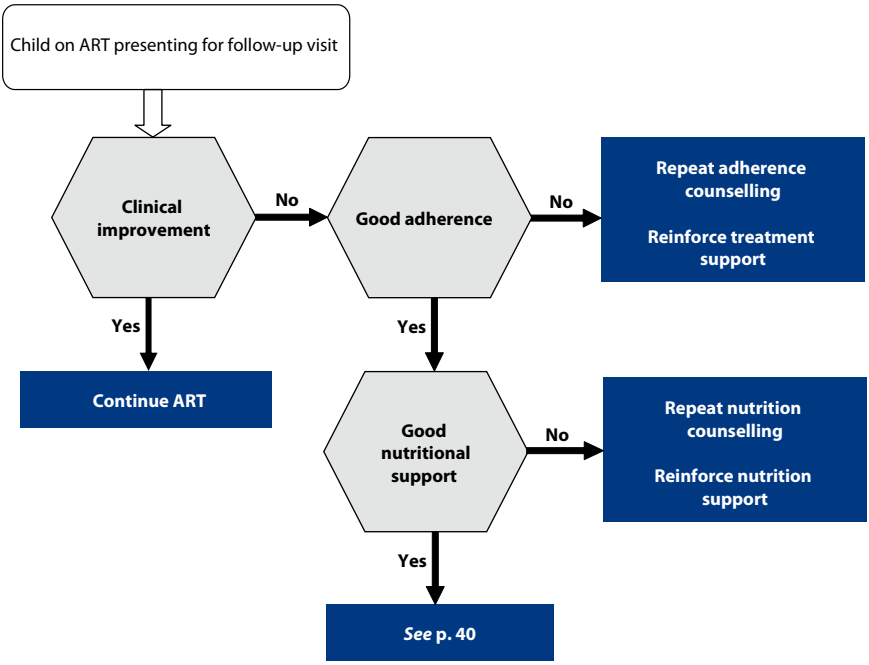
[f] A pregnancy test should be done in adolescent girls, especially those who are about to start EFV, and family planning counselling should be provided.

[g] If signs of clinical progression of disease are seen, a CD4 count should be done. TLC is not suitable for monitoring of ART. If CD4 count is not available, clinical monitoring alone is used.

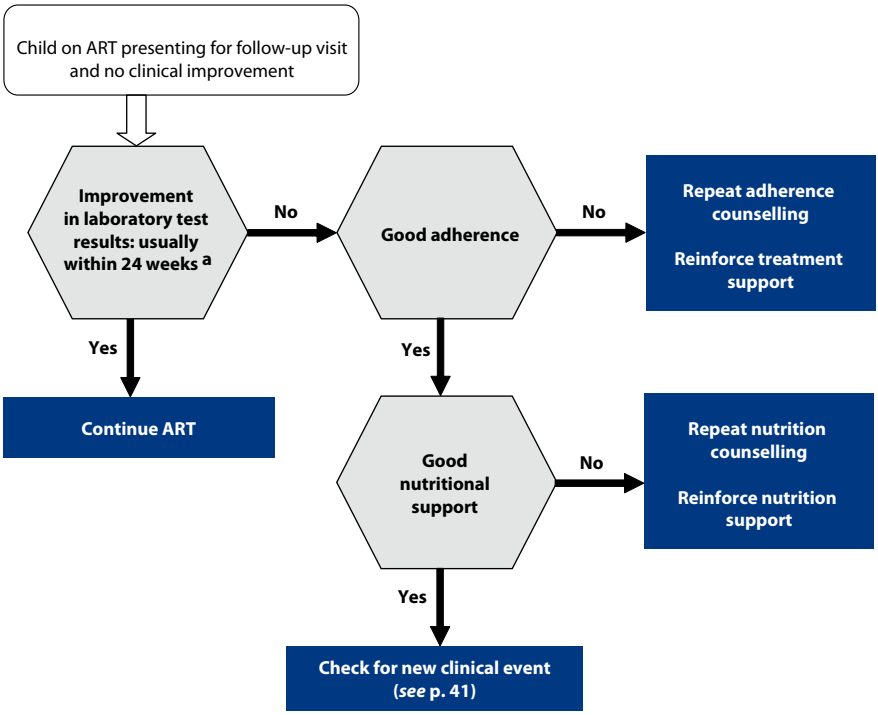
If the child has missed a visit, attempts should be made to contact the child/parent (e.g. call or home visit). In addition to the suggested appointments, caregivers should be encouraged to bring the child in if he/she is sick and especially during the first few months of ART when the child may experience side-effects of and intolerance to ART.

14 Evaluating the response to ART

14.1 Evaluating children on ART at a follow-up visit



14.2 Evaluating the response to ART in a child with no clinical improvement at follow-up visit

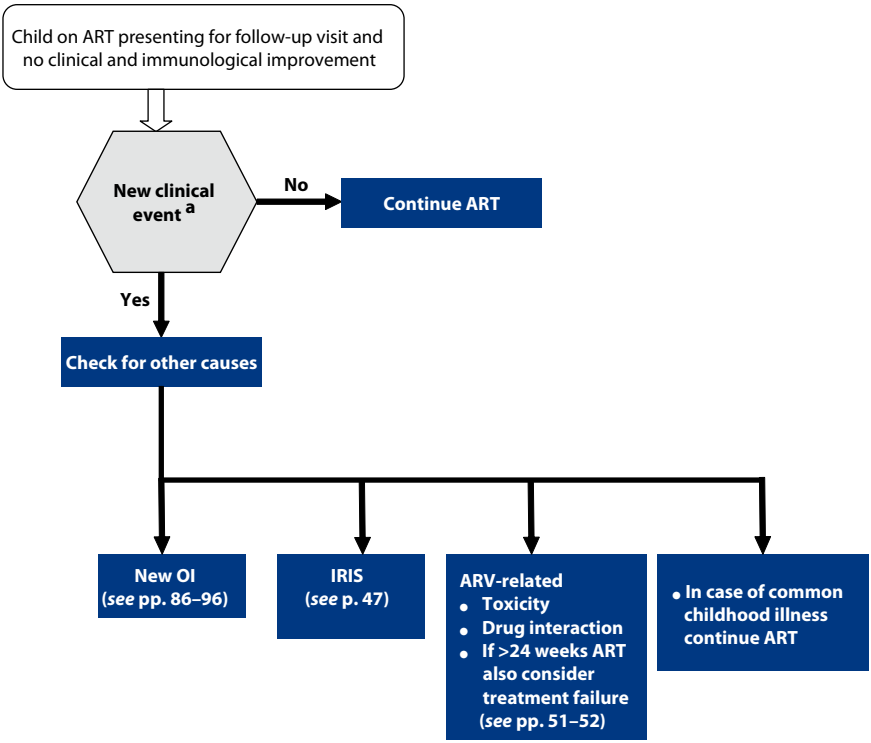


Note

[a] Improvement in laboratory test results usually occurs within 24 weeks and includes

- Rise in CD4% or CD4 count, and
- Increase in Hb, and WBC and platelet counts.

14.3 Evaluating the response to ART in a child with no clinical and immunogical improvement at follow-up visit



Note

[a] According to WHO clinical stage 3 or 4, a new clinical event is defined as a new OI or HIV-associated illness.

15 MANAGING ARV DRUG TOXICITY

15.1 Guiding principles in the management of ARV drug toxicity

1. Determine the seriousness of the toxicity. [a]
2. Evaluate concurrent medications, and establish whether the toxicity is attributable to an ARV or due to other drugs taken at the same time.
3. Consider other diseases (e.g. viral hepatitis in a child on ARV who develops jaundice) as not all problems that arise during treatment are caused by ARVs.
4. Manage the adverse event according to the severity [b]. In general:
   - **Grade 4: Severe life-threatening reactions** (*see* pp. 110–113). Immediately discontinue all ARV drugs and manage the medical event (i.e. symptomatic and supportive therapy) and reintroduce ARVs using a modified regimen (i.e. substituting another ARV drug for the offending drug) when the patient's condition is stable.
   - **Grade 3: Severe reactions.** Substitute the offending drug without discontinuing ART.
   - **Grade 2: Moderate reactions.** Some moderate reactions (e.g. lipodystrophy or peripheral neuropathy) require substitution. For other reactions continue ART as long as is feasible; if the patient does not improve on symptomatic therapy, consider single drug substitution.
   - **Grade 1: Mild reactions.** These are bothersome but they do not require a change in therapy.
5. Stress the importance of adherence to therapy despite toxicity in the case of mild and moderate reactions.
6. If there is a need to discontinue ART because of life-threatening toxicity, all ART drugs should be stopped until the patient's condition is stable.

Notes

[a] The management of severe life-threatening toxicity is given on pp. 103–105.

[b] For grading of severity please see pp. 106–108. Most ARV drug toxicities are not severe and can be managed by giving supportive treatment. Minor side-effects can lead to non-adherence; therefore, health-care professionals must counsel patients and provide supportive treatment.

15.2 When do side-effects and toxicities occur with ARVs?

Time	Side-effects and toxicities
Within the first few weeks	• GI toxicities include nausea, vomiting and diarrhoea. These side-effects are usually self-limiting and require symptomatic treatment only. • Rash and liver toxicity are more common with the NNRTI drugs but are also seen with certain NRTI drugs such as ABC and some protease inhibitors (PIs).
	• A lead-in dose is used for NVP. • to lower the risk of toxicity. • In case of mild-to-moderate rash and liver toxicity, ARV can be continued under close follow up, and symptomatic treatment and supportive care given. • Severe rash and liver toxicity (ALT >5 ULN) can be life-threatening and NVP should be substituted with another drug. (*see* pp. 45–46). • CNS toxicity from EFV can be self-limiting. Because EFV can cause dizziness most physicians advise that it should be taken at night. • ABC hypersensitivity usually occurs within the first 6 weeks and can be life-threatening. ABC must be stopped and re-challenge never attempted.
From 4 weeks onwards	• Drug-induced bone-marrow suppression such as anaemia and neutropenia are most commonly seen with AZT. • Other causes of anaemia should be looked for and treated. • Asymptomatic mild anaemia is common.
	• If there is severe anaemia (Hb <7.5 g/dl) and neutropenia (neutrophil count <500 /mm^3) AZT should be stopped and either ABC or d4T given. (*see* p. 45 and pp. 110–113)
6–18 months	• Mitochondrial dysfunction is primarily seen with the NRTI drugs; these include lactic acidosis, hepatic toxicity, pancreatitis, peripheral neuropathy, lipoatrophy and myopathy. • Lipodystrophy is frequently associated with d4T use and can cause permanent disfigurement. • Lactic acidosis is rare and can occur at any time. It is particularly associated with d4T use. Severe lactic acidosis can be life-threatening. • Metabolic disorders are more common with PIs and include hyperlipidaemia, fat accumulation, insulin resistance, diabetes and osteopenia.
	• Stop the NRTI and switch to another drug with a different toxicity profile (*see* pp. 45–46)
After 1 year	• Nephrolithiasis is commonly seen with indinavir (IDV). • Renal tubular dysfunction is associated with tenofovir disoproxil fumarate (TDF).
	• Stop the PI and switch to another drug with a different toxity profile.

15.3 Severe toxicities associated with specific first-line ARV drugs

Table 11: Potential first-line drug substitutions in infants and children

First-line ARV drug	Most frequent significant toxicity for the ARV drug	Suggested first-line ARV drug substitution
ABC	Hypersensitivity reaction	AZT or d4T
AZT	Severe anaemia or neutropenia [a]	d4T or ABC
	Lactic acidosis	ABC Replace NRTI with PI + NNRTI if ABC is not available
	Severe gastrointestinal intolerance [b]	d4T or ABC
d4T	Lactic acidosis	ABC [c]
	Peripheral neuropathy	AZT or ABC
	Pancreatitis	
	Lipoatrophy/metabolic syndrome [d]	
3TC	Pancreatitis [e]	ABC or AZT
EFV [h]	Persistent and severe central nervous system toxicity [f]	NVP
	Potential teratogenicity (adolescent girl in first trimester of pregnancy or of childbearing potential not taking adequate contraception)	
NVP	Acute symptomatic hepatitis [g]	EFV [h]
	Hypersensitivity reaction	Preferred substitution of NNRTI to: • a third NRTI (disadvantage, may be less potent) **or** • PI (disadvantage, premature start of second-line ARV drug) [j]
	Severe or life-threatening rash (Stevens–Johnson syndrome) [i]	

Notes

[a] Severe anaemia is defined as Hb <7.5 g/dl; severe neutropenia as neutrophil count <500 /mm^3. Exclude malaria in areas where there is stable malaria.

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

[c] ABC is preferred in this situation; however, where ABC is not available, AZT may be used.

[d] Substitution of d4T typically may not reverse lipoatrophy. In children, ABC or AZT can be considered as alternatives.

[e] Lamivudine (3TC)/emtricitabine (FTC)-associated pancreatitis has been described in adults but is considered very rare in children.

[f] Defined as severe central nervous system toxicity such as persistent hallucinations or psychosis.

[g] Symptomatic NVP-associated hepatic toxicity is very rare in HIV-infected children before adolescence.

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

[i] Severe rash is defined as extensive rash with desquamation, angioedema, or serum sickness-like reaction; or a rash with constitutional findings such as fever, oral lesions, blistering, facial oedema, conjunctivitis; Stevens–Johnson syndrome can be life-threatening. For life-threatening rash, most clinicians would not substitute EFV due to the potential for NNRTI class-specific toxicity.

[j] The premature introduction of the PI class of drugs in first-line regimens leads to limitations in the choice of drugs in the event of treatment failure.

16 Immune reconstitution inflammatory syndrome (IRIS)

Definition	• A collection of signs and symptoms resulting from the ability to mount an immune response to antigens or organisms associated with immune recovery while on ART[6]
Frequency	• 10% of all adult patients starting ART • Up to 25% of patients starting ART with a CD4 cell count <50 cells/mm^3 or severe clinical disease (WHO clinical stage 3 or 4)[7, 8]
Timing	• Typically within 2–12 weeks of starting ART but may present later
Signs and symptoms	• Unexpected deterioration of clinical status soon after commencing ART • Unmasking of subclinical infection such as TB, which may present as new active disease or development of abscess at the BCG vaccination site • Worsening of co-existing infections such as a flare-up of hepatitis B or C
Most common IRIS events	• *Mycobacterium tuberculosis*, *M. avium* complex (MAC) and cryptococcal disease
Management	• Continue ART if the patient can tolerate it. • Treat unmasked active OI. • In most cases the symptoms of IRIS resolve after a few weeks; however, some reactions can be severe or life-threatening and may require a short course of corticosteroid treatment to suppress exaggerated inflammatory responses. • Prednisone 0.5–1 mg/kg/day for 5–10 days is suggested in moderate-to-severe cases of IRIS.[9]

[6] Robertson J, Meier M, Wall J, Ying J, Fichtenbaum C. Immune reconstitution syndrome in HIV: validating a case definition and identifying clinical predictors in persons initiating antiretroviral therapy. *Clin Infect Dis* 2006, 42:1639–46.

[7] French MA, Lenzo N, John M, et al. Immune restoration disease after the treatment of immunodeficient HIV-infected patients with highly active antiretroviral therapy. *HIV Med* 2000, 1:107–15.

[8] Breen RAM, Smith CJ, Bettinson H, et al. Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection. *Thorax* 2004, 59:704–7.

[9] McComsey G, Whalen C, Mawhorter S, et al. Placebo-controlled trial of prednisone in advanced HIV-1 infection. *AIDS* 2001, 15:321–7.

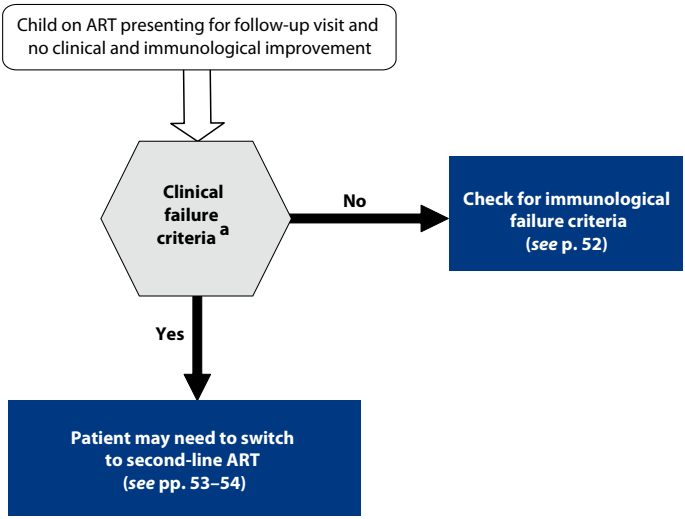
17 Differential diagnosis of common clinical events that develop during the first six months of ART

Table 12: Differential diagnosis of common clinical events during the first six months of ART

Symptoms	Side-effects of ARV or OI prophylaxis	Immune reconstitution inflammatory syndrome (IRIS)
Nausea, vomiting	**ART** • AZT, usually self-limiting after 2 weeks **OI prophylaxis** • Co-trimoxazole or INH	• Hepatitis B and C can occur with IRIS • Suspect if nausea, vomiting plus jaundice
Abdominal or flank pain, and/or jaundice	**ART** • d4T or didanosine (ddI) may cause pancreatitis • NVP (and less commonly EFV) may cause liver dysfunction which require stoppage of these drugs **OI prophylaxis** • Co-trimoxazole or INH	• Hepatitis B and C can occur with IRIS • Suspect if nausea, vomiting plus jaundice
Diarrhoea	**ART** • NFV commonly causes diarrhoea	• IRIS from MAC or CMV may cause diarrhoea
Headache	**ART** • AZT or EFV usually self-limiting but can last 4–8 weeks	• Assess for toxoplasmosis and cryptococcal meningitis
Fever	**ART** • Hypersensitivity reaction to ABC or adverse drug reaction of NVP	• IRIS due to several organisms, e.g. MAC, TB, CMV, *Cryptococcus neoformans*, herpes zoster
Cough, difficulty in breathing	**ART** • NRTI-associated lactic acidosis	• IRIS can be associated with PCP, TB, fungal or bacterial pneumonia
Fatigue, pallor	**ART** • AZT, which usually develops 4–6 weeks after initiation	• Suspect MAC IRIS if there is fever, fatigue and anaemia
Skin rash, itching	**ART** • NVP or ABC • Should assess carefully and consider stopping the drug in case of severe reaction. Rash due to EFV is often self-limiting **OI prophylaxis** • Co-trimoxazole or INH	• Skin conditions which can flare up due to IRIS in the first 3 months of ART — Herpes simplex and zoster — Papillomavirus (warts) — Fungal infections — Atopic dermatitis

18 Antiretroviral treatment failure

Step 1: Assess clinical criteria for treatment failure



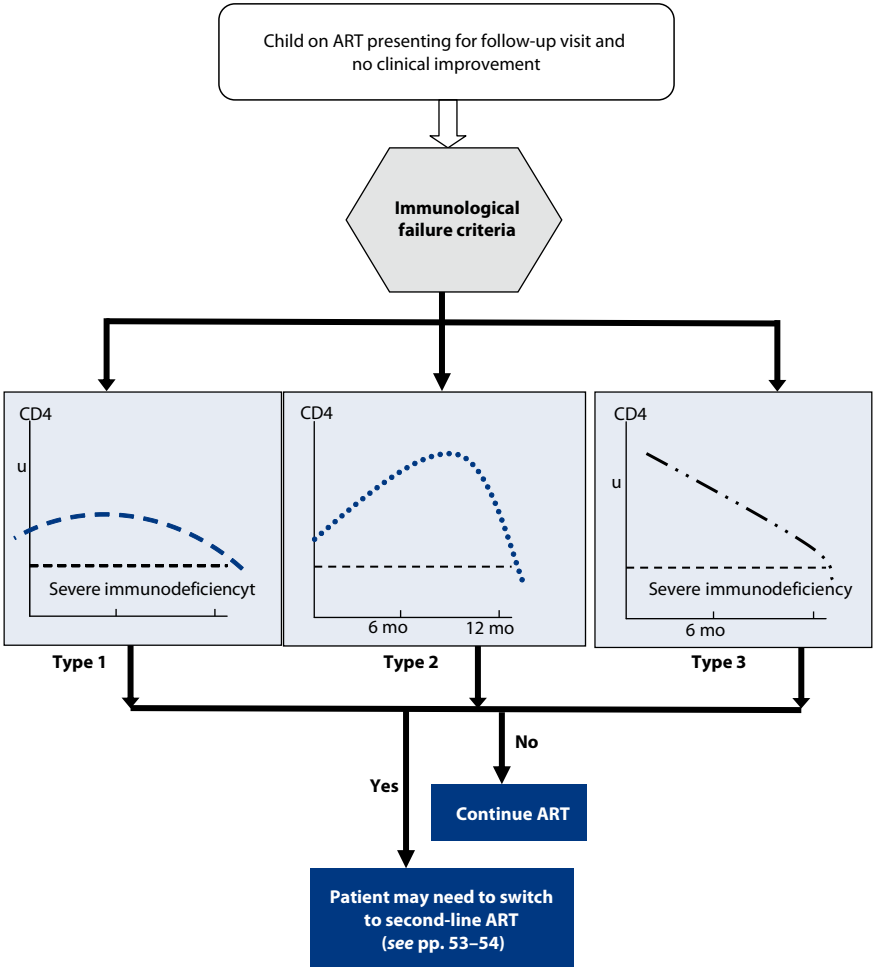
Note

[a] **Clinical failure criteria**

Does the child fulfil any of these clinical failure criteria?

- Lack of or decline in growth rate in children who initially respond to treatment
- Loss of neurodevelopmental milestones or development of encephalopathy
- Occurrence of new OIs or malignancies or recurrence of infections such as oral candidiasis that is refractory to treatment or esophageal candidiasis

Step 2: Assess immunological criteria for treatment failure



Notes

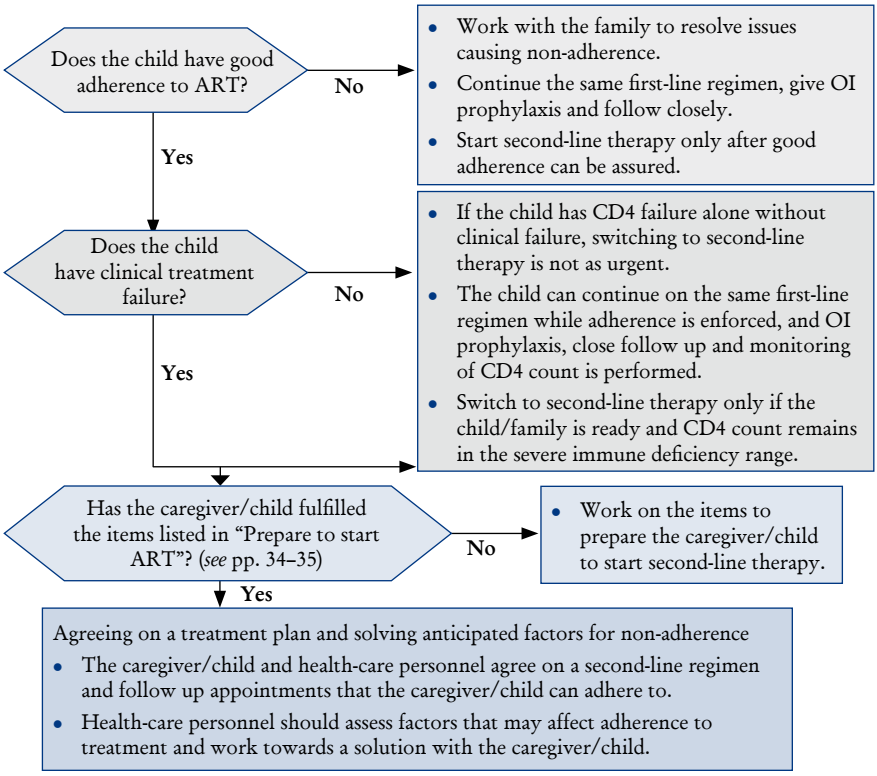
Type 1
Development of age-related severe immune deficiency after initial immune recovery

Type 2
New progressive age-related severe immune deficiency, confirmed with at least one subsequent CD4 measurement

Type 3
Rapid rate of decline to below threshold of age-related severe immune deficiency

19 SWITCHING TO A SECOND-LINE ART REGIMEN

- The most common reason for failure is poor adherence. Adherence must be investigated and supportive mechanisms reinforced prior to any change in regimen.
- Switching to a second-line regimen is not an emergency.
- It is important to ensure that the child is on appropriate OI prophylaxis.
- A failing regimen usually retains some anti-HIV activity; therefore, in general, a child should continue the failing regimen until he/she is ready to switch to a second-line regimen.



20 Recommended second-line regimens in infants and children

Expert consultation is recommended when ART failure is suspected.

20.1 Recommended second-line regimen:

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

Step 1: Choose 2 NRTIs

First-line NRTI	Second-line NRTI
AZT or d4T + 3TC	ddI + ABC
ABC + 3TC	ddI + AZT

Step 2: Choose 1 PI

Preferred PI	Advantages	Disadvantages
Lopinavir/ ritonavir (LPV/r)	— Excellent efficacy especially in PI-naive children — High threshold for development of drug resistance due to its high drug level from boosting with ritonavir (RTV) — It is the only RTV-boosted PI available as a liquid formulation and pills — Paediatric dosages are available for all age groups	— Both liquid and gel capsule formulations require refrigeration. — The gel capsule is large in size. — The heat-stable tablet formulation is now available in some countries but cannot be split. — It is expensive. — Liquid contains 43% alcohol excipient and capsule contains 12% alcohol. — The taste is extremely unpleasant.
Saquinavir/ ritonavir (SQV/r)	— Can be used with RTV boosting — Good efficacy	— Can be used only in children who weigh >25 kg and can swallow capsules — The soft-gel capsule formulation is large in size and requires refrigeration. — The pill load is high. — GI side-effects are frequent.

Alternative PI	Advantages	Disadvantages
NFV	— Long term data show a good efficacy and safety profile — Causes less hyperlipidaemia and lipodystrophy than RTV-boosted PI	— Data in adults show it to be inferior in efficacy compared to boosted PI or EFV — The pill burden is high — GI side-effects are frequent

20.2 Recommended second-line regimen:

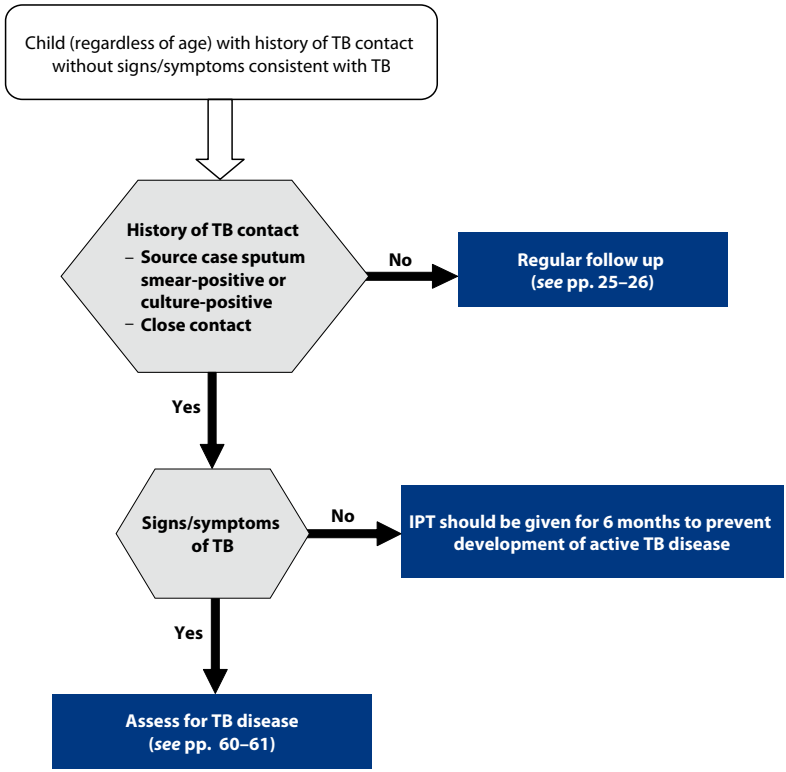
If the first-line regimen is 3 NRTI = 1 NRTI + 1 NNRTI + 1 PI

First-line regimen	Second-line regimen
AZT or d4T + 3TC + ABC	ddI + EFV or NVP + 1 PI (LPV/r or SQV/r preferred. The alternative is NFV.)

- Cross-resistance within ART class occurs commonly, especially in those who have had treatment failure based on clinical or CD4 criteria. Resistance occurs when HIV replicates despite ART. If treatment failure occurs while on NNRTI or 3TC, one would expect that resistance has developed to NNRTI and 3TC. Continuing NNRTI in this circumstance is not useful; however, continuing 3TC may lead to decreased HIV viral fitness and lowering of the HIV viral load.
- AZT and d4T have the same pattern of resistance and one would expect cross-resistance. Therefore, it is not recommended that one be substituted by the other.
- Principle of choosing second-line regimens
  - Choose as many new classes as possible.
  - If the same ARV class has to be used, choose as many new drugs as possible within the same class.
- The goal of a second-line regimen is to achieve clinical and CD4 response but this is less likely than with a first-line regimen due to cross-resistance among ARV drugs.
- Before switching over to a second-line regimen, adherence to treatment needs to be ensured.
- For children who fail a second-line regimen, identifying an effective salvage regimen will be difficult. Expert consultation should be sought.
- For monitoring after changing over to a second-line regimen, *see* pp. 37–38. For RTV-boosted PI-based regimens, the child should also undergo estimation of serum lipids (triglycerides and cholesterol and, if possible, LDL and HDL) every 6–12 months.

21 Tuberculosis (TB)

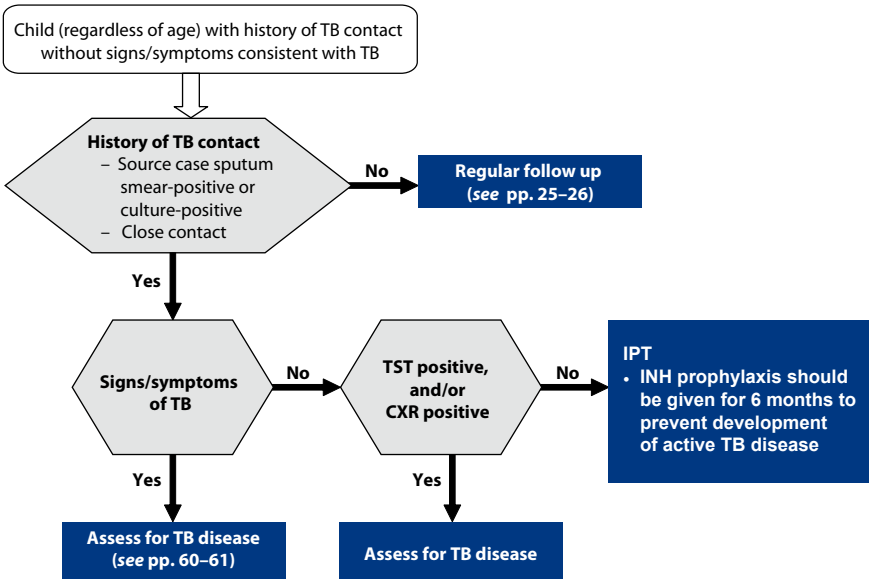
21.1 TB contact screening and management when tuberculin skin test and chest X-ray not available



IPT isoniazid preventive therapy

- Numerous studies have found that investigation of contacts is a valuable means of identifying new TB cases, and is recommended by WHO and the International Union Against Tuberculosis and Lung Disease.
- This section describes how to do this practically in a variety of settings with the available resources.
- It is recommended that all national tuberculosis programmes (NTPs) screen household contacts for symptoms of TB and offer isoniazid preventive therapy (IPT) (i.e. daily isoniazid for at least 6 months) to all HIV-infected children who are household contacts.
- Young children living in close contact with a source case of smear-positive pulmonary TB are at particular risk for TB infection and disease. The risk of infection is greatest if the contact is close and prolonged, such as that between an infant or toddler and the mother or other caregivers in the household.
- Where tuberculin skin testing (TST) and chest X-ray (CXR) are available, these tests should be used to screen exposed contacts. However, this may not be possible when tuberculin solution is unavailable, as is often the case in low-resource settings. Where TST and CXR are not readily available, this should not preclude contact screening and management, as this can be conducted on the basis of simple clinical assessment.
- Clinical assessment alone is sufficient to decide whether the contact is well or symptomatic. Routine assessment of exposed contacts does not require CXR or TST. This approach applies to contacts of smear-positive pulmonary TB cases, but screening should also be available for HIV-infected contacts of smear-negative pulmonary TB cases. If the contact of a source case with smear-negative pulmonary TB is symptomatic, then the diagnosis of TB needs to be investigated as above, whatever the contact's age. If the contact is asymptomatic, further investigation and follow up will depend on national policy and practice.
- The recommended prophylaxis for a healthy contact <5 years of age is isoniazid (INH) 5 mg/kg daily for 6 months.
- Follow up should be carried out at least every 2 months until treatment is complete if TB is suspected at initial assessment or at subsequent follow up.
- Referral to a district or tertiary hospital may be necessary when the diagnosis is uncertain. Contacts with TB disease should be registered and treated.

21.2 TB contact screening and management where TST and CXR are available



Using the tuberculin skin test (TST)[10]

The TST should be standardized for each country using either 5 tuberculin units (TU) of tuberculin or purified protein derivative (PPD) or 2 TU of tuberculin PPD RT23, as these give similar reactions in TB-infected children. Health-care workers must be trained in performing and reading a TST.

A TST should be regarded as positive in the following instances:

- in high-risk children (includes HIV-infected children and severely malnourished children, i.e. those with clinical evidence of marasmus or kwashiorkor): >5 mm diameter of induration;
- in all other children (whether they have received a bacille Calmette–Guérin [BCG] vaccination or not): >10 mm diameter of induration.

Value of the test

The TST can be used to screen children exposed to TB (such as from household contacts with TB), though children can still receive chemoprophylaxis even if the TST is not available.

[10] *Guidance for national tuberculosis programmes on the management of tuberculosis in children.* Geneva, WHO, 2006.

21.3 Diagnosis of pulmonary and extrapulmonary TB

- The diagnosis of TB in children relies on careful and thorough assessment of all the evidence derived from a careful history, clinical examination and relevant investigations, e.g. TST, CXR and sputum smear microscopy.

Recommended approach to diagnose TB in children [10]

1. Careful history (including history of TB contact and symptoms consistent with TB)
2. Clinical examination (including growth assessment)
3. Tuberculin skin testing
4. Bacteriological confirmation whenever possible
5. Investigations relevant for suspected pulmonary and extrapulmonary TB
6. HIV testing (in high HIV-prevalence areas)

- Most children with TB have pulmonary TB. Although bacteriological confirmation is not always feasible, it should be sought wherever possible, e.g. by sputum smear microscopy for children with suspected pulmonary TB who are old enough to produce a sputum sample.
- Up to 25% of TB in children is extrapulmonary. The most common sites are the lymph nodes (LN), pleura, pericardium, meninges and miliary TB. Children with advanced HIV disease are at high risk for extrapulmonary TB.
- A trial of treatment with anti-TB drugs is not recommended as a method of confirming a presumptive diagnosis of TB in children. Once TB is diagnosed a full course of therapy should be administered.

21.4 Case definition of TB

Pulmonary tuberculosis, sputum smear-positive

- two or more initial sputum smear examinations positive for acid-fast bacilli; or
- one sputum smear examination positive for acid-fast bacilli plus CXR abnormalities consistent with active pulmonary TB, as determined by a clinician; or
- one sputum smear examination positive for acid-fast bacilli plus sputum culture positive for *M. tuberculosis*.

Children with smear-positive disease are more likely to be adolescents or those at any age with severe intrathoracic disease.

Pulmonary tuberculosis, sputum smear-negative

➤ *Case of pulmonary TB that does not meet the above definition for smear-positive TB.* This group includes cases without a sputum smear result, which is relatively more frequent in children than in adults.

Note

In keeping with good clinical and public health practices, the diagnostic criteria for pulmonary TB should include:

- at least three sputum specimens negative for acid-fast bacilli; **and**
- radiological abnormalities consistent with active pulmonary TB; **and**
- no response to a course of broad-spectrum antibiotics; **and**
- decision by a clinician to treat with a full course of anti-TB chemotherapy.

Extrapulmonary TB

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

21.5 TB treatment [10]

Anti-TB treatment

Most current international guidelines recommend that TB in HIV-infected children should be treated with a 6-month regimen as in HIV-uninfected children. Where possible, HIV-infected children should be treated with rifampicin for the entire treatment duration, as higher relapse rates among HIV-infected adults have been found when ethambutol is used in the continuation phase. Most children with TB, including those who are HIV-infected, have a good response to the 6-month regimen. Possible causes for failure, such as non-compliance with therapy, poor drug absorption, drug resistance and alternative diagnoses should be investigated in children who are not improving on anti-TB treatment.

Table 13: Recommended doses of first-line anti-TB drugs for adults and children [11]				
Drug	Recommended dose			
	Daily		Three times weekly	
	Dose and range (mg/kg body weight)		Dose and range (mg/kg body weight)	Daily maximum (mg)
Isoniazid	5 (4–6)	300	10 (8–12)	–
Rifampicin	10 (8–12)	600	10 (8–12)	600
Pyrazinamide	25 (20–30)	–	35 (30–40)	–
Ethambutol	Children 20 (15–25) [a] Adults 15 (15–20)	–	30 (25–35)	–
Streptomycin [b]	15 (12–18)	–	15 (12–18)	–

Notes

[a] The recommended daily dose of ethambutol is higher in children (20 mg/kg) than in adults (15 mg/kg), because the pharmacokinetics are different (peak serum ethambutol concentrations are lower in children than in adults receiving the same mg/kg dose). Although ethambutol was frequently omitted from treatment regimens for children in the past, due in part to concerns about the difficulty of monitoring for toxicity (particularly for optic neuritis) in young children, a literature review indicates that it is safe in children at a dose of 20 mg/kg (range 15–25 mg/kg) daily.

[b] Streptomycin should be avoided when possible in children because the injections are painful and irreversible auditory nerve damage may occur. The use of streptomycin in children is mainly reserved for the first 2 months of treatment of TB meningitis.

The need for better data on anti-TB drug pharmacokinetics in children is highlighted by the variation in national recommendations for drug doses in children, particularly for isoniazid (some guidelines, e.g. those of the American Thoracic Society and the Thai Ministry of Public Health recommended a daily dose of isoniazid of 10–15 mg/kg. The recommended treatment regimens for each TB diagnostic category (*see* Table 14) are generally the same for children as for adults.

New cases fall under category I (new smear-positive pulmonary TB; new smear-negative pulmonary TB with extensive parenchymal involvement; severe forms of extrapulmonary TB; severe concomitant HIV disease) or category III (new smear-negative pulmonary TB – other than in category I; less severe forms of extrapulmonary TB). Most children with TB have

[11] *Treatment of tuberculosis: guidelines for national programmes.* Geneva, WHO, 2003.

uncomplicated (smear-negative) pulmonary/intrathoracic TB or non-severe forms of extrapulmonary TB, and therefore fall under diagnostic category III. Those children with smear-positive pulmonary TB, extensive pulmonary involvement or severe forms of extrapulmonary TB (e.g. abdominal or bone/joint TB) fall under diagnostic category I. Children with TB meningitis and miliary TB deserve special consideration. Previously treated cases fall under diagnostic category II (previously treated smear-positive pulmonary TB) or category IV (chronic and multidrug-resistant [MDR]-TB). Treatment of TB in HIV-infected children merits special consideration. Please see *Guidance for national tuberculosis programmes on the management of tuberculosis in children*, Geneva, WHO, 2006, for further information.

Table 14: Recommended treatment regimens for children in each TB diagnostic category

TB diagnostic category	TB cases	Regimen [a]	
		Intensive phase (daily or 3 times weekly [a])	Continuation phase (daily or 3 times weekly [a])
III	New smear-negative pulmonary TB (other than in category I) Less severe forms of extrapulmonary TB	2HRZ [b]	4HR or 6HE
I	New smear-positive pulmonary TB New smear-negative pulmonary TB with extensive parenchymal involvement Severe forms of extrapulmonary TB (other than TB meningitis – *see below*) Severe concomitant HIV disease	2HRZE	4HR or 6HE [c]
I	TB meningitis	2RHZS [d]	4RH
II	Previously treated smear-positive pulmonary TB — relapse — treatment after interruption — treatment failure	2HRZES/1HRZE	5HRE
IV	Chronic and MDR-TB	Specially designed standardized or individualized regimens	

E ethambutol H isoniazid R rifampicin S streptomycin Z pyrazinamide
MDR multidrug-resistant

Notes

[a] Direct observation of drug administration is recommended during the initial phase of treatment and whenever the continuation phase contains rifampicin. In either phase, treatment can be given daily or three times weekly.

[b] In comparison with the treatment regimen for patients in diagnostic category I, ethambutol may be omitted during the initial phase of treatment for patients with non-cavitary, smear-negative pulmonary TB who are known to be HIV-negative, patients known to be infected with fully drug-susceptible bacilli and young children with primary TB.

[c] This regimen (2HRZE/6HE) may be associated with a higher rate of treatment failure and relapse compared with the 6-month regimen with rifampicin in the continuation phase.

[d] In comparison with the treatment regimen for patients in diagnostic category I, streptomycin replaces ethambutol in the treatment of TB meningitis.

There is a standard code for anti-TB treatment regimens, which uses an abbreviation for each anti-TB drug, e.g. isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E). A regimen consists of two phases: the initial and continuation phases. The number at the front of each phase represents the duration of that phase in months. A subscript number (e.g.$_3$) following a drug abbreviation is the number of doses per week of that drug. If there is no subscript number following a drug abbreviation, treatment with that drug is daily. An alternative drug (or drugs) appears as an abbreviation (or abbreviations) in parentheses.

Example: 2HRZ/4H_3R_3

The initial phase is 2HRZ. The duration of this phase is 2 months. Drug treatment is daily (no subscript numbers after the abbreviations) with isoniazid, rifampicin and pyrazinamide. The continuation phase is 4H_3R_3. The duration of this phase is 4 months, with isoniazid and rifampicin three times weekly (subscript numbers after the abbreviations).

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

Table 15: Management of common opportunistic infections

Opportunistic infections	Clinical and laboratory manifestations	Diagnosis	Treatment
***Mycobacterium avium* complex (MAC)**	Fever, night sweats, weight loss, fatigue, chronic diarrhoea and abdominal pain Laboratory findings: neutropenia, raised alkaline phosphatase or lactate dehydrogenase (LDH)	Definitive diagnosis: isolation of organism from blood or specimen from normally sterile sites Histology demonstrating macrophage-containing acid-fast bacilli is suggestive	ART should be provided to restore immune function Treatment with at least 2 drugs: clarithromycin 7.5–15 mg/kg twice daily (max 500 mg/dose) plus ethambutol 15–25 mg/kg/day once daily (max 1 g/dose) Consider adding a third drug, e.g. amikacin or ciprofloxacin in severe cases Duration of treatment: at least 12 months
***Pneumocystis jiroveci* pneumonia (PCP)**	Dry cough, tachypnoea, dyspnoea, cyanosis	Chest X-ray: bilateral diffuse parenchymal infiltrates with "ground-glass" or reticulogranular appearance Associated with a high level of LDH Microscopy of sputum induced by bronchoalveolar lavage (BAL): Gram stain—stains cyst wall brown or black; Wright stain—stains the trophozoites and intracystic sporozoites pale blue	TMP/SMX 15–20 mg/kg/day of TMP in 3–4 divided doses in a 21-day course

Opportunistic infections	Clinical and laboratory manifestations	Diagnosis	Treatment
Candidiasis	**Oral candidiasis:** creamy-white, curd-like patches that can easily be scraped off showing an inflamed underlying mucosa **Esophageal candidiasis:** odynophagia, dysphagia, or retrosternal pain	**Oral candidiasis:** KOH preparation demonstrates budding yeast cells **Esophageal candidiasis:** barium swallow shows cobblestone appearance Endoscopy shows small white raised plaques to elevated confluent plaques with hyperaemia and extensive ulceration	**Oral candidiasis** Clotrimazole oral troches 10 g, **or** Nystatin 400,000–600,000 units 5 times daily for 7–14 days, or oral fluconazole 3–6 mg/kg once daily for 7–14 days **Esophageal candidiasis** Oral fluconazole 3–6 mg/kg once daily for 14–21 days
Penicilliosis	Persistent fever, anaemia, hepatomegaly, generalized lymphadenopathy and translucent umbilicated papules which may resemble molluscum Laboratory findings: anaemia, and/or thrombocytopenia	Definitive diagnosis: isolation of organism from blood, bone marrow aspirate or specimens from normally sterile sites Wright stain of skin scraping shows basophilic, spherical or oval yeast-like organisms with clear central septation (diameter 3–8 μm)	**Induction therapy:** Amphotericin B (0.7–1.5 mg/kg/day) for 2 weeks **Consolidation therapy:** Itraconazole 5–6 mg/kg/dose twice daily for 8 weeks. **Maintenance therapy:** Itraconazole 3–6 mg/kg/day
Cryptococcosis	Manifestations of meningoencephalitis: fever, headache, altered mental status, nuchal rigidity Manifestations of disseminated disease: persistent fever with translucent umbilicated papules which may resemble molluscum	Raised intracranial pressure, elevated cerebrospinal fluid (CSF) protein and mononuclear pleocytosis India ink stain of CSF should show budding yeast Cryptococcal antigen can be detected in the CSF or serum by the latex agglutination test Wright stain of skin scraping shows budding yeast	**Induction therapy:** Amphotericin B (0.7–1.5 mg/kg/day) plus flucytosine (25 mg/kg/dose four times daily) for 2 weeks **Consolidation therapy:** Fluconazole 5–6 mg/kg/dose twice daily for 8 weeks. **Maintenance therapy:** Fluconazole 3–6 mg/kg/day

Opportunistic infections	Clinical and laboratory manifestations	Diagnosis	Treatment
Herpes simplex virus (HSV)	**HSV gingivostomatitis:** fever, irritability, superficial painful ulcers in the gingival and perioral areas, and oral mucosa **HSV encephalitis:** fever, alteration of consciousness, abnormal behaviour	HSV gingivostomatitis is diagnosed by clinical evaluation HSV encephalitis is diagnosed by detection of HSV DNA in the CSF	**HSV gingivostomatitis:** oral acyclovir 20 mg/kg/dose three times daily or intravenous acyclovir 5–10 mg/kg/dose three times daily for 7–14 days **Disseminated HSV or encephalitis:** intravenous acyclovir 10 mg/kg/dose or 500 mg/m^2/dose three times daily for 21 days
Herpes zoster virus (HZV)	**Primary varicella infection:** generalized pruritic vesicular rash **Herper zoster:** painful rash with fluid-filled blisters, dermatomal distribution	Use clinical features for diagnosis If on clinical examination the diagnosis is not clear then Giemsa staining (Tzanck preparation) of cell scrapings from the lesions can be done. These show multinucleated giant cells suggestive of Varicella zoster virus (VZV). (Note that this is also seen in HSV infection.)	**Primary varicella infection:** intravenous acyclovir 10 mg/kg/dose or 500 mg/m^2/dose three times daily for 7 days in children with moderate to severe immunosuppresion. An oral formulation should be used only in a child with mild immunosuppression. **Herper zoster:** Oral acyclovir 20 mg/kg/dose four times daily (max 800 mg/dose) for 7 days
CMV infection	**CMV retinitis:** young HIV-infected children are frequently asymptomatic and the infection is discovered on routine examination. Older children present with floaters or loss of vision Extraocular CMV disease; e.g. CMV colitis, CMV esophagitis, CMV pneumonitis, CMV hepatitis	Diagnosis of CMV retinitis is based on the clinical appearance—white and yellow retinal infiltrates and associated retinal haemorrhages Extraocular CMV disease: recovery of the virus from tissues or histopathological examination of specimens demonstrates	Intravenous ganciclovir 5 mg/kg/dose twice daily for 14–21 days followed by lifelong maintenance therapy

Opportunistic infections	Clinical and laboratory manifestations	Diagnosis	Treatment
		characteristic "owl's eye" intranuclear inclusion bodies or positive staining of biopsy specimens with CMV monoclonal antibodies	
Cryptosporidiosis	Subacute or chronic watery diarrhoea often associated with cramps, nausea and vomiting	Modified Kinyoun acid-fast stain of stool: small oocyst (4–6 μm in diameter)	Effective ART is the only treatment that controls persistent cryptosporidiosis Supportive care includes hydration, correction of electrolyte abnormalities and nutritional supplementation Nitazoxanide is approved for treatment (age 1–3 years: 100 mg twice daily, age 4–11 years: 200 mg twice daily)

ANNEX A
SIX SAMPLE CASES

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

Step 1: Assessment at first visit (*see* p. 13)

Identify risk factors for HIV infection: This child is at risk for HIV infection via MTCT. The use of a single dose of NVP reduces the transmission risk by 50% but breastfeeding increases the transmission risk by about 10%.

Identify signs and symptoms of HIV and OIs, and assess the growth and nutritional status: The child is cachectic and his weight and length is below 3SD. He has tachypnoea and dry cough.

Concomitant medication: The child is not on co-trimoxazole. Co-trimoxazole once daily should have been started at 6–8 weeks of age. The risk of having PCP is high because of the lack of prophylaxis (*see* pp. 15–16).

Perform laboratory diagnostic testing for HIV: At 6 months of age, the diagnostic method is detection of HIV DNA or HIV RNA by polymerase chain reaction (PCR) or p24 antigen.

Step 2: Identification of OIs and diagnosis of HIV (*see* pp. 78–84 and pp. 86–96)

The infant is admitted to the hospital and a presumptive diagnosis of PCP is made. Chest X-ray shows bilateral perihilar diffuse infiltration. The infant is promptly given oral high-dose co-trimoxazole (trimethoprim 15–20 mg/kg/day + sulfamethoxazole 75–100 mg/kg/day) 4 times a day for 3 weeks along with supportive care. The infant improves after this treatment. After completion of 3 weeks of high-dose co-trimoxazole, he is given co-trimoxazole prophylaxis at a dosage of 5 ml suspension or 2 paediatric tablets or 1/2 SS adult tablet equivalent to 200 mg sulfamethoxazole/40 mg trimethoprim once daily.

HIV DNA, HIV RNA by PCR or Up24Ag detection is not available; therefore, confirmation of the diagnosis of HIV infection is not possible at this time. When the child is 18 months of age, HIV antibody testing can be done to confirm the diagnosis.

Step 3: Assessment of ART needs in the absence of a confirmed diagnosis of HIV infection (*see* p. 22)

Without confirmation of the diagnosis, ART should be started only if a child fits the WHO presumptive diagnosis of severe HIV disease. It is possible that this child will fit this diagnosis because an AIDS-indicator condition has been diagnosed (probable PCP). In order to make a presumptive diagnosis of severe HIV disease, HIV antibody testing is done which is positive. The CD4% is 10%, which falls in the severe immune suppression range. ART should be started, preferably after completion of treatment for PCP in order to lower the risk of IRIS. Initiation of ART is not an emergency and assessment of the caregiver's readiness to support the child is crucial. To ensure adherence to therapy, team effort is required (*see* pp. 31–35).

Step 4: Choosing ART

Because this child is <3 years of age and weighs <10 kg, the WHO recommended first-line regimen is 2 NRTIs plus NVP. He has anaemia (haemoglobin 7.5 g/dl); therefore, for the 2 NRTIs, d4T is selected instead of AZT, to be taken with 3TC. He has been exposed to NVP which may put him at risk for NVP resistance; however, data on whether this would affect treatment outcome are not available; therefore, the preferred first-line regimen is NVP-based ART.

CASE II: A 6-year-old boy with recurrent otitis media and pruritic papular eruptions and a CD4 count of 180 cells/mm^3 has been referred to your clinic.

Step 1: Assessment after HIV diagnosis is confirmed (*see* p. 13)

Staging of HIV disease using clinical criteria: Recurrent otitis media and pruritic papular eruptions are conditions seen in patients in WHO stage 2 or mild HIV disease (*see* pp. 78–84).

Staging of HIV disease using immunological criteria: His CD4 count of 180 cells/mm^3 suggests severe immune suppression (*see* p. 19).

Staging of HIV disease using TLC is not needed, as CD4 estimation is available.

Co-trimoxazole prophylaxis: This child is not on co-trimoxazole prophylaxis but should be on it as he has signs of WHO stage 2 disease and his CD4 count is <200 cells/mm^3.

Assess whether the child fits the criteria for ART initiation: The child has had only one CD4 estimation which is within the severe immune suppression range. As the CD4 count can fluctuate depending on the health status at the time of testing, it is recommended that the CD4 count be repeated prior to starting ART in children who do not satisfy the clinical criteria for starting ART (WHO stage 3 or 4).

Concomitant medication: The child is not on any medication.

Assess for signs and symptoms of OIs: The child does not have any.

Assess the growth and nutritional status: The child's growth is normal and he is on a balanced diet.

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

Step 2: Starting ART (*see* p. 21)

This boy does not satisfy the clinical criteria for starting ART (is not in WHO stage 3 or 4). His second CD4 count is 170 cells/mm^3, which confirms that he has severe immune suppression and should be started on ART.

Step 3: Choose the regimen (*see* p. 27)

The preferred regimen is 2 NRTI plus 1 NNRTI. The health-care worker chose AZT + 3TC as the 2 NRTIs, as AZT is associated with less lipodystrophy than d4T and ABC is not available. The NNRTI chosen is EFV because rash and hepatotoxicity are less likely. However, his

mother is concerned about his compliance with this regimen because of its pill burden and the possibility of EFV causing headache and dizziness. Therefore, the regimen selected is an FDC of d4T (30 mg), 3TC (150 mg) and NVP (200 mg). He weighs 20 kg and is 110 cm tall (body surface area is 0.78 m^2) so the dosage of ART should be d4T 20 mg, 3TC 80 mg, NVP 156 mg, which can be rounded off to 150 mg when 3–4 pills of this FDC are given every 12 hours. The mother is informed that the medication has to be given to him on time every day to prevent resistance. The pills are cut with a pill cutter. The child cannot swallow pills and they have to be crushed and mixed with water.

Step 4: Preparing the family and child for ART (*see* p. 31)

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

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

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

CASE III: A 4-year-old child with presumed pulmonary TB and CD4% of 8% is referred to your clinic.

Step 1: Diagnosis of OIs, staging of HIV disease and initiation of ART/co-trimoxazole

The child presents with a poor appetite and poor weight gain, low-grade fever, chronic non-productive cough and generalized lymphadenopathy. There is no family history of recent contact with a person having TB. On physical

examination the child looks chronically ill and cachectic, and on auscultation of the lungs, there are bilateral crackles. The chest X-ray shows bilateral hilar adenopathy and infiltration. The child cannot produce sputum. A tuberculin skin test was not performed. A presumptive diagnosis of pulmonary TB is made. The child's weight and height are below 2 SD. He has a poor appetite and bad dental hygiene. He does not have chronic diarrhoea.

The presence of pulmonary TB puts him in WHO stage 3 (*see* pp. 78–84). His CD4% of <15% signifies severe immune suppression (*see* pp. 19–20). Staging of HIV disease using TLC is not needed as CD4 estimation is available. This child should be on co-trimoxazole prophylaxis as he has signs of WHO stage 3 disease and his CD4 count is <15%. According to the clinical criteria (WHO stage 3), the child may be started on ART. This child's CD4 count is in the severe immune deficiency range (CD4% <15%); therefore, he should be started on ART. Both parents have passed away. He lives with his grandmother.

Step 2: Starting treatment for TB (*see* pp. 61–64)

A regimen of isoniazid, rifampicin, ethambutol and pyrazinamide is started. The child improves within 2 weeks and has a better appetite, no fever and less cough. The 4-drug TB regimen is continued for 2 months followed by a 2-drug regimen of isoniazid and rifampicin. The plan is to continue this regimen for 9 months according to the guidelines of his country.

Step 3: Choose when to start ART and choose the regimen (*see* pp. 21–30)

This child has presumptive pulmonary TB and severe immune deficiency (CD4% <15%); therefore, ART should be initiated. In children with HIV and TB co-infection, ART should be started 2–8 weeks after commencing anti-TB treatment. In this case, ART is started 8 weeks after anti-TB treatment; there is no urgency to start ART since the child shows good clinical improvement with anti-TB treatment. ART is started after initiation of anti-TB treatment to lower the chances of overlapping toxicity of ART and anti-TB medications, and of IRIS.

Normally, the preferred regimen is 2 NRTI plus 1 NNRTI but in children who start ART after rifampicin-based anti-TB treatment, a triple NRTI regimen with d4T or AZT + 3TC + ABC is recommended as these drugs do not interact with anti-TB medications (*see* pp. 29–30 and pp. 103–105). However, in this health-care facility, ABC is not available because of its high cost; therefore, an

alternative regimen with 2 NRTI plus EFV was selected. Rifampicin can lower the drug level of EFV by 25%. At present, there are no data on whether the dose of EFV needs to be adjusted. In this case, the standard dosage of EFV is used in combination with AZT + 3TC. NRTIs are not affected by rifampicin and can be selected as in patients without TB.

Step 4: Preparing the family and child for ART (*see* pp. 34–35)

The caregiver is prepared and understands the need to start ART. The caregiver is also counselled on the signs and symptoms of IRIS and the overlapping toxicity of ART and anti-TB medications.

CASE IV: A 16-year-old adolescent girl infected via sexual transmission and having a CD4 count of 220 cells/mm^3

Step 1: Staging of HIV disease and assessing the need for ART/co-trimoxazole

She is asymptomatic and classified as being in WHO clinical stage 1. Her CD4 count of 220 cells/mm^3 signifies advanced immunodeficiency (*see* p. 19). Staging of HIV disease using a TLC is not needed as CD4 estimation is available. She may need co-trimoxazole at this time as CD4 count is slightly >200 cells/mm^3 (*see* p. 15). She fulfils the criteria for starting ART. She is on oral contraceptive pills (OCP). If there is a need to use ART in the future, she should be counselled that the effectiveness of OCP can be reduced when used with ART as ART can lower the level of OCP (*see* p. 104).

Assess the family situation: She lives with her mother. She is sexually active and uses a barrier contraceptive (male condom) most of the time.

Step 2: Starting ART (*see* p. 21)

Though this girl fulfils the criteria to start ART, it is not started at this time as adherence to treatment is not assured. She is asked to take co-trimoxazole on time every day as a test for adherence to ART. She is subsequently followed up every month for 2 more months and reports that she is able to take co-trimoxazole on time and is ready to start ART. At every visit she receives counselling on HIV, ART, contraceptives and adherence to treatment. Six months after the first visit, her CD4 count is 170 cells/mm^3 and she has oral candidiasis. It is decided that she should start ART.

Step 3: Choose the regimen (*see* p. 27)

The regimen of choice is 2 NRTI + 1 NNRTI. For a teenage girl who is at risk for becoming pregnant, EFV should be avoided as it has a teratogenic effect. Females are at a higher risk of having NVP-related hepatotoxicity and rash if the CD4 count is >250 cells/mm^3 but our patient has a CD4 count of <250 cells/mm^3 and should be at similar risk as others. Therefore, the regimen of choice in this girl should be 2 NRTI + NVP. AZT + 3TC is chosen as she has a risk of pregnancy and these two NRTIs have a good safety profile in pregnancy. An alternative regimen, an FDC of AZT/3TC/ABC has the advantage of a low pill burden and restriction of resistance to only the NRTI class in patients in whom poor adherence to treatment is anticipated. However, 3 NRTI regimens have been shown to be inferior in their ability to suppress HIV viraemia compared with regimens with at least 2 classes of drugs. In this case, an FDC of AZT/3TC/NVP is chosen in which 1 pill is taken twice daily.

Step 4: Preparing the family and child for ART (*see* p. 31)

In this case, it is the patient who has to be responsible for taking ART. Adherence to treatment in teenagers depends on the personality and the living situation. In this case close follow up by telephone and a monthly visit during the first 3 months of ART is needed to ensure compliance and treat side-effects promptly as these can affect adherence. Counselling on adherence as well as other psychosocial issues should be done at every visit. Her mother is encouraged to support the patient in complying with her treatment. The patient is encouraged to be involved in treatment decisions and is told the results of her CD4 estimation at every visit. She is encouraged to join the teenagers' counselling group held by the clinic where she can make friends and learn more about her disease.

CASE V. A 6-year-old girl developed painful vesicles on the left chest wall 4 weeks after initiation of ARV

Step 1: Assess whether it is due to ARV-related toxicity

- She received a regimen comprising AZT + 3TC + NVP. The common NVP-associated rash is an erythematous maculopapular rash distributed on the face or trunk. The onset of rash is usually during the first 2–8

weeks. The rash in this child is a painful group of vesicles distributed on the left chest wall and is dermatomal in distribution. The most likely diagnosis is herpes zoster.

Step 2: Assess whether it is due to treatment failure

- She received ARV for <24 weeks, therefore it is not counted as a sign of ARV treatment failure. She should continue with the same ART.

Step 3: Assess whether it is a new OI or IRIS

- IRIS is the most likely diagnosis, because it occurs during the first month after starting ART. Immunological assessment to document the CD4 response should be performed if available. Before initiation of ARV treatment her CD4% was 3% (40 cells/mm^3), which rapidly increased to 8% (150 cells/mm^3).
- She should continue the same ARV regimen along with oral acyclovir 20 mg/kg/dose four times daily for 7 days.

CASE VI: A 10-year-old HIV-infected girl who has been receiving ART (a regimen containing AZT + 3TC + NVP) for 3 years presents with oral candidiasis

Step 1: Evaluate adherence to ARV

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

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

- The child has taken ARV for >24 weeks and develops a new OI; therefore, she meets the criteria for clinical failure.
- A CD4 count should be done if available. The CD4 count is 12% (180 cells/mm^3). The previous CD4 count performed a year ago was 20% (350 cells/mm^3). The CD4 count has declined significantly from the peak level.

The CD4 count also fall when there is severe immunodeficiency. The child fulfils the criteria for immunological failure.

Step 3: Switch to a second-line regimen

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

ANNEX B

PART A: WHO CLINICAL STAGING OF HIV/AIDS FOR CHILDREN WITH CONFIRMED HIV INFECTION

Clinical Stage 1

Asymptomatic
Persistent generalized lymphadenopathy

Clinical Stage 2

Unexplained [a] persistent hepatosplenomegaly
Papular pruritic eruptions
Fungal nail infection
Angular cheilitis
Lineal gingival erythema
Extensive wart virus infection
Extensive molluscum contagiosum
Recurrent oral ulceration
Unexplained [a] persistent parotid enlargement
Herpes zoster
Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis)

Clinical Stage 3

Unexplained [a] moderate malnutrition or wasting not adequately responding to standard therapy
Unexplained [a] persistent diarrhoea (14 days or more)
Unexplained [a] persistent fever (above 37.5º C intermittent or constant, for longer than one month)
Persistent oral candidiasis (after the first 6–8 weeks of life)
Oral hairy leukoplakia
Acute necrotizing ulcerative gingivitis/periodontitis
Lymph node TB
Pulmonary TB
Severe recurrent bacterial pneumonia
Symptomatic lymphoid interstitial pneumonitis
Chronic HIV-associated lung disease including bronchiectasis
Unexplained anaemia (<8 g/dl), neutropenia ($<0.5 \times 10^9/L^3$) or chronic thrombocytopenia ($<50 \times 10^9/L^3$)

Clinical Stage 4 [b]

Unexplained [a] severe wasting, stunting or severe malnutrition not responding to standard therapy
Pneumocystis pneumonia
Recurrent severe bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)
Chronic herpes simplex infection (orolabial or cutaneous of more than one month's duration or visceral at any site)
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Extrapulmonary/disseminated TB
Kaposi sarcoma
Cytomegalovirus infection: retinitis or CMV infection affecting another organ, with onset at age >1 month
Central nervous system toxoplasmosis (after one month of life)
Extrapulmonary cryptococcosis (including meningitis)
HIV encephalopathy
Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidioidomycosis)
Disseminated non-tuberculous mycobacterial infection
Chronic cryptosporidiosis (with diarrhoea)
Chronic isosporiasis
Cerebral or B cell non-Hodgkin lymphoma
Progressive multifocal leukoencephalopathy
Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

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[a] Unexplained refers to where the condition is not explained by other causes.

[b] Some additional specific conditions can also be included in regional classifications (e.g. reactivation of American trypanosomiasis [meningoencephalitis and/or myocarditis] in Americas region, penicilliosis in Asia and HIV-associated rectovaginal fistula in Africa).

Part B:

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

(For use in children aged less than 15 years with confirmed HIV infection)

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

Clinical event	Clinical diagnosis	Definitive diagnosis
Unexplained persistent parotid enlargement	Asymptomatic bilateral swelling that may spontaneously resolve and recur, in absence of other known cause, usually painless	Clinical diagnosis
Herpes zoster	Painful rash with fluid-filled blisters, dermatomal distribution, can be haemorrhagic on erythematous background, and can become large and confluent. Does not cross the midline	Clinical diagnosis
Recurrent or chronic upper respiratory tract infection (URTI)	Current event with at least one episode in past 6 months. Symptom complex; fever with unilateral face pain and nasal discharge (sinusitis) or painful swollen eardrum (otitis media), sore throat with productive cough (bronchitis), sore throat (pharyngitis) and barking croup-like cough (LTB). Persistent or recurrent ear discharge	Clinical diagnosis
Clinical Stage 3		
Unexplained moderate malnutrition	Weight loss: low weight-for-age, up to −2 standard deviations (SDs) from the mean, not explained by poor or inadequate feeding and or other infections, and not adequately responding to standard management	Documented failure to gain weight or weight loss: body weight of –2 SD, failure to gain weight on standard management and no other cause identified during investigation
Unexplained persistent diarrhoea	Unexplained persistent (14 days or more) diarrhoea (loose or watery stool, three or more times daily), not responding to standard treatment	Stools observed and documented as unformed. Culture and microscopy reveal no pathogens
Unexplained persistent fever (>37.5ºC intermittent or constant, for longer than one month)	Reports of fever or night sweats for longer than one month, either intermittent or constant, with reported lack of response to antibiotics or antimalarials. No other obvious foci of disease reported or found on examination. Malaria must be excluded in malarious areas	Documented fever of >37.5ºC with negative blood culture, negative malaria slide and normal or unchanged CXR, and no other obvious foci of disease
Persistent oral candidiasis (after first 8 weeks of life)	Persistent or recurring creamy white to yellow soft small plaques which can be scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender (erythematous form)	Microscopy or culture
Oral hairy leukoplakia	Fine small linear patches on lateral borders of tongue, generally bilaterally, which do not scrape off	Clinical diagnosis

Clinical event	Clinical diagnosis	Definitive diagnosis
Acute necrotizing ulcerative gingivitis or stomatitis, or acute necrotizing ulcerative periodontitis	Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odour, and rapid loss of bone and/or soft tissue	Clinical diagnosis
Lymph node TB	Non-acute, painless "cold" enlargement of peripheral lymph nodes, localized to one region. Response to standard anti-TB treatment in one month	Histology or fine needle aspirate positive for Ziehl–Neelsen (ZN) stain or culture
Pulmonary TB	Nonspecific symptoms, such as chronic cough, fever, night sweats, anorexia and weight loss. In the older child also productive cough and haemoptysis. History of contact with adult with smear-positive PTB. No response to standard broad spectrum-antibiotic treatment	One or more sputum smear positive for acid-fast bacilli and/or radiographic abnormalities consistent with active TB and/or culture positive for *M. tuberculosis*
Severe recurrent bacterial pneumonia	Cough with fast breathing, chest in drawing, nasal flaring, wheezing, and grunting. Crackles or consolidation on auscultation. Responds to course of antibiotics. Current episode plus one or more in previous 6 months	Confirmed by isolation of bacteria from appropriate clinical specimens (induced sputum, BAL, lung aspirate)
Symptomatic lymphocytic interstitial pneumonitis (LIP)	No presumptive clinical diagnosis	CXR: bilateral reticulonodular interstitial pulmonary infiltrates present for more than two months with no response to antibiotic treatment and no other pathogen found. Oxygen saturation persistently <90%. May present with cor pulmonale and may have increased exercise-induced fatigue. Characteristic histology
Chronic HIV-associated lung disease (including bronchiectasis)	History of cough productive of copious amounts of purulent sputum (bronchiectasis only), with or without clubbing, halitosis, and crepitations and/or wheezes on auscultation	CXR may show honeycomb appearance (small cysts) and/or persistent areas of opacification and/or widespread lung destruction, with fibrosis and loss of volume
Unexplained anaemia (<8 g/dl), neutropenia (<0.5 x $10^9/L^3$) or chronic thrombocytopenia (<50 x $10^9/L^3$)	No presumptive clinical diagnosis	Laboratory testing not explained by other non-HIV conditions, not responding to standard therapy with haematinics, antimalarials or anthelmintics as outlined in WHO IMCI guidelines

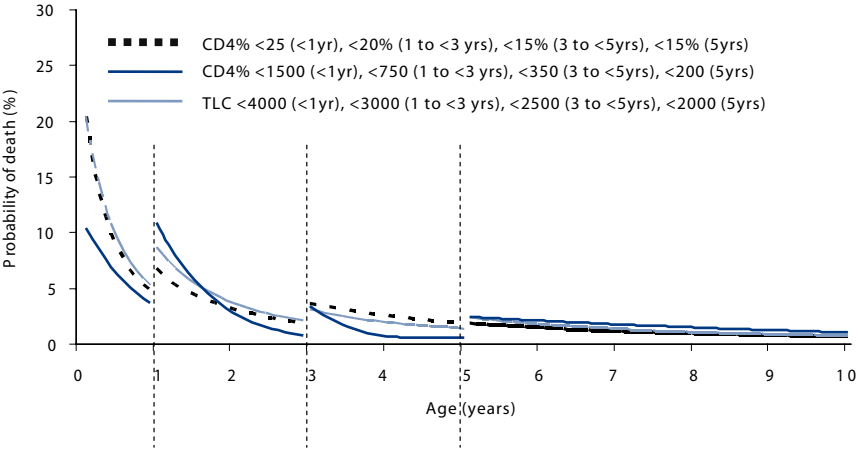
Clinical event	Clinical diagnosis	Definitive diagnosis
Clinical Stage 4 [b]		
Unexplained [a] severe wasting, stunting or severe malnutrition not adequately responding to standard therapy	Persistent weight loss not explained by poor or inadequate feeding, other infections and not adequately responding in two weeks to standard therapy. Characterized by: visible severe wasting of muscles, with or without oedema of both feet, and/or weight-for-height of – 3SD, as defined by WHO IMCI guidelines	Documented weight for height or weight for age of more than – 3SD from the mean with or without oedema
Pneumocystis pneumonia (PCP)	Dry cough, progressive difficulty in breathing, cyanosis, tachypnoea and fever; chest indrawing or stridor. (Severe or very severe pneumonia as in IMCI.) Usually of rapid onset especially in infants under six months of age. Response to high-dose co-trimoxazole with/without prednisolone. CXR typical bilateral perihilar diffuse infiltrates	Cytology or immunofluorescent microscopy of induced sputum or bronchoalveolar lavage (BAL), or histology of lung tissue
Recurrent bacterial infection, e.g. empyema, pyomyositis, bone or joint infection, meningitis but excluding pneumonia	Fever accompanied by specific symptoms or signs that localize infection. Responds to antibiotics. Current episode plus one or more in previous 6 months	Culture of appropriate clinical specimen
Chronic herpes simplex infection (orolabial or cutaneous of more than 1 month's duration or visceral at any site)	Severe and progressive painful orolabial, genital, or anorectal lesions caused by HSV infection present for more than one month	Culture and/or histology
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)	Difficulty in swallowing, or pain on swallowing (food and fluids). In young children, suspect particularly if oral candida observed and food refusal occurs and/or difficulties/crying when feeding	Macroscopic appearance at endoscopy, microscopy of specimen from tissue or macroscopic appearance at bronchoscopy or histology
Extrapulmonary TB	Systemic illness usually with prolonged fever, night sweats, weight loss. Clinical features depend on organs involved, such as sterile pyuria, pericarditis, ascitis, pleural effusion, meningitis, arthritis or orchitis, pericardial or abdominal	Positive microscopy showing acid-fast bacilli or culture of *M. tuberculosis* from blood or other relevant specimen except sputum or BAL. Biopy and histology
Kaposi sarcoma	Typical appearance in skin or oropharynx of persistent, initially flat, patches with a pink or blood-bruise colour, skin lesions that usually develop into nodules	Not required but may be confirmed by: – typical redpurple lesions seen on bronchoscopy or endoscopy; – dense masses in lymph nodes, viscera or lungs by palpation or radiology; – histology

Clinical event	Clinical diagnosis	Definitive diagnosis
CMV retinitis or CMV infection affecting another organ, with onset at age over 1 month	Retinitis only CMV retinitis may be diagnosed by experienced clinicians: typical eye lesions on serial fundoscopic examination; discrete patches of retinal whitening with distinct borders, spreading centrifugally, often following blood vessels, associated with retinal vasculitis, haemorrhage and necrosis	Definitive diagnosis required for other sites. Histology. CSF polymerase chain reaction (PCR)
CNS toxoplasmosis onset after age 1 month	Fever, headache, focal neurological system signs and convulsions. Usually responds within 10 days to specific therapy	Computed tomography (CT) scan (or other neuroimaging) showing single/multiple lesions with mass effect/enhancing with contrast
Extrapulmonary cryptococcosis (including meningitis)	Meningitis: usually subacute, fever with increasing severe headache, meningism, confusion, behavioural changes that respond to cryptococcal therapy	CSF microscopy (India ink or Gram stain), serum or CSF cryptococcal antigen test or culture
HIV encephalopathy	At least one of the following, progressing over at least two months in the absence of another illness: – failure to attain, or loss of, developmental milestones, loss of intellectual ability; **or** – progressive impaired brain growth demonstrated by stagnation of head circumference; **or** – acquired symmetrical motor deficit accompanied by two or more of the following: paresis, pathological reflexes, ataxia, gait disturbances	Neuroimaging demonstrating atrophy and basal ganglia calcification and excluding other causes
Disseminated mycosis (coccidioidomycosis, histoplasmosis, penicilliosis)	No presumptive clinical diagnosis	Histology: usually granuloma formation Isolation: antigen detection from affected tissue; culture or microscopy from clinical specimen or blood culture
Disseminated non-tuberculous mycobacterial infection	No presumptive clinical diagnosis	Nonspecific clinical symptoms including progressive weight loss, fever, anaemia, night sweats, fatigue or diarrhoea; plus culture of atypical mycobacteria species from stool, blood, body fluid or other body tissue, excluding lung

Clinical event	Clinical diagnosis	Definitive diagnosis
Chronic cryptosporidiosis	No presumptive clinical diagnosis	Cysts identified on modified ZN microscopic examination of unformed stool
Chronic isosporiasis	No presumptive clinical diagnosis	Identification of *Isospora*
Cerebral or B cell non-Hodgkin lymphoma	No presumptive clinical diagnosis	Diagnosed by CNS neuroimaging, histology of relevant specimen
Progressive multifocal leukoencephalopathy (PML)	No presumptive clinical diagnosis	Progressive neurological disorder (cognitive dysfunction, gait/speech disorder, visual loss, limb weakness and cranial nerve palsies) together with hypodense white matter lesions on neuroimaging or positive polyomavirus JC (JCV) PCR on CSF
Symptomatic HIV-associated nephropathy	No presumptive clinical diagnosis	Renal biopsy
Symptomatic HIV-associated cardiomyopathy	No presumptive clinical diagnosis	Cardiomegaly and evidence of poor left ventricular function confirmed by echocardiography

ANNEX C

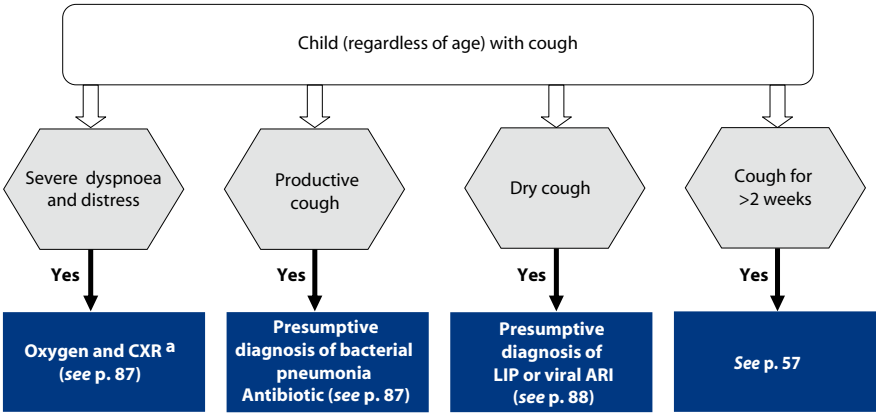
12-Month mortality risk at selected thresholds for CD4%, absolute CD4 count and total lymphocyte count (TLC), by age



ANNEX D SYNDROMIC APPROACH TO THE MANAGEMENT OF COMMON OPPORTUNISTIC INFECTIONS [14,15]

I. Respiratory infections

- Does the child have cough?



Note

[a] A chest X-ray should be performed, if available.

Bacterial pneumonia: lobar or patchy infiltration

PCP: bilateral interstitial infiltrates

Primary TB: enlarged hilar or paratracheal lymph nodes with pulmonary infiltration

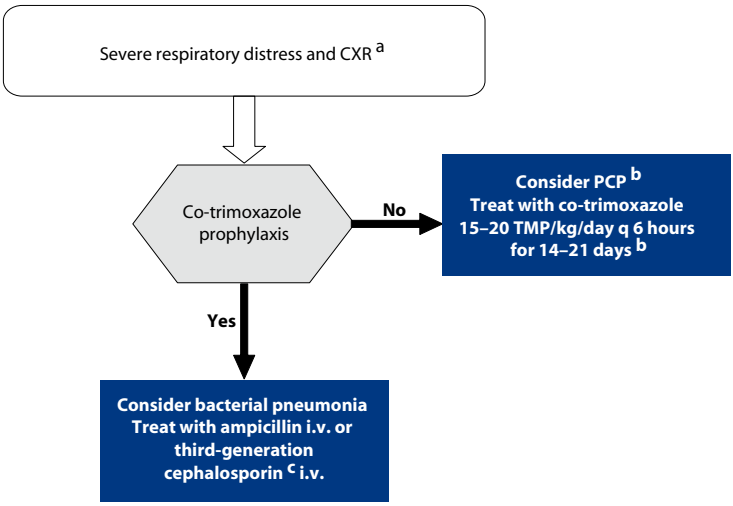
Lymphocytic interstitial pneumonia: persistent bilateral reticulonodular interstitial infiltrates

Any diagnosis based on chest X-ray should be substantiated through clinical signs and additional investigations where possible, e.g. microscopy of sputum and pleural effusion.

[14] *Integrated management of adolescent and adulthood and illness.* Geneva, WHO, 2006 (in print).

[15] *Clinical management of HIV/AIDS*, Thailand, Ministry of Public Health, 2004.

- Child presents with cough, severe respiratory distress and findings on chest X-ray



Notes

[a] A chest X-ray should be performed, if available.

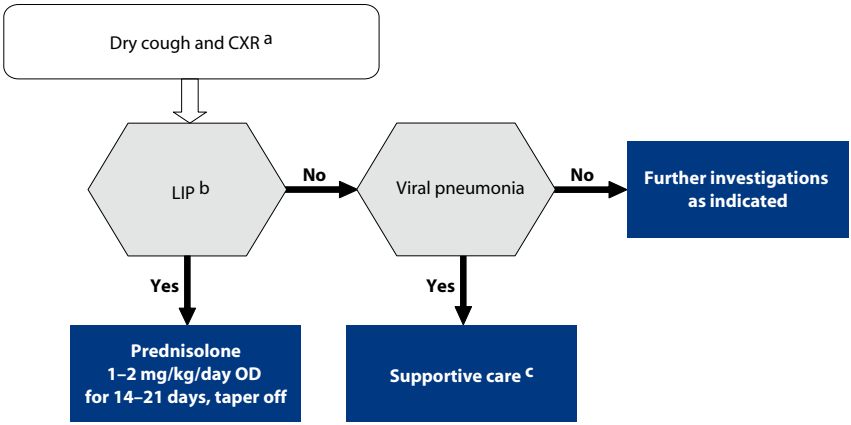
Bacterial pneumonia: Lobar or patchy infiltration

PCP: bilateral interstitial infiltrates

[b] PCP is the most serious disease in HIV-infected children. In children presenting with acute respiratory distress and no history of taking primary prophylaxis, PCP is most likely. High-dose TMP–SMZ treatment must be initiated immediately. Steroid reduces mortality in severe case of PCP. In case of TMP–SMZ intolerance, alternative treatments are dapsone + trimethoprim or primaquin + clindamycin.

[c] Ampicillin 25 mg/kg i.v./i.m. every 6 hours. In areas where drug-resistant *Streptococcus pneumoniae* (DRSP) is prevalent a third-generation cephalosporin is recommended: cefotaxime 50 mg/kg i.v. every 6 hours or ceftriaxone i.v./i.m. 80 mg/kg/day given over 30 minutes for at least 10 days.

- Child presents with dry cough and findings on chest X-ray



Notes

[a] A chest X-ray should be performed, if available.

[b] **Lymphocytic interstitial pneumonia (LIP):** persistent bilateral reticulonodular interstitial infiltrates. LIP requires treatment only where symptoms of hypoxaemia are present.

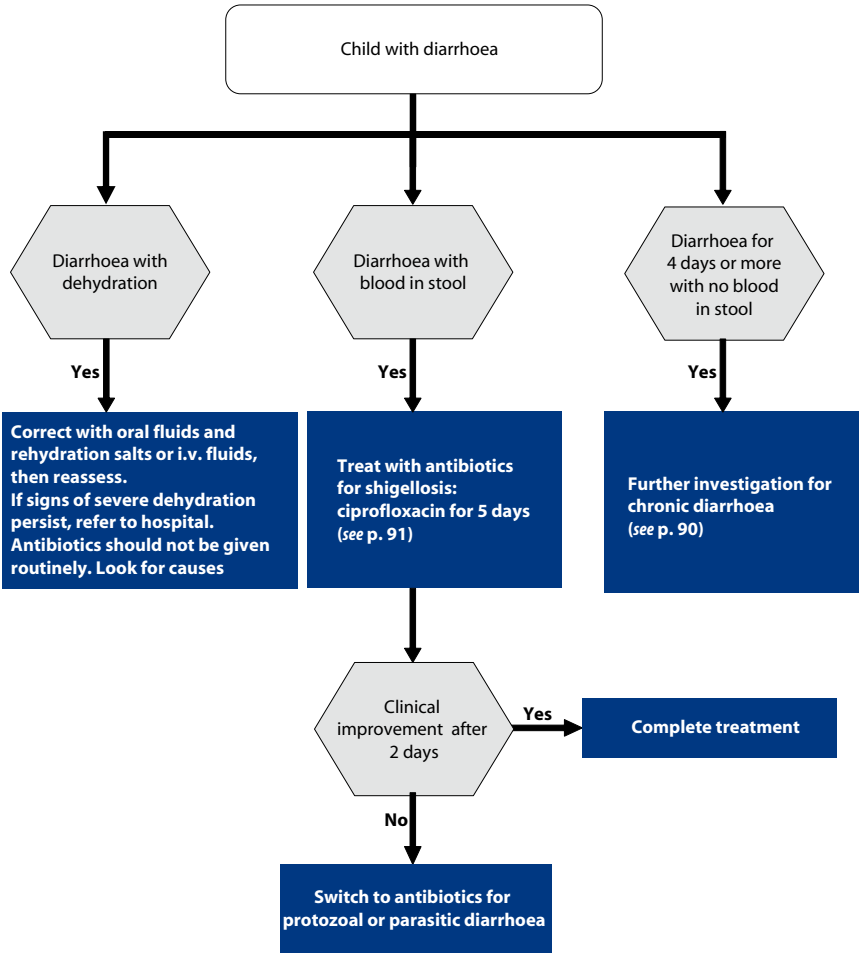
[c] Supportive care:[16]

- If the child has fever (>39ºC), which appears to be causing distress, give paracetamol.
- If wheeze is present, give a rapid-acting bronchodilator.
- Remove by gentle suction any thick secretions in the throat which the child cannot clear.
- Ensure that the child receives daily maintenance fluids appropriate for age, but avoid overhydration.
- Encourage the child to eat as soon as food can be taken.

[16] *Pocket book of hospital care for children. Guidelines for the management of common illnesses with limited resources.* Geneva, WHO, 2005.

II. Diarrhoea

- Does the child have diarrhoea?



Acute diarrhoea

Acute diarrhoea can occur in symptomatic HIV-infected children. Acute watery diarrhoea is defined as more than 3 stools per day and no blood. The management of acute diarrhoea should follow the guidelines of the national programme for the control of diarrhoeal diseases and guidelines for the management of common illnesses with limited resources.

Other bacterial infections can be accompanied by diarrhoea. Careful physical examination should also look for other infections such as pneumonia.

Stool culture may identify *Salmonella, Shigella* and *Vibrio cholerae* as well as other bacterial pathogens.

Blood culture is indicated if the child is febrile or toxic. *Salmonella*, MAC and other bacteria are frequently isolated from blood cultures of HIV-infected children. For specific treatment *see* p. 91.

The child should be examined again after 2 days in case of any of the following circumstances: being initially dehydrated, <1-year-old, persistence of blood in the stool, or no improvement in symptoms. Improvement is defined as follows: weight gain, disappearance of fever and blood in the stool, passage of fewer stools and improved appetite.

Dysentery is diarrhoea presenting with frequent loose stools containing blood. Most episodes are due to *Shigella* and nearly all require antibiotic treatment. If available, stool culture may identify *Shigella* as well as other bacterial pathogens. This diagnostic signs are:

- Visible red blood
- Abdominal pain
- Convulsion, lethargy
- Rectal prolapse
- Frequent loose stools
- Fever
- Dehydration

The child should be examined again after 2 days in case of any of the following circumstances: being initially dehydrated, <1-year-old, persistence of blood in the stool, or no improvement in symptoms. Improvement is defined as follows: weight gain, disappearance of fever and blood in the stool, passage of fewer stools and improved appetite.

Give an oral antibiotic for 5 days, to which most strains of *Shigella* are sensitive. Examples of antibiotics to which *Shigella* strains can be sensitive are fluoroquinolones such as ciprofloxacin.

Co-trimoxazole and ampicillin are not effective any more due to widespread resistance.

Chronic diarrhoea

Definition of chronic diarrhoea: Liquid stools (>3 times/day) for ≥14 days in children with symptomatic HIV infection.

Chronic diarrhoea is common in HIV-infected children. If the child is not severely ill (no blood in the stool, afebrile, not dehydrated, not malnourished), observe the child while maintaining hydration and nutrition. Other causes of diarrhoea include mucosal damage, bacterial overgrowth, bile acid diarrhoea, or CMV infection. Empirical treatment with oral neomycin or colistin plus cholestyramine may relieve the symptoms. HIV infection itself may cause diarrhoea, which may be successfully treated with ART.

Stool microscopy is done to identify *Candida, Cryptosporidium, Microsporidia*, and parasites that can cause persistent diarrhoea. Faecal smears stained with modified acid-fast and modified trichrome stains should be performed. Look for blood and neutrophils in the faecal smear. These findings can support the diagnosis of some bacterial infections (e.g. those due to *Shigella, Salmonella, Campylobacter*). Stool cultures can identify bacterial infections.

Antibiotic treatment for diarrhoea

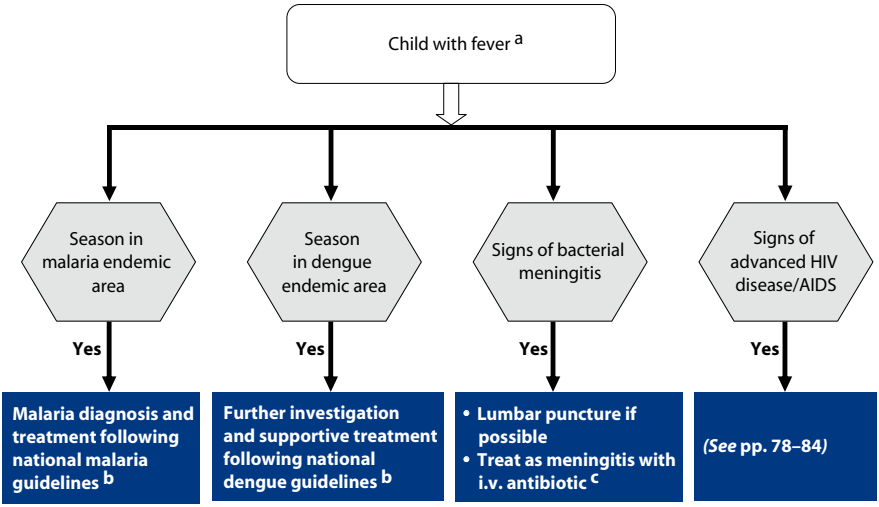
Bacterial pathogens in chronic diarrhoea	
Etiology	**Treatment**
BACTERIA	
Salmonella (non-typhoidal)	Ciprofloxacin* 10–15 mg/kg 2 times a day for 5 days
Shigella	Ciprofloxacin* 10–15 mg/kg 2 times a day for 5 days
Escherichia coli	No antibiotic
Campylobacter jejuni	Erythromycin 12.5 mg/kg 4 times a day for 5 days Or ciprofloxacin* 10–15 mg/kg 2 times a day for 5 days.
Mycobacterium avium complex	Clarithromycin 15 mg/kg/day 2 times a day plus Ethambutol 15–25 mg/kg 4 times a day (plus rifabutin 6 mg/kg once daily§)
M. tuberculosis	Standard treatment for tuberculosis
Yersinia enterocolitica	TMP—SMZ: TMP 4 mg/kg + SMZ 20 mg/kg 2 times a day for 5 days
VIRUS	
Cytomegalovirus	Supportive treatment as the internationally recommended treatment with ganciclovir is very expensive
Rotavirus	Supportive treatment
PROTOZOA	
Cryptosporidium	No therapy proven efficacious, spontaneous resolution may occur after antiretroviral therapy
Isospora belli	TMP–SMZ TMP 4 mg/kg + SMZ 20 mg/kg 4 times a day for 10 days then 2 times a day for 10 days. Maintenance therapy may be considered
Giardia lamblia	Metronidazole 5 mg/kg 3 times a day for 5 days
Entamoeba histolytica	Metronidazole 10 mg/kg 3 times a day for 10 days
Microsporidia	Albendazole 10 mg/kg 2 times a day for 4 weeks (maximum 400 mg/dose)
PARASITE	
Strongyloides	Albendazole 10 mg/kg once daily for 3 days (maximum 400 mg/dose)
YEAST	
Candida albicans	Nystatin 100,000 IU orally tid for 5–7 days for mild cases Alternative: ketoconazole 5 mg/kg/dose once daily or 2 times a day or fluconazole 3–6 mg/kg once daily (also for moderate -to-severe cases)

* Use is not licensed for use in infants and children less than 5 years of age. Quinolones taken by mouth have been shown to cause bone problems in very young animals and caution is advised in children.

§ **Rifabutin is currently not available in South-East Asia.**

III. Persistent or recurrent fever

- Does the child have fever?



Notes

[a] Fever is defined as a body temperature of >37.5ºC axillary, 38.0ºC oral, 38.5ºC rectal.

- **Persistent fever:** fever for >5 days
- **Recurrent fever:** more than one episode of fever over a period of 5 days.

Children may also have fever as a consequence of intercurrent common childhood illnesses, endemic diseases, and serious bacterial infections or OI, neoplasms and/or HIV itself. Under many of these circumstances the fever will be associated with specific localizing signs and symptoms.

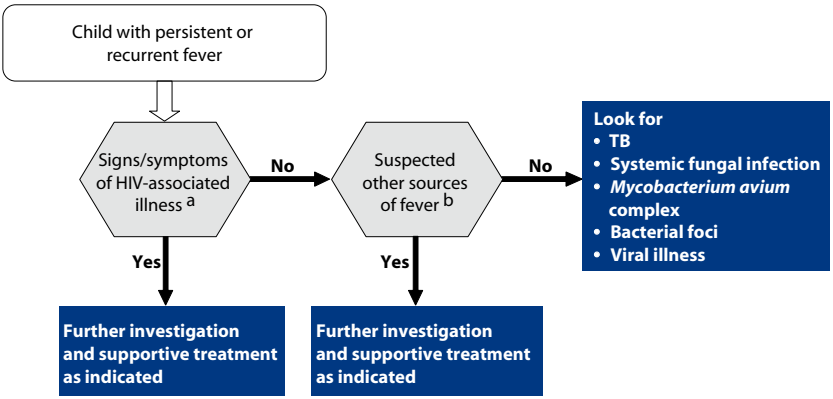
Careful history-taking

- How many days of fever?
- Any other symptoms?
- What medication did the child receive during the past days?

[b] Follow specific guidelines for management.

[c] In CNS infections there may be persistent or recurrent fever without abnormal neurological signs. A cranial ultrasound and/or CT scan might be beneficial. For finding other foci an abdominal ultrasonogram might be helpful. Bone marrow culture may give a better yield than routine blood culture. Mycobacteraemia can be easily detected by culture.

- Child presents with persistent or recurrent fever



Notes

[a] Consider

- Signs/symptoms of HIV-associated illness
- Look for oral thrush
- Look for skin lesions
- Look for specific localized signs
- If on ART check for adverse events due to ARV
- If on ART check for IRIS

[b] In case there is persistent fever and bacterial infection is suspected, look for focal infection. Empirical treatment with cefotaxime 50 mg/kg i.v./i.m. every 6 hours or ceftriaxone 80 mg/kg/day as a single dose given over 30 minutes may be considered. If the fever subsides but a source is not identified, treatment can be stopped after 7–10 days.

IV. Neurological abnormalities

- Does the child have any neurological abnormalities and/or headache?

Careful history-taking

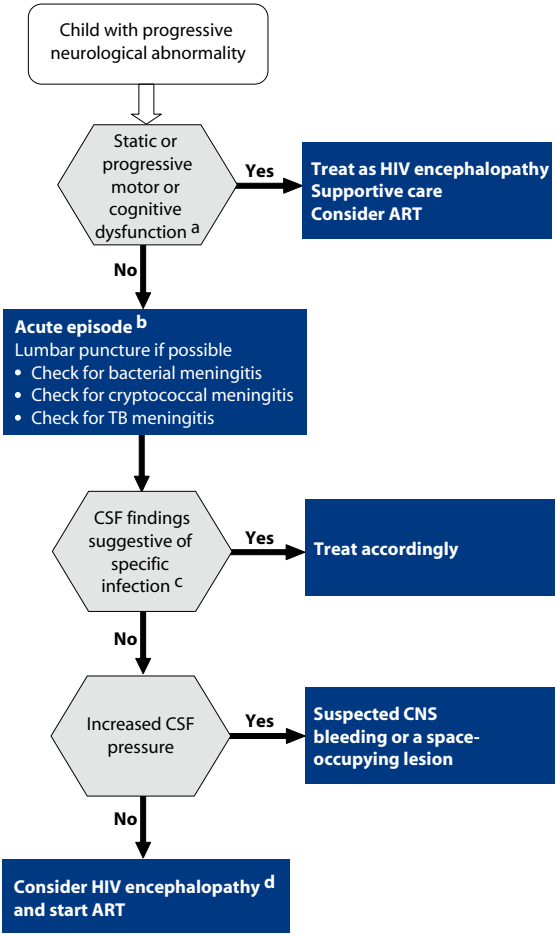
- Weakness in any part of the body?
- Recent accident or injury?
- Recent convulsion?
- What medication did the child receive during past days?
- Child has trouble concentrating/paying attention?
- Has the child's behaviour changed recently?
- Does the child have memory problems?
- Is the child confused?
- Did symptoms occur suddenly?
- Did symptoms develop progressively?

Clinical examination

- Are there any focal neurological signs?
- Look for flaccid paralysis
- Test strength
- Problem walking
- Problem talking
- Problem moving eyes
- Look for stiff neck
- Is the child confused?

If a pathogen is identified, treat OI as recommended. If there is a focal neurological deficit peform neuroimaging, e.g. CT scan, if available. In acquired *Toxoplasma* infection, CT scan demonstrates multiple hypodense masses with ring enhancement. In CNS lymphoma, CT scan usually demonstrates an isodense or hypodense single lesion that enhances with contrast. Brain atrophy on CT scan is more indicative of HIV encephalopathy. Other possible causes of neurological abnormality in HIV-infected children are CMV encephalitis, CNS tuberculoma, or PML.

- Child presents with a neurological abnormality



Notes

[a] Definition: **Progressive encephalopathy:** Progressive decline in motor, cognitive or language function, evidence of loss or increasing delay in achieving developmental milestones; onset can be as early as the first year of life but can occur at any time. **Static encephalopathy:** Motor dysfunction and other developmental deficits of varying severity which are non-progressive as documented on serial neurological and developmental examination.

Acute episodes: Acute onset of seizures, focal neurological abnormalities (e.g. toxoplasmosis) or meningism (e.g. cryptococcal meningitis, bacterial meningitis, tuberculous meningitis or CMV encephalitis).

A careful history and physical examination including neurological examination and developmental examination are particularly important because the management of an acute episode will differ from that of progressive or static encephalopathy.

[b] An acute episode can occur in a previously healthy HIV-infected child or can be superimposed on HIV encephalopathy.

[c] Examination of the CSF can show the following:

- Acute meningitis: white cell count >100/mm^3. Gram-staining and culture of the CSF, where possible, can show bacteria.
- Cryptococcal meningitis: India ink staining can show yeast. Cryptococcal antigen can be detected in serum and CSF.
- Fungal meningitis: CSF culture can detect fungal infection.

[d] ART regimens should include either AZT or d4T due to their high CNS penetration.

Name of drug	Formulations	Pharmaco-kinetic data available	Age (weight), dose and dosage frequency	Other comments
Nucleoside analogue reverse transcriptase inhibitors				
Zido-vudine (AZT)	Syrup: 10 mg/ml Capsules: 100 mg; 250 mg Tablet: 300 mg	All ages	<6 weeks: 4 mg/kg/ dose twice daily 6 weeks to 13 years: 180–240 mg/m²/dose twice daily Maximum dose: ≥13 years: 300 mg/ dose twice daily	Large volume of syrup is not well tolerated in older children. Syrup needs to be stored in glass jars and is light-sensitive Can be given with food Doses of 600 mg/m²/dose per day are required for HIV encephalopathy Capsule can be opened and contents dispersed or tablet crushed and contents mixed with a small amount of water or food and taken immediately (solution is stable at room temperature) Do not use with d4T (antagonistic ARV effect)
Lami-vudine (3TC)	Oral solution: 10 mg/ml Tablet: 150 mg	All ages	<30 days: 2 mg/kg/ dose twice daily ≥30 days or <60 kg: 4 mg/kg/dose twice daily Maximum dose: >60 kg: 150 mg/dose twice daily	Well tolerated Can be given with food Store solution at room temperature (use within one month of opening) Tablet can be crushed and contents mixed with a small amount water or food and taken immedi-ately
FDC of AZT + 3TC	No liquid prepara-tion available Tablet: 300 mg AZT + 150 mg 3TC	Adolescents and adults	Maximum dose: >13 years or >60 kg: 1 tablet/dose twice daily (should not be given if weight <30 kg)	Ideally, the tablet should not be split Tablet can be crushed and contents mixed with a small amount of water or food and taken im-mediately At weight <30 kg, the correct dose of AZT and 3TC cannot be given in tablet form

Name of drug	Formulations	Pharmaco-kinetic data available	Age (weight), dose and dosage frequency	Other comments
Stavudine (d4T)	Oral solution: 1 mg/ml Capsules: 15 mg, 20 mg, 30 mg, 40 mg	All ages	<30 kg: 1 mg/kg/dose twice daily 30–60 kg: 30 mg/dose twice daily	Large volume of solution Keep solution refrigerated; stable for 30 days; must shake well. Needs to be stored in glass bottles Capsules can be opened and mixed with a small amount
			Maximum dose: >60 kg: 40 mg/dose twice daily. Consider using a maximum dose of 30 mg twice daily in order to limit mitochondrial toxicity)	of food or water (stable in solution for 24 hours if kept refrigerated) Do not use with AZT (antagonistic ARV effect)
Fixed dose combination of d4T + 3TC	No liquid preparation available Tablet: d4T 30 mg + 3TC 150 mg; d4T 40 mg + 3TC 150 mg	Adolescents and adults	Maximum dose: 30–60 kg: one 30 mg d4T-based tablet twice daily ≥60 kg: one 40 mg d4T-based tablet twice daily	Ideally the tablet should not be split
Didanosine (ddI, dideoxyinosine)	Oral suspension paediatric powder/ water: 10 mg/ml. In many countries needs to be made up with additional antacid Chewable tablets: 25 mg; 50 mg; 100 mg; 150 mg; 200 mg	All ages	<3 months: 50 mg/m^2/dose twice daily 3 months to <13 years: 90–120 mg/m^2/dose twice daily or 240 mg/m^2/dose once daily Maximum dose: ≥13 years or >60 kg: 200 mg/dose twice daily or 400 mg once daily	Keep suspension refrigerated; stable for 30 days; must be shaken well Administer on empty stomach, at least 30 minutes before or 2 hours after eating If tablets are dispersed in water, at least 2 tablets of appropriate strength should be dissolved for adequate buffering Enteric-coated beadlets in capsules can be opened and sprinkled on a small amount of food

Name of drug	Formulations	Pharmaco-kinetic data available	Age (weight), dose and dosage frequency	Other comments
	Enteric-coated beadlets in capsules: 125 mg; 200 mg; 250 mg; 400 mg			
Abacavir (ABC)	Oral solution: 20 mg/ml Tablet: 300 mg	>3 months	<16 years or <37.5 kg: 8 mg/kg/dose twice daily Maximum dose: >16 years or ≥3 7.5 kg: 300 mg/dose twice daily	Can be given with food Tablet can be crushed and contents mixed with a small amount water or food and ingested immediately MUST WARN PARENTS ABOUT HYPERSENSITIVITY REACTION ABC should be stopped permanently if hypersensitivity reaction occurs
FDC of AZT + 3TC + ABC	No liquid preparation available Tablet: AZT 300 mg + 3TC 150 mg + ABC 300 mg	Adolescents and adults	Maximum dose: >40 kg: 1 tablet/dose twice daily	Ideally, the tablet should not be split At weight <30 kg, AZT/3TC/ABC the correct dose cannot be given in tablet form MUST WARN PARENTS ABOUT HYPERSENSITIVITY REACTION AZT/3TC/ABC should be stopped permanently if hypersensitivity reaction occurs
Non-nucleoside reverse transcriptase inhibitors				
Nevirapine (NVP)	Oral suspension: 10 mg/ml Tablet: 200 mg	All ages	15–30 days: 5 mg/kg/dose once daily for 2 weeks, then 120 mg/m^2/dose twice daily for 2 weeks, then 200 mg/m^2/dose twice daily	Avoid using if rifampicin is being co-administered Store suspension at room temperature Must shake well Can be given with food

Name of drug	Formulations	Pharmaco-kinetic data available	Age (weight), dose and dosage frequency	Other comments
NVP (contd.)			>30 days to 13 years: 120 mg/m^2/dose once daily for 2 weeks, then 120–200 mg/m^2/dose twice daily Maximum dose: >13 years: 200 mg/dose once daily for first 2 weeks, then 200 mg/dose twice daily	Tablets are scored and can be divided into two equal halves to give a 100 mg dose; can be crushed and combined with a small amount of water or food and administered immediately MUST WARN PARENTS ABOUT RASH Do not increase the dose if rash occurs (if mild/moderate rash, hold drug; when rash clears, restart dosage from beginning of dose escalation; if severe rash, discontinue drug)
Efavirenz (EFV)	Syrup: 30 mg/ml (note: syrup requires a higher dosage than capsules, *see* dosage chart) Capsules: 50 mg, 100 mg, 200 mg	Only for children over 3 years of age or weight > 10 kg	Capsule (liquid) dose: 10–15 kg: 200 mg (270 mg = 9 ml) once daily 15 to <20 kg: 250 mg (300 mg = 10 ml) once daily 20 to <25 kg: 300 mg (360 mg = 12 ml) once daily 25 to <33 kg: 350 mg (450 mg = 15 ml) once daily 33 to <40 kg: 400 mg (510 mg = 17 ml) once daily Maximum dose: ≥40 kg: 600 mg once daily	Capsules may be opened and added to food but have a very peppery taste; however, can mix with sweet foods or jam to disguise taste Can be given with food (but avoid after high fat meals which increase absorption by 50%) Best given at bedtime, especially in the first 2 weeks, to reduce central nervous system side-effects

Name of drug	Formulations	Pharmaco-kinetic data available	Age (weight), dose and dosage frequency	Other comments
FDC of d4T + 3TC + NVP	No liquid preparation available Tablet: 30 mg d4T/150 mg 3TC/200 mg NVP 40 mg d4T/150 mg 3TC/200 mg NVP	Adolescents and adults	Maximum dose: 30–60 kg: one 30 mg d4T-based tablet twice daily ≥60 kg: one 40 mg d4T-based tablet twice daily	Ideally, the tablet should not be split At weight <30 kg, d4T/3TC/NVP the correct dose cannot be given in tablet form; if tablets are split, NVP dose requirements will be inadequate for very young children and additional NVP is needed to give a total of at least 150 mg/m^2/dose twice daily. Optimum NVP dosage is 200 mg/ m^2/dose twice daily Since the FDC contains NVP, dose escalation is required (*SEE* NVP DOSING RECOMMENDATIONS)
Protease inhibitors				
Nelfinavir (NFV)	Powder for oral suspension (mix with liquid): 200 mg per level teaspoon (50 mg per 1.25 ml scoop): 5 ml Tablet: 250 mg (tablets can be halved; can be crushed and added to food or dissolved in water)	All ages However, extensive pharmacokinetic variability in infants, with requirement for very high doses in infants <1 year	<1 year: 50 mg/kg/dose three times daily or 75 mg/kg/dose twice daily >1 year to <13 years: 55–65 mg/kg/dose twice daily Maximum dose: ≥13 years: 1250 mg/dose twice daily	Powder is sweet, faintly bitter, but gritty and hard to dissolve; must be reconstituted immediately prior to administration in water, milk, formula, pudding, etc. Do not use acidic food or juice (increases bitter taste); solution stable for 6 hours Because of difficulties with use of powder, use of crushed tablets preferred (even for infants) if appropriate dose can be given Powder and tablets can be stored at room temperature Can be taken with food Drug interactions (less than ritonavir-containing PIs)

Name of drug	Formulations	Pharmaco-kinetic data available	Age (weight), dose and dosage frequency	Other comments
Lopinavir/ritonavir (LPV/r)	Oral solution: 80 mg/ml lopinavir plus 20 mg/ml ritonavir Note: oral solution contains 42% alcohol Capsules: 133.3 mg lopinavir plus 33.3 mg ritonavir	6 months of age or older	>6 months to 13 years: 225 mg/m^2 LPV/57.5 mg/m^2 ritonavir twice daily or weight-based dosages 7–15 kg: 12 mg/kg LPV/3 mg/kg ritonavir/dose twice daily 15–40 kg: 10 mg/kg lopinavir/5 mg/kg ritonavir twice daily Maximum dose: >40 kg: 400 mg LPV/100 mg ritonavir (3 capsules or 5 ml)	Oral solution and capsules should preferably be refrigerated; however, can store at room temperature up to 25°C (77°F) for 2 months; at temperatures >25^{0}C (>77^{0}F), drug degrades more rapidly Liquid formulation has a small volume but bitter taste Capsules large Capsules should *not* be crushed or opened, but must be swallowed whole Should be taken with food
Saquinavir/r	Soft-gel capsule: 200 mg Hard-gel capsule: 200 mg and 500 mg	>25 kg	Approved dosage in adults: SQV 1000 mg/RTV 100 mg twice daily There are no data in children. For children weighing >25 kg, the approved adult dose can be used If possible, monitoring of SQV	Capsules large Capsules should *not* be crushed or opened, but must be swallowed whole Should be taken with food

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

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

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

AUC area under the curve C_{max} maximum concentration C_{min} minimum concentration

Note: Concomitant use of fluticasone with RTV results in markedly reduced serum cortisol concentrations. Co-administration of fluticasone with RTV or any RTV-boosted PI regimen is not recommended unless the potential benefit outweighs the risk of systemic corticosteroid side-effects.

(Adapted from the *Guidelines for the use of antiretroviral agents in pediatric HIV infection*, Nov 3, 2005, www.aidsinfo.nih.gov.

ANNEX G

SERIOUS ACUTE AND CHRONIC TOXICITIES DUE TO ARV DRUGS THAT MAY REQUIRE THERAPY MODIFICATION[a]

Possible clinical manifestations (most common ARV drug(s) associated with the toxicity)	Possible laboratory abnormalities[b]	Implications for ARV drug treatment
Acute serious adverse reactions		
Acute symptomatic hepatitis (NNRTI class, particularly NVP, more rarely EFV; NRTIs or PI class)		
▪ Jaundice ▪ Liver enlargement ▪ Gastrointestinal symptoms ▪ Fatigue, anorexia ▪ May have hypersensitivity component (rash, fever, systemic symptoms), usually occurs within 6–8 weeks ▪ May have accompanying lactic acidosis (*see below*) if secondary to NRTI drug	▪ Raised transaminase levels ▪ Raised bilirubin level	▪ Discontinue all ARVs until symptoms resolve ▪ If possible, monitor transaminases, bilirubin ▪ If receiving NVP, NVP should NOT be readministered to the patient in future ▪ Once symptoms resolve, either – restart ART by changing to an alternative ARV (if on NVP regimen, this is required); or – restart current ART regimen under close observation; if symptoms recur, substitute with an alternative ARV
Acute pancreatitis (NRTI class, particularly d4T, ddI; rarely 3TC)		
▪ Severe nausea and vomiting ▪ Severe abdominal pain ▪ May have accompanying lactic acidosis (*see below*)	▪ Raised pancreatic amylase level ▪ Raised lipase level	▪ Discontinue all ARVs until symptoms resolve ▪ If possible, monitor serum pancreatic amylase, lipase ▪ Once symptoms resolve, restart ART by substituting the offending drug with an alternative NRTI, preferably one without pancreatic toxicity

Possible clinical manifestations (most common ARV drug(s) associated with the toxicity)	Possible laboratory abnormalities [b]	Implications for ARV drug treatment
Hypersensitivity reaction (ABC or NVP)		
▪ *ABC:* Acute onset of a combination of both respiratory and gastrointestinal symptoms after starting ABC, including fever, fatigue, myalgia, nausea, vomiting, diarrhoea, abdominal pain, pharyngitis, cough, dyspnoea; rash (usually mild) may or may not occur; progressive worsening of symptoms soon after receipt of ABC dose, usually occurs within 6–8 weeks ▪ *NVP:* Systemic symptoms of fever, myalgia, arthralgia, hepatitis, with or without rash	▪ Raised transaminase levels ▪ Raised eosinophil count	▪ Immediately discontinue all ARVs until symptoms resolve ▪ NVP or ABC should NOT be readministered to the patient in future ▪ Once symptoms resolve, restart ART by substituting an alternative ARV for ABC or NVP [c]
Lactic acidosis (NRTI class, particularly d4T)		
▪ Generalized fatigue and weakness ▪ Gastrointestinal features (nausea, vomiting, diarrhoea, abdominal pain, hepatomegaly, anorexia, poor weight gain and/or sudden unexplained weight loss) ▪ May have hepatitis or pancreatitis (*see above*) ▪ Respiratory features (tachypnoea and dyspnoea) ▪ Neurological symptoms (including motor weakness)	▪ Increased anion gap ▪ Lactic acidosis ▪ Raised aminotransferase levels ▪ Raised CPK level ▪ Raised LDH level	▪ Discontinue all ARVs until symptoms resolve ▪ Symptoms associated with lactic acidosis may continue or worsen despite discontinuation of ART ▪ Once symptoms resolve, restart ART by substituting the offending drug with an alternative NRTI that has a lower risk of mitochondrial toxicity (e.g. ABC or AZT) [c]
Severe rash/Stevens–Johnson syndrome (NNRTI class, particularly NVP, less common with EFV)		
▪ Rash usually occurs during the first 6–8 weeks of treatment ▪ *Mild-to-moderate rash:* erythematous, maculopapular, confluent, most often on the body and arms, with no systemic symptoms ▪ *Severe rash:* extensive rash with moist desquamation, angioedema, or serum sickness-like reaction; or a rash with constitutional findings such as fever, oral lesions, blistering, facial oedema, conjunctivitis ▪ Life-threatening Stevens–Johnson syndrome or toxic epidermal necrolysis	▪ Raised aminotransferase levels	▪ If mild or moderate rash, ART can be continued 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 in the future ▪ Once symptoms resolve, restart ART by substituting an alternative ARV for NVP (*note:* most experts would not change to another NNRTI drug if the patient had severe or life-threatening Stevens–Johnson syndrome with NVP) [c]

Possible clinical manifestations (most common ARV drug(s) associated with the toxicity)	Possible laboratory abnormalities [b]	Implications for ARV drug treatment
Severe, life-threatening anaemia (AZT)		
▪ Severe pallor, tachycardia ▪ Marked fatigue ▪ Congestive heart failure	▪ Low haemoglobin	▪ If refractory to symptomatic treatment (e.g. transfusion), discontinue only AZT and substitute an alternative NRTI [c]
Severe neutropenia (AZT)		
▪ Sepsis/infection	▪ Low neutrophil count	▪ If refractory to symptomatic treatment (e.g. transfusion), discontinue only AZT and substitute an alternative NRTI [c]
Chronic late serious adverse reactions		
Lipodystrophy/Metabolic syndrome (d4T; PIs)		
▪ Fat loss and/or fat accumulation in distinct regions of the body: – Fat deposited around the abdomen, buffalo hump, breast hypertrophy – Fat loss from limbs, buttocks and face occurs to a variable extent ▪ Insulin resistance, including diabetes mellitus ▪ Potential risk for development of coronary artery disease	▪ Hypertriglyceridaemia; ▪ Hypercholesterolaemia; ▪ Low HDL levels ▪ Hyperglycaemia	▪ Substitute ABC or AZT for d4T; may prevent progression of lipoatrophy ▪ Substitute an NNRTI for a PI; may decrease serum lipid abnormalities
Severe peripheral neuropathy (d4T, ddI; rarely 3TC)		
▪ Pain, tingling, numbness of hands or feet; inability to walk ▪ Distal sensory loss ▪ Mild muscle weakness and areflexia can occur	▪ None	▪ Stop suspected NRTI only and substitute with a different NRTI that is not associated with neurotoxicity ▪ Symptoms may take several weeks to resolve

Notes

[a] Alternative explanations for the toxicity must be excluded before concluding that it is secondary to the ARV drug. (Note: This table does not describe the management of clinical toxicity in detail, only management of the ART regimen.)

[b] All laboratory abnormalities may not be observed.

[c] *See* p. 45 for recommended substitutes of ARV drugs.

ANNEX H

STORAGE OF ARV DRUGS

Generic name	Storage requirements
Nucleoside RTIs	
Abacavir (ABC)	Room temperature
Zidovudine (AZT)	Room temperature
Didanosine (ddI)	Room temperature for tablets and capsules. Reconstituted buffered powder should be refrigerated; oral solution for children is stable after reconstitution for 30 days if refrigerated.
Emtricitabine (FTC)	Room temperature
Lamivudine (3TC)	Room temperature
Stavudine (d4T)	Room temperature. After reconstitution, oral solution should be kept refrigerated; if so, it is stable for 30 days.
Stavudine (d4T)+lamivudine (3TC) + nevirapine (NVP)	Room temperature
Zidovudine (AZT) + lamivudine (3TC) + abacavir (ABC)	Room temperature
Zidovudine (AZT) + lamivudine (3TC) + nevirapine (NVP)	Room temperature
Non-nucleoside RTIs	
Efavirenz (EFV)	Room temperature
Nevirapine (NVP)	Room temperature
Protease inhibitors	
Atazanavir (ATV)	Room temperature
Indinavir (IDV)	Room temperature
Fos-amprenavir (Fos-APV)	Room temperature
Lopinavir/ritonavir (LPV/r) capsules	Refrigerate for long term storage At room temperature: stable for 30 days
Lopinavir/ritonavir (LPV/r) heat-stable tablets	Room temperature
Nelfinavir (NFV)	Room temperature
Ritonavir (RTV)	Refrigerate capsules until dispensed Stable at room temperature for 30 days Room temperature for oral solution (do not refrigerate)
Saquinavir – hard gel caps. (SQV_{hgc})	Room temperature
Room temperature is defined as 15–30°C. Refrigeration is defined as 2–8°C	

ANNEX I

SEVERITY GRADING OF SELECTED CLINICAL AND LABORATORY TOXICITIES MOST COMMONLY SEEN WITH RECOMMENDED ARV DRUGS

Parameter	Mild	Moderate	Severe	Severe, potentially life-threatening
General guidance to estimating grade of severity[a]				
Characterization of symptoms and general guidance on management	Symptoms causing no or minimal interference with usual social and functional activities: [b] No therapy needed, monitor	Symptoms causing greater than minimal interference with usual social and functional activities: [b] May require minimal intervention and monitoring	Symptoms causing inability to perform usual social and functional activities: [b] Requires medical care and possible hospitalization	Symptoms causing inability to perform basic self-care functions: [c] Requires medical or operative intervention to prevent permanent impairment, persistent disability or death
HAEMATOLOGY (*Standard International Units are listed in italics*)				
Absolute neutrophil count	750– <1000/mm^3 *0.75x10^9 – <1x10^9/L*	500–749/mm^3 *0.5x10^9– 0.749x10^9/L*	250–500/mm^3 *0.25x10^9– 0.5x10^9/L*	<250/mm^3 *<0.250x10^9/L*
Haemoglobin (child >60 days of age)	8.5–10.0 g/dl *1.32–1.55 mmol/L*	7.5– <8.5 g/dl *1.16– <1.32 mmol/L*	6.5– <7.5 g/dl *1.01– <1.16 mmol/L*	<6.5 g/dl *<1.01 mmol/L* or severe clinical symptoms due to anaemia (e.g. cardiac failure) refractory to supportive therapy
Platelets	100,000–<125,000/mm^3 *100x10^9– 25x10^9/L*	50,000– <100,000/mm^3 *50x10^9– <100x10^9/L*	25,000–<50,000/mm^3 *25x10^9– <50x10^9/L*	<25,000/mm^3 *<25x10^9/L* or bleeding
GASTROINTESTINAL				
Laboratory[a]				
ALT (SGPT)	1.25–2.5 x ULN	2.6–5.0 x ULN	5.1–10.0 xULN	>10.0 x ULN
AST (SGOT)	1.25–2.5 x ULN	2.6–5.0 x ULN	5.1–10.0 xULN	>10.0 x ULN
Bilirubin (>2 weeks of age)	1.1–1.5 x ULN	1.6–2.5 x ULN	2.6–5.0 x ULN	>5.0 x ULN
Lipase	1.1–1.5 x ULN	1.6–3.0 x ULN	3.1–5.0 x ULN	>5.0 x ULN
Pancreatic amylase	1.1–1.5 x ULN	1.6–2.0 x ULN	2.1–5.0 x ULN	>5.0 x ULN

Parameter	Mild	Moderate	Severe	Severe, potentially life-threatening
Clinical				
Diarrhoea ≥1 year of age	Transient or intermittent episodes of unformed stools or increase of ≤3 stools over baseline per day	Persistent episodes of unformed to watery stools or increase of 4–6 stools over baseline per day	Grossly bloody diarrhoea or increase of ≥7 stools per day or i.v. fluid replacement indicated	Life-threatening consequences (e.g. hypotensive shock)
<1 year of age	Liquid stools (more unformed than usual) but usual number per day	Liquid stools with increased number of stools per day or mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated or hypotensive shock
Nausea	Transient (<24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24–48 hours	Persistent nausea resulting in minimal oral intake for >48 hours or aggressive rehydration indicated (e.g. i.v. fluids)	Persistent nausea with no or minimal oral intake resulting in dehydration and aggressive rehydration indicated
Pancreatitis	NA	Symptomatic and hospitalization not indicated (other than emergency treatment)	Symptomatic and hospitalization not indicated (other than emergency treatment)	Life-threatening consequences (e.g. circulatory failure, haemorrhage, sepsis)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension or aggressive rehydration indicated (e.g. i.v. fluids)	Life-threatening consequences (e.g. hypotensive shock)
ALLERGIC/DERMATOLOGICAL				
Acute systemic allergic reaction	Localized urticaria (wheals) lasting for a few hours	Localized urticaria with indication for medical intervention or mild angioedema	Generalized urticaria or angioedema with indication for medical intervention or symptomatic mild bronchospasm	Acute anaphylaxis or life-threatening bronchospasm or laryngeal oedema

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

Parameter	Mild	Moderate	Severe	Severe, potentially life-threatening
OTHER LABORATORY PARAMETERS (*Standard International Units are listed in italics*)				
Cholesterol (fasting, paediatric <18 years old)	170– <200 mg/dl *4.4–5.15 mmol/L*	200–300 mg/dl *5.16–7.77 mmol/L*	>300 mg/dl *>7.77 mmol/L*	NA
Glucose, serum, high: non-fasting	116– <161 mg/dl *6.44– <8.89 mmol/L*	161– <251 mg/dl *8.89– <13.89 mmol/L*	251–500 mg/dl *13.89–27.75 mmol/L*	>500 mg/dl *>27.75 mmol/L*
Glucose, serum, high: fasting	110– <126 mg/dl *6.11–<6.95 mmol/L*	126– <251 mg/dl *6.95– <13.89 mmol/L*	251–500 mg/dl *13.89–27.75 mmol/L*	>500 mg/dl *>27.75 mmol/L*
Lactate	<2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH <7.3 without life-threatening consequences or related condition present	Increased lactate with pH <7.3 with life-threatening consequences (e.g. neurological findings, coma) or related condition present
Triglycerides (fasting)	NA	500– <751 mg/dl *5.65– <8.49 mmol/L*	751–1200 mg/dl *8.49–13.56 mmol/L*	>1200 mg/dl *>13.56 mmol/L*

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

Notes

[a] Values are provided for children in general except where age groups are specifically noted.

[b] Usual social and functional activities in young children include those that are culturally- and age-appropriate (e.g. social interactions, play activities, learning tasks, etc.).

[c] Activities that are culturally- and age-appropriate (e.g. feeding self with culturally appropriate eating implement, walking or using hands)

ANNEX J GUIDELINES FOR PRIMARY AND SECONDARY OI PROPHYLAXIS

Guidelines for primary OI prophylactic treatment in children

Organism	When to give prophylaxis	Drug regimen
PCP (*Pneumocystis jiroveci* pneumonia)	**For HIV-exposed children:** co-trimoxazole prophylaxis is universally indicated, starting at 4–6 weeks after birth and maintained until cessation of risk of HIV transmission and exclusion of HIV infection **For children with confirmed HIV infection:** **Age <1 year:** co-trimoxazole prophylaxis indicated regardless of CD4% or clinical status[3] **Age 1–5 years:** WHO stages 2, 3 and 4 regardless of CD4% **or** Any WHO stage and CD4% <25% [a] **Age ≥6 years:** Any WHO clinical stage and CD4 count <350 [b] cells/mm^3 **or** WHO stage 3 or 4 and any CD4 count level	**Co-trimoxazole:** suspension (200 mg SMX, 40 mg TMP), paediatric tablet (100 mg SMX, 20 mg TMP), single strength (SS) adult tablet (400 mg SMX, 80 TMP) **Recommended** **<6 months:** 2.5 ml suspension or 1 paediatric tablet or 1/4 SS adult tablet equivalent to 100 mg sulfamethoxazole/ 20 mg trimethoprim **6 months–5 years:** 5 ml suspension or 2 paediatric tablets or 1/2 SS adult tablet equivalent to 200 mg sulfamethoxazole/40 mg trimethoprim **6–14 years:** 10 ml suspension or 4 paediatric tablets or 1 SS adult tablet **>14 years:** 1 SS adult tablet (or 1/2 double strength adult tablet) equivalent to 400 mg sulfamethoxazole/ 80 mg trimethoprim **Alternative** 1. Dapsone 2 mg/kg once daily or 2. Dapsone 4 mg/kg once weekly
Mycobacterium tuberculosis	All children exposed to active TB cases, particularly household contacts, regardless of CD4 counts (need to exclude clinical disease by physical examination and CXR)	**For known INH-sensitive strain or unknown** **Recommended:** INH (5 mg/kg) (max 300 mg) daily for 6–9 months

Notes

[a] In resource-limited settings where co-trimoxazole is used to prevent other bacterial infections and malaria, prophylaxis should be started at CD4 <25%.

[b] In resource-limited settings where co-trimoxazole is used to prevent other bacterial infections and malaria, prophylaxis should be started at CD4 <350/µl.

Organism	When to give prophylaxis	Drug regimen
Mycobacterium avium complex (MAC)	CD4 count <50 cells/mm^3 in >6-year-old CD4 count <75 cells/mm^3 in 2–6-year-old CD4 count <500 cells/mm^3 in 1–2-year-old CD4 count <750 cells/mm^3 in <1-year-old Stop when CD4 level above threshold for >3 months	**Recommended** 1. Clarithromycin 7.5 mg/kg/dose (max 500 mg) twice daily or 2. Azithromycin 20 mg/kg (max 1200 mg) once weekly **Alternative** Azithromycin 5 mg/kg (max 250 mg) once daily

Guidelines for secondary prophylaxis to prevent recurrence of OIs in children

Opportunistic infection	When to give prophylaxis	Drug regimen
PCP (*Pneumocystis jiroveci* pneumonia)	Children who have a history of PCP should be administered prophylaxis for life to prevent recurrence. The safety of discontinuing secondary prophylaxis among HIV-infected children has not been studied extensively	As for primary prophylaxis
TB *(Mycobacterium tuberculosis)*	Not recommended	
Mycobacterium avium complex (MAC)	Children with a history of disseminated MAC should be administered lifelong prophylaxis to prevent recurrence. The safety of discontinuing secondary prophylaxis among HIV-infected children has not been studied extensively	**Recommended** Clarithromycin 7.5 mg/kg/dose (max 500 mg) twice daily plus ethambutol 15 mg/kg/dose (max 800 mg) daily **Alternative** Azithromycin 5 mg/kg/dose (max 250 mg) plus ethambutol 15 mg/kg/dose (max 800 mg) daily
Cryptococcus neoformans *Coccidioides immitis*	Children who have a history of cryptococcal meningitis should be administered prophylaxis for life to prevent recurrence. The safety of discontinuing secondary prophylaxis among HIV-infected children has not been studied extensively	**Recommended** Fluconazole 3–6 mg/kg/once daily **Alternative** Itraconazole 2–5 mg/kg once daily

Opportunistic infection	When to give prophylaxis	Drug regimen
Histoplasma capsulatum *Penicillium marneffei*	Children who have a history of histoplasmosis/penicilliosis should be administered prophylaxis for life to prevent recurrence. The safety of discontinuing secondary prophylaxis among HIV-infected children has not been studied extensively	Itraconazole 2–5 mg/kg once daily
Toxoplasma gondii	Children who have a history of cerebral toxoplasmosis should be administered prophylaxis for life to prevent recurrence. The safety of discontinuing secondary prophylaxis among HIV-infected children has not been studied extensively.	**Recommended** Sulfadiazine 85–120 mg/kg/day in divided doses 2–4 times/day plus pyrimethamine 1 mg/kg (max 25 mg) once daily plus leucovorin 5 mg every 3 days **Alternative** Clindamycin 20–30 mg/kg/day in 4 divided doses plus pyrimethamine and leucovorin as above Alternative TMP–SMX as for PCP

ANNEX

K

USEFUL INTERNET LINKS

http://www.searo.who.int/en/Section10/Section18.htm

http://www.searo.who.int/en/Section10/Section18/Section356.htm

http://www.who.int/hiv/en/

http://www.who.int/3by5/about/en/

http://www.who.int/3by5/publications/documents/arv_guidelines/en/

http://www.who.int/hiv/pub/prev_care/pub18/en/

http://www.who.int/hiv/pub/mtct/guidelines/en/

http://mednet3.who.int/prequal/

http://www.who.int/medicines/organization/par/ipc/drugpriceinfo.shtml#hiv/aids

http://www.who.int/medicines

http://www.medscape.com/home/topics/aids/aids.html

http://www.amfar.org

http://www.hivandhepatitis.com

http://www.womenchildrenhiv.org

http://www.bhiva.org/

http://www.bnf.org/

http://www.aidsinfo.nih.gov/guidelines/

http://www.cdc.gov/hiv/treatment.htm

http://www.fda.gov/oashi/aids/hiv.html

http://www.aidsinfo.nih.gov

http://www.clinicaloptions.com/hiv.aspx

http://www.hopkins-aids.edu/

http://hivinsite.ucsf.edu/insite

http://www.aidsmap.com

http://www.thebody.com/

http://www.aidsmeds.com/

http://aids.org

http://www.hivnat.org/

http://www.paho.org/english/hcp/hca/antiretrovirals_hp.htm

Successful scaling-up of antiretroviral therapy (ART) requires rational use of antiretroviral drugs. These simplified and standardized guidelines on the appropriate and rational use of ART in resource-limited settings for South and South-East Asia are intended as a resource for:

- Physicians and other health care providers caring for children with known exposure to the human immunodeficiency virus (HIV), HIV-infected children and sick children with unknown HIV exposure but suspected to have HIV infection;
- National AIDS programme managers, maternal and child health programme managers and other health planners as a reference for developing national guidelines on the management of HIV infection and ART in infants and children, and
- NGOs and other civil society organizations supporting people living with and affected by HIV.

These guidelines cover the diagnosis of HIV infection in infants and children, followed by patient evaluation, prevention and management of opportunistic infections, pre-enrolment information and counselling process for ART, and ensuring treatment adherence.

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