MEDECINS SANS FRONTIERES

PAEDIATRIC HIV HANDBOOK

Internal document

2015 edition

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Foreword

This is a concise handbook to help in the management of children exposed to or infected with HIV. Many of the principles of adult HIV care apply to children as well, but there are specificities around diagnosis, clinical presentation and antiretroviral therapy (ART) that are dealt with in this guide. It is intended as a technical guide for clinicians and not as a manual on how to implement and organise paediatric HIV care in programs. In most contexts, programmatic aspects should follow national or WHO recommended guidelines.

This handbook does not go into all the details of every aspect of HIV care in children and should be used in conjunction with other relevant MSF, WHO or national guidelines available.

For details regarding guidance on integrated HIV care, refer to the AWG document I*ntegrating HIV & TB care in basic health care package in MSF projects: a programmatic guide* (2015 edition).

For details regarding infant feeding options and follow up of the HIV exposed child, refer to the AWG MSF PMTCT protocol (2015 edition).

For details regarding general paediatric clinical management, refer to the MSF *Clinical Guidelines* and/or the next OCP/OCG paediatric guidelines.

For details regarding the management of HIV infected children with severe acute malnutrition, refer to the MSF (or national) *Nutrition guidelines*.

It goes without saying that long term adherence to ART cannot work well without proper counselling and adherence support. This guideline is mainly confined to technical medical advice; however a short chapter on counselling and adherence is included. For comprehensive guidance on counselling, please refer to the MSF OCB document (Goetghebuer D, Bosteels K) *Patient Support for HIV Infected Children*, 2009.

Since knowledge on HIV is advancing fast, some aspects of this document might become outdated. We will try to provide regular updates when necessary.

Comments should be addressed to Suna.Balkan@paris.msf.org and to the HIV advisor of your section.

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Abbreviations and acronyms

3TC	Lamivudine
ABC	Abacavir
ART	Antiretroviral Treatment
ARV	Antiretroviral
ATFC	Ambulatory Therapeutic Feeding Center
ATV/r	Atazanavir/ritonavir
AZT	Zidovudine
BD	Twice a day (“Bis in Die”)
CMV	CytoMegaloVirus
CNS	Central Nervous System
CSF	CerebroSpinal Fluid
CTX	Cotrimoxazole
CXR	Chest X-Ray
d4T	Stavudine
DBS	Dried Blood Spot
DTP	Diphteria Tetanus Pertussis
EAC	Enhanced Adherence Counselling
ECG	Electrocardiogram
EFV	Efavirenz
EID	Early Infant Diagnosis
ENT	Ear Nose Throat
EPI	Enlarged Program of Immunization
EPTB	Extra-pulmonary tuberculosis
FDC	Fixed Dose Combination
FDA	Food and Drug Administration
FTC	Emtricitabine
HBV	Hepatitis B virus
Hib	Haemophilus influenzae b
HTC	HIV Testing and Counselling
ICP	Intracranial Pressure
IMCI	Integrated Management of Childhood Illness
INH	Isoniazid
IPT	Isoniazid Preventive Therapy
IRIS	Immune Reconstitution Inflammatory Syndrome
IV	IntraVeinous
LIP	Lymphoid Interstitial Pneumonitis
LP	Lumbar Puncture
LPV/r	Lopinavir/ritonavir
MAC	Mycobacterium Avium Complex

MCH	Mother and Child Health
MoH	Ministry of Health
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
OD	Once Daily (“Omni Dei”)
OPV	Oral Polio Vaccination
PCP	Pneumocystis Carinii Pneumonia
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
PI	Protease Inhibitor
PMTCT	Prevention of Mother to Child Transmission (of HIV)
PoC	Point of Care
RDT	Rapid Diagnostic Test
RR	Respiratory Rate
RSV	Respiratory Syncitial Virus
RTV	Ritonavir
TB	Tuberculosis
TDF	Tenofovir
TST	Tuberculin Skin Test
ULN	Upper Limit of Normal
VL	Viral load
WBC	White Blood Cells
WCC	White Cell Count

HIV in children[a] in a nutshell

The vast majority of children with HIV are infected during pregnancy (10-25%), childbirth (35-40%) or breastfeeding (35-40%). Hence, HIV hits them when their immune system is still premature, naive and developing. The timing of infection and the inability to raise a sufficient immune response, result in a persistently high HIV viral load. Clinically the consequences are multiple and devastating. Immature, developing organs are more susceptible to the damaging effects of the virus itself; common childhood infections are more frequent, severe and do not respond well to treatment and the presence of a chronic infection increases nutritional and metabolic demands leading to malnutrition, poor growth and development. Unlike in adults, the progression to advanced disease is rapid, leading to high early mortality. Without appropriate intervention, over 50% of HIV infected children will die before they are two years of age. Amongst those infected during pregnancy and delivery, peak mortality rate is around 2 to 3 months of age. Early Infant Diagnosis (EID) and early Antiretroviral Treatment (ART) are crucial to improve the survival of young children infected with HIV.

Efficacious interventions to Prevent Mother-To-Child HIV Transmission (PMTCT) are crucial and can reduce transmission rates to less than 2%. Yet despite significant progress in prevention strategies, amongst the 21 priority countries[b] in Africa where over 90% of children infected with HIV are born, access to PMTCT varies from 13% to 65%. Despite evidence that early diagnosis and early ART saves young lives, in 2012 only a third of babies born to mothers infected with HIV had accessed HIV testing before 2 months of age. Children infected during the breastfeeding period tend to progress more slowly towards AIDS and are not picked up via Early Infant Diagnosis. Thus it is crucial, especially in high HIV prevalence settings, to ensure that at all points of access to healthcare services, children can access HIV testing and counselling (HTC). This means that HTC should be available not only in PMTCT and other HIV services, but also at any entry point where children 0 to 15 years of age present: nutrition programs, maternal and child health clinics, OPD departments, in-patient paediatric wards and immunisation clinics.

The WHO recommends that all children less than 5 years of age with HIV infection should be started on ART, whatever their clinical or immunological status. From a programmatic aspect, this 'test-and-treat' approach simplifies HIV integration into paediatric and nutrition projects. ART is increasingly available at country level and even in contexts where ART is not immediately available, HTC should still be offered as provision of cotrimoxazole prophylaxis improves child survival and other Opportunistic Infections (OIs) can be diagnosed and treated. However in these situations MSF should strongly advocate to national programs for access of HIV treatment and care in the setting and provide in the meantime access to HIV care and treatment[c]. Where ART is provided, counselling should be provided in order to support adherence and retention and disclosure to the child.

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a Children 0-15 years of age.

b UNAIDS Global Plan 21 Priority Countries: Botswana, Ethiopia, Ghana, Malawi, Namibia, Zambia, Zimbabwe, Burundi, Cameroon, Kenya, Mozambique, South Africa, Swaziland, Uganda, Tanzania, Angola, Chad, Côte d'Ivoire, DR Congo, Lesotho, Niger.

c MSF does not necessarily need to provide ART to provide HIV care, but can find practical solutions to link to existing national services when accessible. This can have better long term implications.

Part 1:
HIV testing, counselling and treatment

1.1 HIV testing and counselling

As a minimum, MSF recommends HIV testing for children in the following situations:

1. All HIV-exposed infants and children (refer to MSF PMTCT protocol 2015).
2. All children with signs or symptoms suggestive of HIV infection: severe or repeated episodes of pneumonia, severe or chronic diarrhoea, shingles, recurrent or chronic ear infection, severe repeated anaemia, suspected or confirmed tuberculosis.
3. All children with Severe Acute Malnutrition requiring hospitalisation.

Pending on context (feasibility and constraints), optimally MSF recommends HIV testing for children in the following situations:

1. All criteria above plus all children with severe acute malnutrition not requiring hospitalisation (ATFC) in a high HIV prevalence setting (> 1%);

And/or

2. Any child who presents at any point to healthcare services who does not already know his HIV status in any prevalence settings.

1.1.1 HIV diagnostic tests

HIV tests can be categorised into serological or virological tests.

Serological (antibody) test is used to diagnose HIV infection in children > 18 months of age:

- Two consecutive positive tests confirms HIV infection.
- Exist as rapid diagnostic test (RDT) with high sensitivity (> 98%) and specificity (> 99%) with results in 10-20 minutes.
- In children < 18 months of age, a positive antibody test confirms exposure to HIV.

Virological (PCR) test is used to diagnose HIV infection in children < 18 months of age:

- Antibody based serology tests can be positive up to 18 months of age even if the child is not infected because maternal HIV antibodies cross the placenta during pregnancy. Although the antibodies are progressively cleared from the baby's blood from 6 months of age, they can be present up until 18 months of age.
- Virological tests are a direct test of the virus and thus can be used to test and diagnose a baby soon after birth.
- HIV DNA PCR is the current standard choice and is the gold standard for infant diagnosis with high sensitivity (>96%) and high specificity (>99%) from 6 weeks of age.
- Standard sampling methodology is via Dried Blood Spot (DBS) which allows specimens to be sent to external laboratories. See Appendix D.
- Using DBS, turn-around time for result is usually over 2 weeks, but Point-of-Care Early Infant Diagnosis (POC EID) platforms for HIV DNA PCR will be available soon and are the most practical option. Results will be available within a couple hours. Consult your laboratory/HIV advisor for further information.

– False positives can occur in contexts with high maternal ART/PMTCT coverage (reduced positive predictive value).
– False negatives can occur in babies less than 6 - 10 weeks old if they are receiving ARV prophylaxis.

All positive PCR test results require *confirmation* by a second virological (PCR) test:
– This should be performed in the same laboratory within 4 weeks of collection of the first specimen. This allows follow-up on consistency of the results and investigation on discordant results.
– Data should be collected including information and age of the child, results of DBS 1 and 2 and dates of blood collection.

Where virological test is not available for children <18 months of age, a "presumptive diagnosis" of HIV infection can be made based on:

Positive serological test

AND

Child is symptomatic with 2 or more of the following:
Oral thrush (recurrent or chronic)
Severe pneumonia
Severe sepsis

OR

Diagnosis of any AIDS-indicator condition

Breastfed infants remain at risk of contracting HIV infection due to the presence of HIV virus in breast milk.
Any breast fed child with a negative serological test must be retested 6 weeks after cessation of breastfeeding to confirm HIV negativity.

1.1.2 Counselling and consent

HIV testing and counselling (HTC) can be self-initiated (parents, guardian, older child) or initiated by the healthcare provider, but should always be voluntary. Whenever testing of a child is performed, the "six Cs" (informed Consent, Counselling, Confidentiality, Correct test results, Comfort and Connection to HIV prevention, treatment and care) should be observed.

The three steps of HTC are:
1. Pre-test education, including informed consent (individual or group);
2. HIV diagnostic testing (individual);
3. Post-test counselling (individual).

Pre- and post-test counselling should be done by the same counsellor, be it on the same day or another day.

Consent for testing

– National legislation and/or policies related to consent and age of consent need to be consulted in each context (if national legislation or cultural norms block testing despite the best interests of the child, discuss with HIV advisor).
– Verbal communication is usually adequate but verify with national requirements.

– Confidentiality of the parent's HIV status should be guaranteed (children should not be told they are being tested because their mother is HIV + unless the mother has given her consent).
– In all cases, even if a child is too young to give "consent", obtain *the assent of the child* to be pricked (ie do not force them).

Children < 10-12 years old
– Consent is usually obtained from a parent or legal guardian and the child should be tested in their presence (that is, do not test children brought by a suspicious neighbour). Usually consent from one parent is sufficient, but local cultural norms may require paternal consent.
– The child can be given partial but truthful information for the reason of testing: for example, that the test can identify a bug that might make them sick and that needs special treatment.
– If there is no parent or legal guardian (eg orphans, street children etc), check any existing national legislation. Assess if testing is in the best interest of the child and if so, try to explain to the child according to his/her level of maturity.

Children > 10-12 years old
– Usually able to give fully informed consent for testing.
– Explain they are being tested for HIV to assess their health status; most of them will have some knowledge of what HIV is.
– Adolescents coming on their own for HIV testing should not be denied access to testing. Counselling is a good opportunity to discuss safer sex strategies with them.

Step 1: Pre-test education

Wherever possible, counsellors should first speak with the caregiver only. Meanwhile, the child should be welcomed and kept occupied in the children's area.

This first part of the counselling should include:
– Explanation of the procedure of counselling and testing: principles of confidentiality and the right to decline the test.
– Assessment of knowledge and perception about HIV/AIDS, modes and risk of transmission, explanation of possible test results and evaluation of the readiness of the caregiver to hear the results.
– Determination of whether caregiver is the parent or legal guardian of the child, and if so, obtain informed consent.
– Assessment of the family situation. For example: has the caregiver been tested? Are there HIV positive parents in the family? Is the mother alive?
– Finding out what the child knows concerning his health and the reason of his visit.
– Assessment of the maturity and developmental stage of the child.
– Discussion of how much information can be given to the child pre-test and how a positive result should be announced to the child (immediate total disclosure or progressive disclosure). The caregiver should feel confident that you won't tell things to the child if he/she doesn't feel ready for it.

The child will then be asked to join his caregiver and the counsellor. How much to discuss with the child prior to the HIV test will be determined by the child's developmental stage, understanding of illness and HIV/AIDS as well as the caregivers readiness to give information.

Step 2: HIV test

Explain briefly to the child and parents/caregivers what the test involves: drawing of blood or finger-prick, testing procedure, time to get the results etc.

Step 3: Post-test counselling

Results of the test should always be delivered on individual basis – that is to child and caregiver, not in front of other patients. Depending on the age and maturity of the child, this can be done first with the caregiver alone or can include the child or adolescent from the start.

Counsellor and caregiver

This part of the counselling should include:

- Confirmation that the caregiver or adolescent is ready to hear the result.
- Giving the result in a brief clear manner:
  - *If positive result:* ensure immediate emotional support, assess comprehension of the result, discuss modalities of treatment and guarantee MSF support
  - *If negative result:* reassure the caregiver and the child. However if the child is still breastfed by an HIV positive mother, he should receive NVP prophylaxis and the mother should be treated (refer to MSF PMTCT guideline 2015). The test must be repeated 6 weeks after complete cessation of breastfeeding (see algorithm following page).
- Repeat discussion on how much information can be given to the child. Take into consideration the pre-test counselling that was done.

Counsellor, caregiver, and child

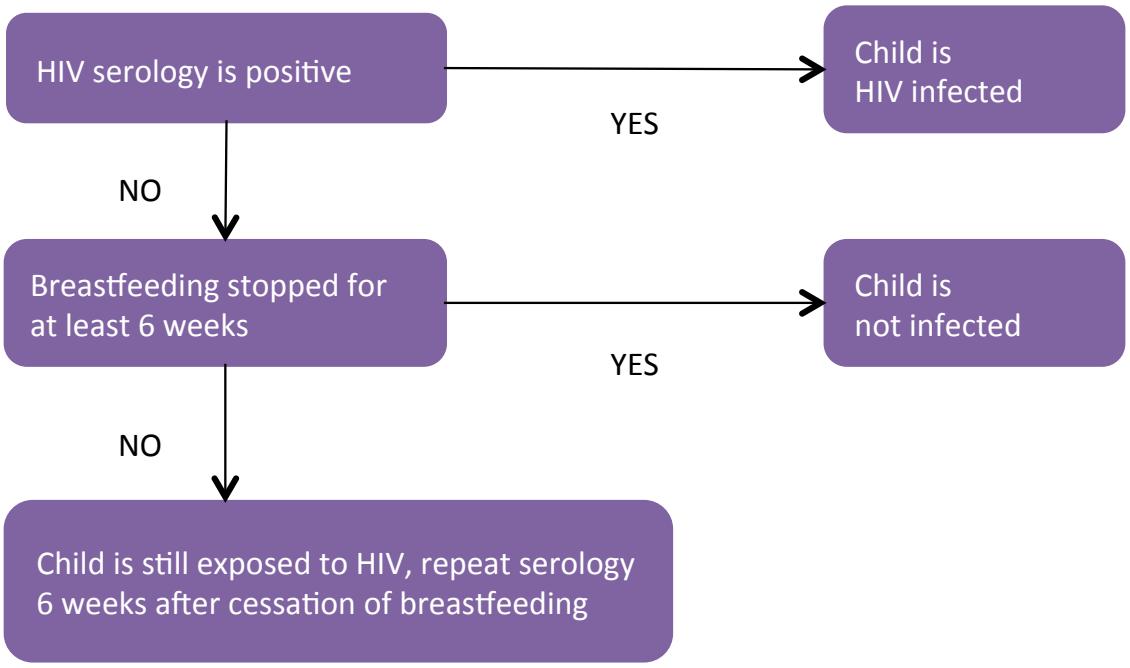
- In the case of adolescents, if the pre-test counselling has determined that he/she should hear the result immediately, then the post-test counselling can be done directly with the caregiver and the adolescent.
- In other cases, after the result was announced to the caregiver alone, the child will then be asked to join his caregiver and the counsellor:
  - *Young children under 6 years:* the diagnosis will not be announced to the child. But it is important to make the child feel comfortable and include him in the discussion.
  - *Children between 6 - 10 years*: a process of progressive disclosure should be done.
  - *Children above 10 years:* it is recommended to proceed immediately with total disclosure of the HIV positive test results.
- The next steps should then be organised: medical exams, health advice, planning of visits to the clinic and social support

Refer to Chapter 3 for further details on counselling and for disclosure, treatment education and adherence support.

1.1.3 Diagnostic approach

HIV diagnosis in children over 18 months of age

For all children over 18 months of age, use the same serology (antibody) tests and the same testing algorithm recommended for adults. Lab testing algorithms may vary with regards to serial versus parallel testing, which rapid tests used and the definition of positive, negative and indeterminate results. For parallel testing, 2 serological tests must be negative to provide a negative result. For serial testing, the first serological negative test provide a negative result. In all cases, two positive serological tests must be done to provide a positive result.



HIV diagnosis in children less than 18 months of age

1) Early infant diagnosis (EID) in HIV-exposed newborns and infants

Refer to MSF *PMTCT* Guideline (2015) for details on the follow-up of exposed children, ARV prophylaxis, feeding recommendations.

Key points:

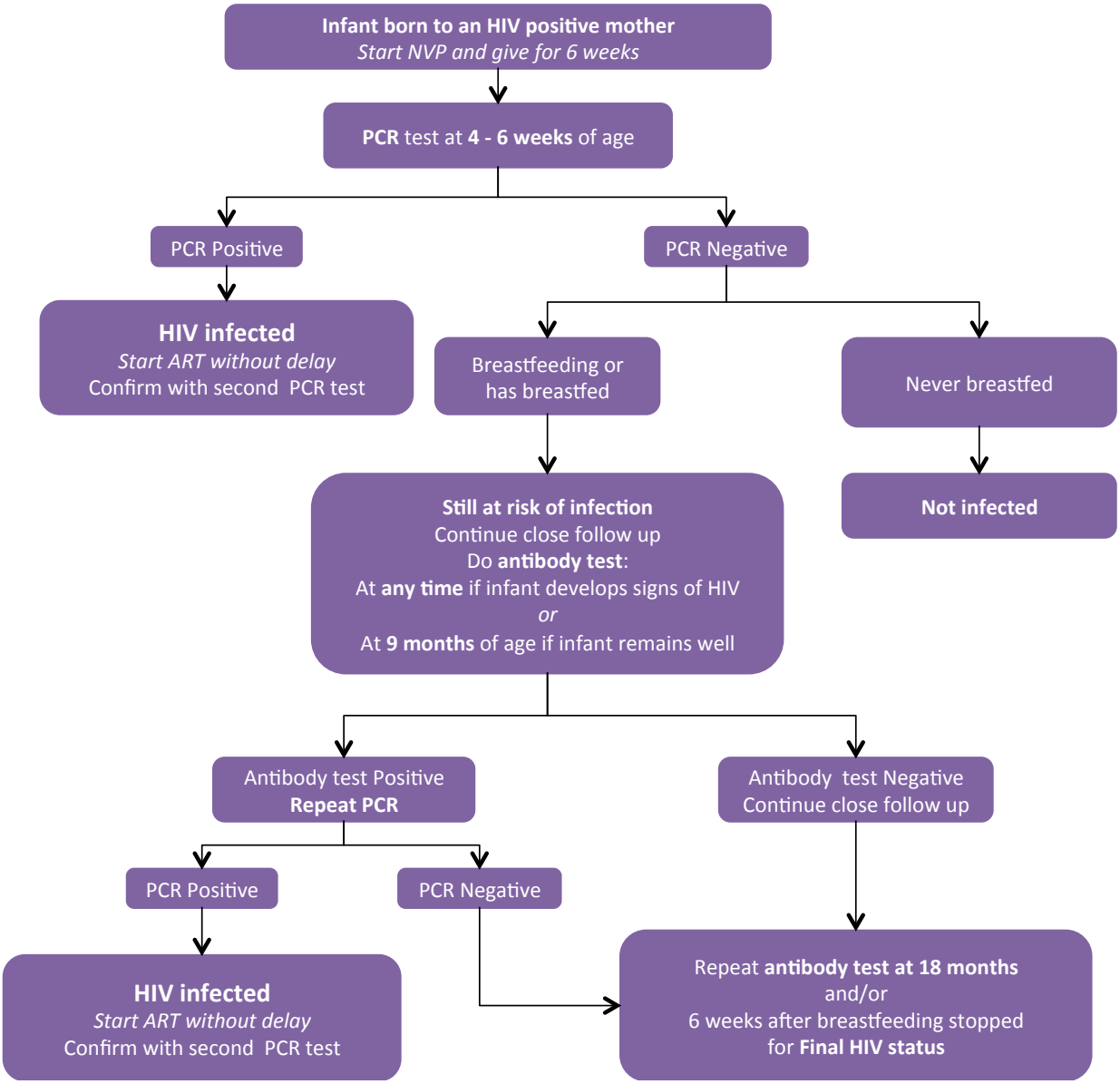
- First HIV DNA PCR test is usually performed around 4 – 6 weeks[d] of age when babies present for their first DTP vaccine or post-natal visit. It is recommended that EID is coordinated with EPI and post-natal visits where feasible.
- The timing of the first HIV DNA PCR test is flexible; it should be done whenever the parent or caregiver presents for the test, even if before or after 4-6 weeks of age. Never turn away parents because they present early or later.
- All infants with an *initial positive* HIV DNA PCR test should *start ART without delay* while at the same time, *a second sample for confirmation must be sent*.

Early infant diagnosis algorithm

See following page.

[d] Currently being discussed (and adopted by some countries) is to move the first virological testing to at or soon after birth. Infants infected in utero, during or around delivery have a high risk of early mortality without early ART. Testing at birth will pick up in utero infections but will miss those infected during or around delivery as it takes 1-2 weeks for the virus to be detectable by viral assays. In babies tested at birth, all those with a negative result should have a repeat test at around 6-10 weeks of age.

Early infant diagnosis algorithm



Refer to Appendix D explaining Dried Blood Spots (DBS) for DNA-PCR.

Discordant results

It is important to register all DBS results and follow up and record discordant results. As discordant results need to be considered case by case, discuss each case with your HIV and lab advisor.

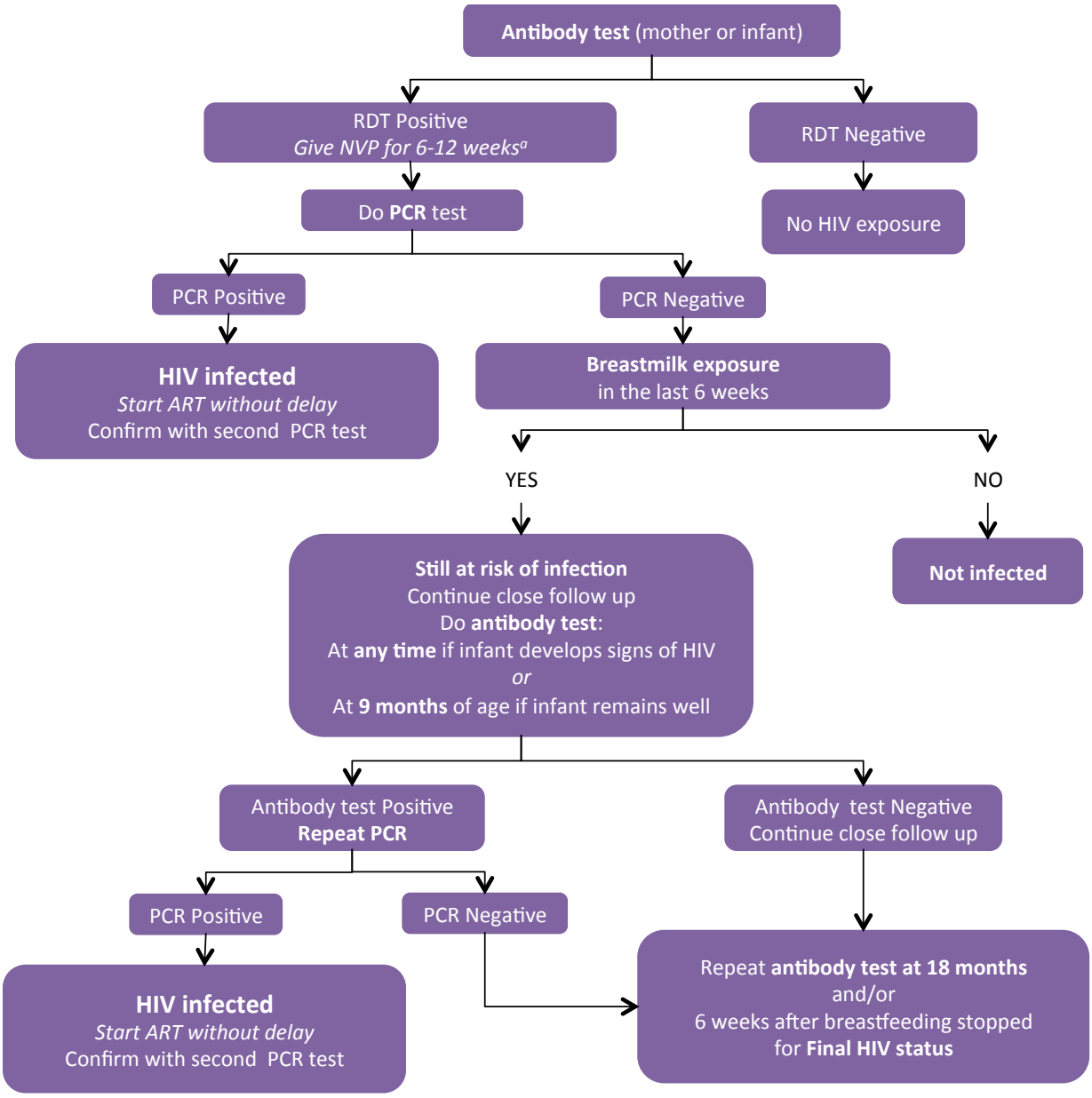
2) Children < 18 months of age (not followed in PMTCT/EID program)

Key points:

– Confirmation of HIV exposure with a Rapid Diagnostic Test (RDT) can be done either directly on the child or by testing the mother. Consider the national guidelines, social circumstances, local context/culture, and mother's acceptance/understanding.

– Lack of access to virological testing should not delay diagnosis and ART initiation; a 'presumptive diagnosis of HIV infection' can be made if exposure is confirmed.
– As virological testing by HIV DNA PCR can be done by Dried Blood Spot (DBS), samples can be sent to external laboratories nationally or internationally. Discuss options with lab or HIV advisor to implement access to DNA PCR by DBS.
– POC EID will be soon available and will be a very practical option.

Where virological (HIV DNA PCR) testing is available:



[a] Nevirapine prophylaxis should be prolonged up to 12 weeks if the mother has just recently started ART and thus not likely to be virally suppressed and the infant is breastfeeding.

Where virological testing is NOT available:

A presumptive clinical diagnosis of severe HIV disease can be made if:

Child confirmed as HIV antibody positive

and

The child is symptomatic with **2 or more of**:
Oral thrush
Severe pneumonia
Severe sepsis

OR

The diagnosis of any AIDS-indicator condition(s) can be made.

Other supportive factors to consider:

Recent HIV-related maternal death or advanced HIV disease in the mother

Child % CD4 < 20%

As per IMCI definition[e]:

- *Oral thrush:* creamy white to yellow soft small plaques on red or normally coloured mucosa which can often be scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender.
- *Severe pneumonia:* cough or difficult breathing in a child with chest indrawing, stridor or any of the IMCI general danger signs, i.e. lethargic or unconscious, not able to drink or breastfeed, vomiting, and presence or history of convulsions during current illness; responding to antibiotics.
- *Severe sepsis:* fever or hypothermia in a young infant with any severe sign, e.g. fast breathing, chest indrawing, bulging fontanelle, lethargy, reduced movement, not feeding or sucking breast milk, convulsions.
- *AIDS indicator conditions* include some but not all HIV clinical stage 4 conditions such as pneumocystis pneumonia, cryptococcal meningitis, severe wasting or severe malnutrition, Kaposi sarcoma or EPTB.

Once HIV exposure or infection is confirmed

- Establish linkage to care with HIV or MCH services.
- Fill in child follow-up card (national IMCI, ART, EID or PMTCT cards preferred, but if not available see with HIV advisor for MSF sectional or WHO cards).
- Ensure birth history noted, including exposure to maternal ART and feeding choice.
- Ensure full clinical examination, including ENT.
- Ensure routine under-5 care: deworming, vitamin A, immunisations, nutritional and growth assessment and support.
- Screen for opportunistic infections, including tuberculosis, and treat any infections correctly
- Start cotrimoxazole prophylaxis.
- Start NVP prophylaxis if exposed newborn.
- Use the start of counselling and education to encourage the mother to be tested for HIV if not already done as well as any siblings.

[e] WHO/UNICEF IMCI 2008 classification.

1.2 Antiretroviral treatment (ART)

1.2.1 Antiretroviral (ARV) drugs in a nutshell

What is ART and what are the objectives of taking ART?

- Antiretroviral treatment (ART) is a combination of 3 (or more) antiretroviral drugs to treat HIV infection.
- Currently available ARVs work by interrupting the HIV life cycle at specific target sites.
- Key objective is to increase survival & decrease HIV-related morbidity and mortality.
- The viral load should fall and remain below the threshold.
- The CD4 count should rise and remain above the baseline count.

Table 1 - Key antiretroviral drugs currently or soon available*

Class	Nucleoside reverse transcriptase inhibitors	Nucleotide reverse transcriptase inhibitors	Non-nucleoside reverse transcriptase inhibitors	Protease inhibitors	Integrase inhibitors
Abbr.	NRTIs “Nucs”	NtRTI	NNRTIs “Non-Nucs”	PIs	INSTIs
Eg.	Zidovudine (AZT) Abacavir (ABC) Lamivudine (3TC) Stavudine (d4T) Emtricitabine (FTC)	Tenofovir (TDF)	Efavirenz (EFV) Nevirapine (NVP)	Ritonavir (RTV) Lopinavir (LPV) Atazanavir (ATV) Darunavir* (DRV)	Raltegravir (RAL) Dolutegravir* Elvitegravir+ Cobicistat*

Paediatric ARV formulations

Wherever possible, use pre-qualified paediatric fixed dose combinations (FDCs) (FDC is designed with a / between drugs, ex.: AZT/3TC/NVP is a triple FDC).

See Appendix B for paediatric ARV dosing recommendations and available FDCs.
To optimise adherence, especially in children with potential adherence concerns (eg orphans, co-morbidities requiring more drugs, etc.), final daily pill count should also be considered when choosing a regimen.

NVP requires a ‘lead in’ period of a half dose for the first 2 weeks of ART (ie. give once daily instead of twice daily).

If a mild rash appears, the once daily dosing should be continued until the rash subsides (though do not continue lead in dose for longer than a further 2 weeks). Thereafter, if the rash has resolved, the full dose can be given by twice daily administration. If a severe rash occurs especially in association with fever, blistering or mucosal involvement - discontinue the drug immediately. Caregivers must be informed about this potential adverse effect.

LPV/ritonavir

– Syrup formulation is heat-sensitive and tastes very bitter. Cold-chain is required until the syrup is dispensed. If refrigeration is not possible at home, it can be stored in a cool, dark place up to 42 days.
  Tips to overcome the poor palatability:
  - Infants < 6 months – position infant and introduce a syringe containing LPV/r in a way that will induce the sucking reflex. Alternatively, try mixing with expressed breast milk in a spoon.
  - For infants/children > 6 months – Try locally available sweet food products or breastmilk to either mix with the syrup, to give straight after the syrup or to coat the mouth prior to the medicine. Examples of sweet foods include jam, peanut butter, fruits.

  In all cases, if a child spits out the syrup, give another dose and ensure it is swallowed.
– Heat-stable tablets should not be cut or crushed; they will lose their bioavailability.
– Heat-stable pellets are now FDA approved and should be available soon for the field. Sprinkle on food or give with breastmilk. It is still bitter in taste and may alter the taste of the food it is given in, but should be more palatable than the syrup. Ensure the caregiver is able to open the capsules.

Tenofovir

Tenofovir based FDCs are first-line for adults, pregnant women and adolescents > 10 years of age. It can be used as an alternative regimen for children from 3 years of age, but the paediatric formulations currently available only exist as single doses of Tenofovir per weight band and are very limited in availability and accessibility. There are concerns of reduced bone mineralisation and its long-term impact in children is not fully understood. Where available, creatinine clearance should be done to monitor for renal toxicity.

Table 2 - ARV contraindications

Drug	Contraindication
d4T	• Association with AZT • D4T is now only used where all other NRTIs are contraindicated
AZT	• Hb level < 8 g/dl • Association with d4T
ABC	• Previous hypersensitivity reaction to ABC
TDF	• Pre existing renal impairment (Creat Cl < 50) • Children < 3 years or < 10 kg
NVP	• Pre-existing, clinically severe hepatic impairment or baseline ALAT grades 3 or 4 • History of severe hypersensitivity reaction
EFV	• Children < 3 years or < 10 kg • Pre-existing clinically severe hepatic impairment or baseline ALAT grades 3 or 4

1.2.2 When to start ART

WHO recommends ART should be initiated in:
- All children infected with HIV below 5 years of age, regardless of WHO clinical stage or CD4 cell count[f].
- All HIV-infected children 5 years of age and older with a CD4 cell count < 500 cells/mm^3, regardless of WHO clinical stage.
- All children infected with HIV with severe or advanced symptomatic disease (WHO clinical stage 3 or 4) regardless of age and CD4 cell count.
- Any child younger than 18 months of age who has been given a presumptive clinical diagnosis of HIV infection.

Table 3 - When to start ART in infants and children

Age	Criteria to start ART
Infants (< 1 year)	Treat all
1 year to < 5 years	Treat all (Prioritise age < 2 years or WHO stage 3 or 4 or CD4 < 750 cells/mm^3 or < 25%)
5 years and above	WHO stage 3 or 4 or CD4 < 500 cells/mm^3 (Prioritise CD4 < 350 cells/mm3)

1.2.3 Which ART regimen to start with (first-line)

In most contexts the choice of ART regimen should follow the national ART guidelines. This ensures easier linkage to local MCH, HIV and supportive services, as well as easier follow up of patient care. Most national guidelines should be more or less in line with recent WHO recommendations for ARV guidance and are unlikely to conflict with MSF recommendations.

In exceptional contexts where no national ART guidance is established or is considered not in line with either WHO or MSF recommendations, consult your HIV advisor. Similarly, if paediatric ARV procurement and supply at the national program level is a concern, consult your HIV advisor.

Table 4 - WHO recommended first-line ART regimen for children < 3 years of age

Preferred	ABC/3TC + LPV/r or AZT/3TC + LPV/r
Alternative	ABC/3TC + NVP or AZT/3TC/NVP
Special circumstances	d4T/3TC + LPV/r d4T/3TC/NVP

[f] Depending on the context, capacity and feasibility, if necessary, prioritise all children < 2 years of age.

Notes:
- Currently there is no FDC available for the recommended first line with LPV/r.
- AZT/3TC/NVP is available as a paediatric triple FDC and its simplicity may be a more practical option depending on context or family circumstances.
- ABC is the preferred NRTI over AZT but its higher price and non-availability as a triple FDC needs to be considered.
- If the child is anaemic, AZT should be replaced by ABC.
- d4T should be phased out, but due to the lack of paediatric drug choices it may still be used in special circumstances where preferred or alternative regimens cannot be used or is unavailable, such as significant toxicity, drug-drug interactions, or drug procurement issues.

Table 5 - WHO recommended first-line ART regimen for children > 3 years and adolescents

	Children > 3 years to < 10 years and adolescents < 35 kg	Adolescents (10 – 19 years) > 35kg
Preferred	ABC/3TC + EFV	TDF/3TC (ou FTC)/EFV
Alternative	ABC/3TC + NVP AZT/3TC/NVP or AZT/3TC + EFV TDF + 3TC (or FTC) + EFV TDF + 3TC (or FTC) + NVP	AZT/3TC + EFV AZT/3TC/NVP TDF/3TC (or FTC) + NVP
Special circumstances	d4T/3TC + EFV d4T/3TC/NVP	ABC/3TC + EFV ABC/3TC + NVP

Notes:
- Although there is no triple ABC/3TC/EFV FDC yet, ABC/3TC exists as a dual FDC and with EFV allows for once daily dosing.
- AZT based regimens allow for triple FDC but is twice daily dosing and can cause anaemia.

Special situations

- *Tuberculosis co-infection:* refer to Part 2, Chapter 2, for recommended ART in conjunction with TB treatment.
- *Hepatitis B co-infection:* treatment should include lamivudine and tenofovir, so first-line can be continued in children > 10 years of age (and in children > 3 years of age if the paediatric tenofovir formulation is available). Otherwise, for most co-infected children < 10 years of age, there are currently no good alternatives to continuing their age-appropriate first-line regimen. The risk of developing resistance to lamivudine (3TC) must be noted. It is vital to ensure Hepatitis B vaccination to all children from birth and at least to the one born from a positive HBV mother.
- *HIV type 2 infection:* treatment should be with a PI-based regimen. NNRTI's (NVP, EFV) are not effective as the HIV-2 virus is not sensitive to this class of drugs. Prevalence is > 1% in the general population in many West African countries, but it is also found in Angola and Mozambique. HIV-1 and HIV-2 disease have the same spectrum of signs and symptoms and treatment of opportunistic infections is the same. However, HIV-2 is less virulent resulting in a slower progression to severe immune suppression.

1.2.4 Monitoring, follow up and ARV side-effect management

Clinical assessment and laboratory monitoring of ART

Both clinical and laboratory based monitoring of children once on ART is essential to ensure their treatment is succeeding. Early identification of any adherence problems, drug interactions, toxicity/significant side effects or incorrect dosing due to a changing weight or co-morbidity is vital.

Key points:

– The lack of viral load (VL), CD4 or blood tests for toxicity should not prevent children from starting ART.
– Where viral load testing is available, this is the preferred laboratory monitoring tool. CD4 monitoring can be used where VL is not available.
– Infants and young children have a high baseline viral load and may require longer to achieve virological suppression.
– Monitoring growth, nutritional status and development are useful clinical tools to assess treatment response and compliance.

Before starting treatment

Clinical assessment

- Clinical staging of HIV disease
- Screening and management of TB
- Identification of other co morbidities: malaria, hepatitis B, opportunistic infections
- Growth: plot on a growth chart, note developmental and nutritional status
- Counselling and preparation of patient and caregiver for therapy

Laboratory assessment

*The **essential** laboratory tests before ART initiation are:*
- Positive HIV rapid test
- Haemoglobin if AZT will be given

*The **desirable** laboratory tests before ART initiation are:*
- DNA PCR for confirmation of HIV infection in children < 18 months
- CD4 count and % CD4 for children < 5 years
- Screening for Hepatitis B if the child has not been immunised (check immunisation card)
- Creatinine clearance if starting TDF

Monitoring while on treatment

Clinical assessment

Frequency of visits depends upon the child's clinical condition, the response to ART, and the context.
As a minimum, follow up visits should occur at weeks 2, 4, 8, 12 and then when clinically stable:
- Infants (< 12 months old) - every month
- Children (> 12 months old) – every 3 months

Clinical assessment

At each visit it is necessary to assess:

- Understanding of and adherence to therapy
- Clinical response to treatment
- Signs of drug toxicities
- Signs of emerging OI's especially TB
- Growth: plot on a growth chart, note development and nutritional status
- Change in drug dosage according to weight

Laboratory assessment

*The **essential** laboratory tests for ART follow-up are:*

- Haemoglobin (if AZT is used): baseline, then M1, M2 and as clinically indicated thereafter

*The **desirable** laboratory tests for ART follow-up are:*

- Viral load: At M6, M12 then every 12 months thereafter. Repeat at any time if suspicion of treatment failure.
  If VL monitoring is available, once VL below threshold, CD4 monitoring is no longer necessary.
  If VL not available, CD4 and % CD4: every 6 months or any time if suspicion of treatment failure.
- ALAT: For patients on TB treatment: at baseline then as clinically indicated thereafter
- Lactate: as clinically indicated
- If TDF used, creatinine clearance: baseline, M6, M12 and then every 12 months

Side-effects from ARV drugs

Although there are fewer data on ARV drug toxicity in children than in adults, the full spectrum of ARV toxicities observed in adults has also been reported in children. Nearly all ARVs can cause mild constitutional symptoms such as headache, nausea and fatigue. Only the significant and drug specific side effects are listed here.

Table 6 - ARV side-effects

Drug	Side-effects to anticipate
D4T	Mitochondrial toxicity* *Less common in children than in adults*
AZT	Anaemia – usually within initial 4-6weeks Neutropenia – usually after initial 12-24 weeks Rare: Mitochondrial toxicity*
3TC	Rare: Mitochondrial toxicity*
FTC	Rare: Mitochondrial toxicity*

Table 6 - ARV side-effects *(continued)*

Drug	Side-effects to anticipate
ABC	Genetically mediated hypersensitivity syndrome (5% gene prevalence among Caucasians, < 1% in Africans, 15% in Thais and Indians; 0% in Chinese and Japanese) occurs within the first six weeks of treatment, usually after 10 days Non-specific symptoms: fever, respiratory symptoms, abdominal pain, rash. Can be fatal Very rare: Mitochondrial toxicity*
TDF	Decrease in bone mineral density Renal tubular toxicity, Fanconi syndrome Very rare: Mitochondrial toxicity*
NVP	Hepatotoxicity – less common in children that in adults Severe skin reactions –Stevens-Johnson syndrome, toxic epidermal necrolysis. Usually within first 6 weeks of treatment Hypersensitivity syndrome: fever, myalgia and arthralgia, hepatitis, rash
EFV	CNS disturbances: dizziness, headache, insomnia, depression, impaired concentration, agitation, disturbing dreams, nightmares and somnolence Hepatotoxicity - less frequent than with NVP Skin toxicity - less frequent than with NVP, but mild rash is more common in children than in adults
LPV/r	Diarrhoea common at beginning of treatment, usually diminishes after one month ECG abnormalities (prolonged PR and QT interval) Hepatotoxicity Metabolic syndrome: dyslipidemia, insulin resistance, diabetes, lipodystrophy
ATV/r	ECG abnormalities (prolonged PR interval) Indirect hyperbilirubinaemia

* Mitochondrial Toxicity is associated with a range of manifestations including: peripheral neuropathy, myopathy, lipodystrophy, pancreatitis, lactic acidosis, hepatic steatosis and other hepatotoxicities. It can occur with all NRTI's, but is most frequent with d4T.

Diagnosing and managing important side effects

Grade tables of severity can be found in Appendix E.

Skin reactions

Likely agent	NVP or EFV
Differential diagnosis	ABC reaction (see 'hypersensitivity' below), cotrimoxazole drug reaction, TB drugs

Symptoms	Erythematous maculopapular rash. Most often on the body and arms. Usually within the first 6 weeks of treatment. In severe cases (grade 3 or 4): vesicles, ulceration, epidermolysis mucous membrane involvement or fever
Management	If mild (grade 1 or 2), continue NVP at induction dose and monitor closely. Do not continue induction dose for more than a total of 4 weeks. For severe reactions (grade 3 or 4) all ARVs and other drugs including cotrimoxazole must be stopped immediately (no NRTI tail). No drugs should be restarted until the rash is completely resolved. For grade 3 reactions, a switch to EFV can be considered only if the patient can be very closely monitored during the first days to weeks of therapy. If there is any sign of recurrence of the rash, EFV should be stopped, and NNRTIs never restarted (write it clearly in the child health card). If close monitoring is not possible, switch to PIs. For grade 4 skin reactions, after resolution, switch to PI's. Do not administer NNRTIs again.

Hepatitis

Likely agent	NVP - although rare in pre-pubertal children, it is more common after puberty in female adolescents with CD4 > 350 or male adolescents with CD4 > 400. It usually occurs during the first 6 to 8 weeks of treatment.
Differential diagnosis	Acute viral hepatitis, IRIS (usually Hep B), other ARVs: EFV, NRTI's or PIs, other drugs especially TB drugs
Symptoms	Jaundice, liver enlargement, vomiting, anorexia, abdominal pain. Hypersensitivity component possible: fever, rash, systemic symptoms
Management	If mild (grade 1 or 2), continue NVP at induction dose and monitor closely. Do not continue induction dose for more than a total of 4 weeks. If symptomatic or ALAT grade 3 or 4 - stop all drugs (no NRTI tail) until clinical resolution, or until ALAT is < 2.5 × ULN, or back to baseline value. If NVP is the suspected cause, it should be discontinued and never restarted. Switch to a PI. In case of cholestasis, the presence of intra-abdominal nodes suggestive of TB and cryptosporidium should be investigated.

Hypersensitivity reaction

Likely agent	ABC - usually within 6 to 8 weeks of treatment initiation
Differential diagnosis	NVP reactions, allergy to antibiotics (including cotrimoxazole), systemic infections (viral, bacterial, malaria)
Symptoms	Fever, headache, nausea and vomiting, diarrhoea, cough, dyspnoea and rash, myalgia, arthralgia If due to ABC – usually observe worsening of symptoms immediately after taking the drug.
Management	Stop all drugs immediately. Permanently discontinue offending drug. Do not give any drugs until complete symptom resolution. For NVP, a grade 4 hypersensitivity reaction necessitates a switch to PI's. For grade 3 reactions, a switch to EFV can be considered only if the patient can be closely monitored in the first days to weeks of therapy.

Haematological abnormality

Likely agent	AZT – anaemia usually within initial 4-6 weeks, neutropaenia 12-24 weeks after treatment initiation
Differential diagnosis	Malaria, TB, iron deficiency, sickle cell disease, cotrimoxazole, hemorrhages, malignancy, TB drugs
Symptoms	Pallor, generalized fatigue and weakness, tachypnea, tachycardia, sepsis (if neutropaenia present)
Management	If well tolerated: treat malaria and iron deficiency, provide nutritional support. If tachycardia or tachypnea and Hb < 6.5 g/dl give transfusion. Discontinue AZT if anaemia is severe and refractory to treatment and substitute an alternative NRTI.

1.2.5 Food and drug interactions with ART – important considerations

Drug	Interaction
Efavirenz	• Amodiaquine: use alternative antimalarial agent. • Avoid taking with high fat content foods.
Boosted PI (LPV/r, ATV/r)	• Take LPV/r solution with food.

Drug	Interaction
NNRTI's and PI's	Interaction with the cytochrome P450 liver enzyme system results either in inhibition or induction of these enzymes. Co-administration of other drugs metabolised by cytP450 results in either increased toxicity because of elevated drug concentrations or drug failure attributable to sub-therapeutic drug concentrations. *Important considerations:* • *Rifampicin:* reduces some of ARV drug levels. NVP should be substituted by EFV in children > 3 years. Boosted PI's should be super boosted with additional ritonavir or use triple NRTIs. • *Oral contraceptive pills:* efficacy reduced by NNRTI's and PI's. Condoms should be used in complement. • *Ketoconazole:* blood levels are significantly lowered with use of NVP. For patients on NVP, fluconazole is the preferred option. • *Herbal or traditional treatments:* all traditional herbal treatments should be avoided as they can cause inadequate ARV drug concentrations. e.g. garlic supplement or St John's Wort (millepertuis). • *Anti-epileptic drugs:* avoid carbamazepine and phenobarbitone. Use valproic acid if possible. Many other drugs can have significant interactions, check before starting a patient on any new drug.

1.2.6 Diagnosing treatment failure and deciding when to switch

Treatment failure should be recognised early to prevent clinical and developmental deterioration in the child and to reduce the accumulation of drug-resistant mutations. The most common reason for treatment failure is poor adherence. Prior to considering switching regimens, adherence issues need to be fully addressed to avoid an unnecessary switch. If adherence is not improved, the second regimen is unlikely to succeed. As the young child is dependent on the caregiver(s), social circumstances or family issues affecting adherence need to be evaluated and addressed. Similarly in adolescents, where disclosure, stigma, social/schooling and peer/family circumstances play a significant role on adherence.

Always check first that failure is not being caused by:
– Improper ARV dosages due to increase in the child's weight;
– Drug side-effects/toxicities or drug interactions;
– NNRTI exposure during PMTCT if child on NVP based regimen;
– Malabsorption due to gastrointestinal illness;
– Other opportunistic infections;
– IRIS;
– HIV 2 co-infection in some contexts.
These issues can be addressed and/or treated appropriately and resolve failure.

Defining treatment failure

	Definition
Clinical failure	Appearance of new or recurrent clinical stage 3 or 4 events after at least 6 months of effective ART
Immunological failure	In children < 5 years of age, persistent CD4 < 200 or % CD4 < 10% after at least 6 month of effective ART In children ≥ 5 years, persistent CD4 < 100 after at least 6 month of effective ART
Virological failure	Viral load persistently over 1000 copies/ml, based on two consecutive VL measurements spaced at least 3 months apart, despite adherence support

Viral load is the preferred monitoring tool to diagnose and confirm treatment failure. As more children start ART earlier and at higher CD4 counts, VL monitoring will be increasingly beneficial. In contexts where viral load or CD4 count is not available, treatment failure can be diagnosed on clinical grounds.

Management of cases of treatment failure should be discussed in a multidisciplinary team. It is also recommended that home visits are conducted or, where available and appropriate, to involve social workers or engage community support to identify a support group member to support the child and family.

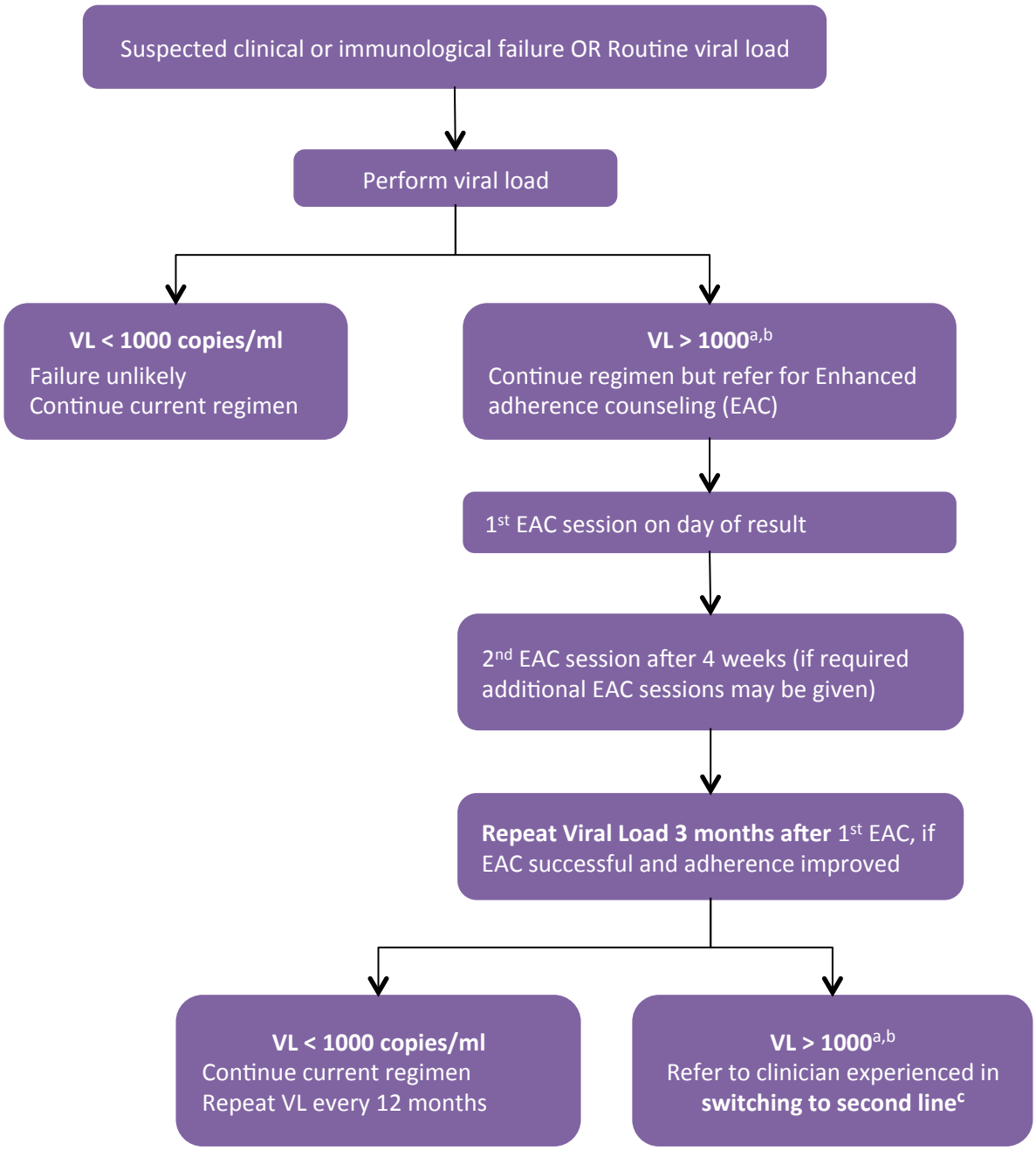
Ensure in ALL cases that enhanced adherence counselling (EAC) is started on suspicion of failure and EAC sessions are completed as part of the work up towards switching to a second line regimen.

Deciding when to switch

Steps towards a decision to switch to second line can vary depending on whether viral load testing is available, whether only CD4 monitoring is available or whether no lab monitoring test is available. In all situations, adherence problems must be addressed, EAC sessions done and other potential factors[g] causing failure corrected or treated.

[g] Improper dosage due to increase in the child's weight, drug side-effects/toxicities or drug interactions, NNRTI exposure during PMTCT if child on NVP based regimen, Malabsorption due to gastrointestinal illness, other opportunistic infections, IRIS, HIV 2 co-infection in some contexts.

Where viral load testing is available:

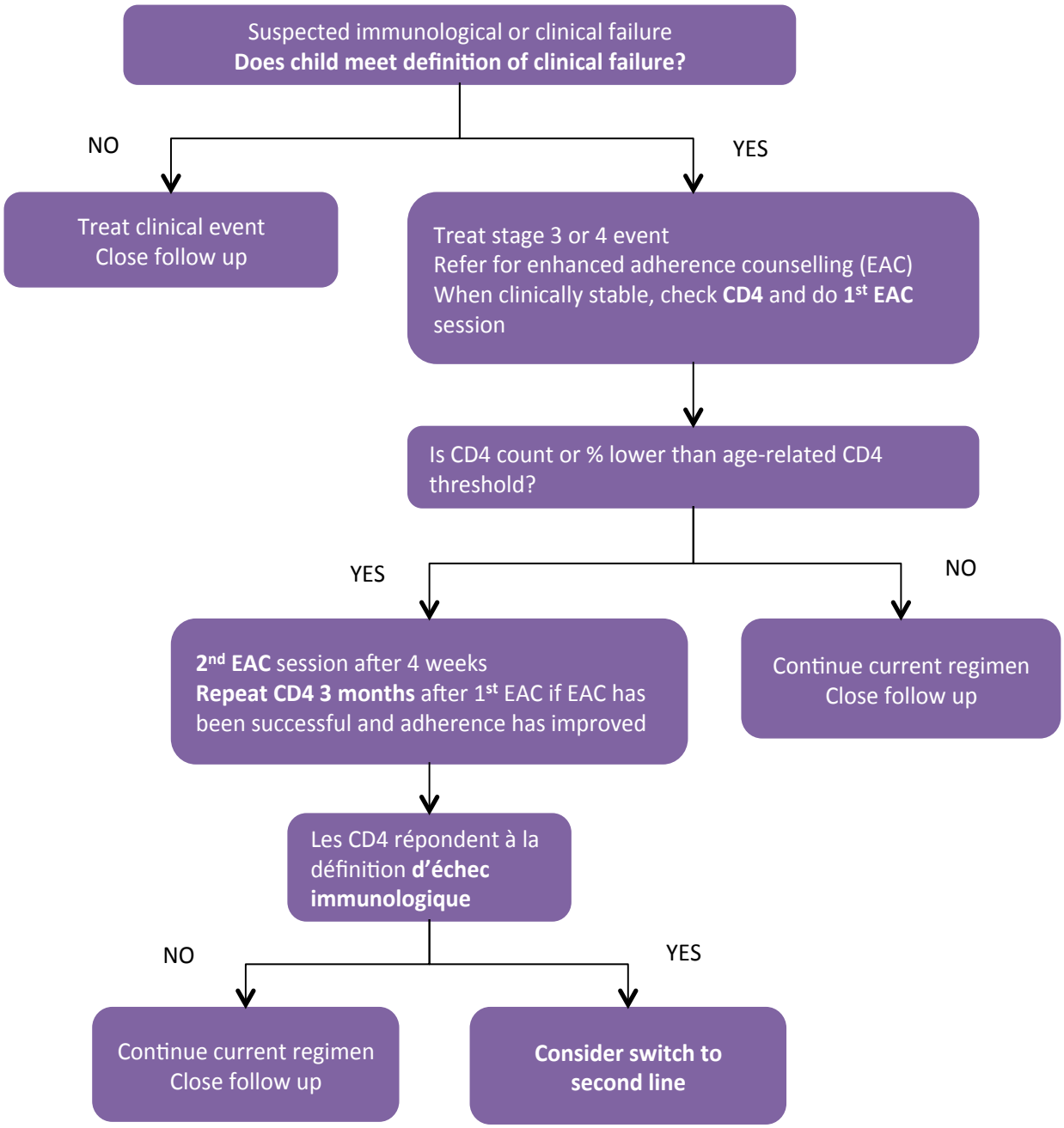


[a] Pending on platform used, some concern of poorer sensitivity of VL using DBS that recommends using a higher VL threshold eg 3000. For Biomerieux, use 1000 threshold. For Abbot, use 3000 threshold. Discuss with HIV or Lab advisor.

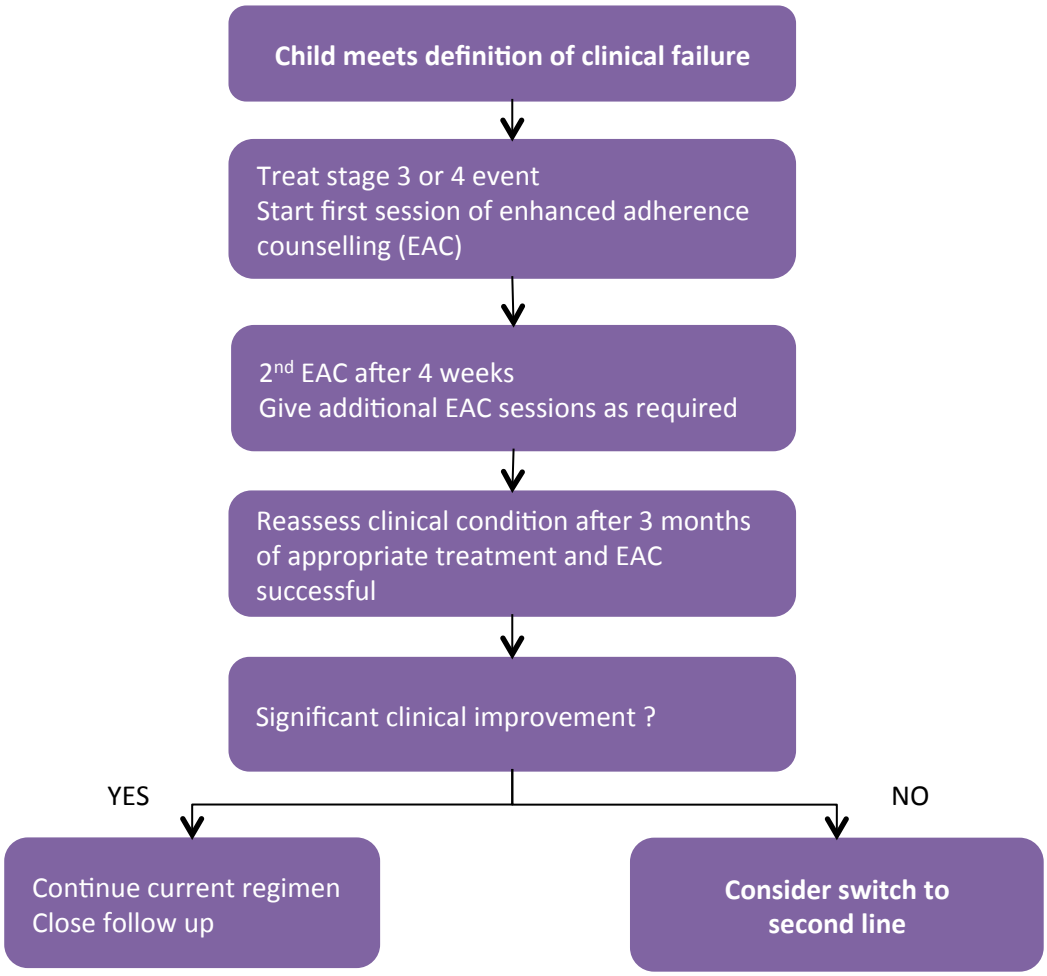
[b] If VL > 50,000 at any time when on treatment: consider patient might have hardly taken any drugs and thus might not be resistant. If CD4 allows, a switch should be postponed until adherence issues have been clarified.

[c] If the child is well and immunity stable, you can propose to continue EAC, do a VL in 3 months and take the decision to switch for 2nd line after this 3rd VL result.

Where only CD4 count or % is available:



Where no laboratory monitoring is available:



Which ART regimen to switch to (second-line regimens)

Table 7 - WHO recommendation for second-line ART regimen for children and adolescents

Second-line ART			Preferred 2nd line regimen	Alternative regimen
Adolescents (> 10 years)			TDF/3TC (or FTC) + ATV/r or LPV/r (if D4T or AZT was used in first-line ART) AZT/3TC + ATV/r or LPV/r (if TDF was used in first line ART)	
Children	If NNRTI-based 1st line was used		ABC/3TC + LPV/r[a]	TDF + 3TC (or FTC) + LPV/r[a]
	If PI-based 1st line was used	< 3 years	No change. Continue first-line regimen[b]	AZT (or ABC)/3TC + NVP
		3 years to < 10 years	AZT (or ABC)/3TC + EFV	ABC/3TC + NVP or TDF + 3TC + NVP

[a] In children > 6 years, ATV + ritonavir can be used instead of LPV/r. Lower pill count with ATV + ritonavir and to be taken once daily.

[b] Unless poor adherence is a result of poor palatability of LPV/r (could consider AZT/3TC/NVP if there was no NVP exposure through PMTCT).

1.3 Treatment education and adherence support

This chapter is a summary of the main recommendations related to patient education and counselling for children. For more details and practical procedures refer to the MSF-OCB guideline[h].

Basic principles for paediatric care and support

Because children are passing through several cognitive, emotional and psychological stages, it is necessary to adapt the general approach in the clinics, and with your staff, and apply some basic concepts related to children.

The main principles are:

- To provide medical care and patient support to a child by addressing 3 actors: the child, the caregiver and the family.
- To make the whole clinic an environment in which the child feels at ease: physically and emotionally secure. For example, friendly wall decorations or a children's corner or room.
- To gather all children at the clinic ideally on the same day of the week for their medical follow-up. This "children's day" or "family day" will allow for more adapted care and support to children: they will see that other children are like them, they can access the children's space with games, toys, films etc. It is also crucial to have the child and the HIV+ caregiver being seen on the same day by the same consultant.
- To adapt to the stage of development of child:
  - *Under the age of 6 years*, the counselling sessions will mainly engage the caregiver
  - *Between 6 -12 years*, both the caregiver and the child will be involved
  - *Above 12 years*, most of the counselling work can be done with the adolescent alone. However, it is necessary to keep the caregiver coming and involved in the adolescent's support.
- To have a multidisciplinary approach. Like for adults, it is essential to maintain coordination and coherence between all health care providers involved in the care and support of the child.
- To keep a child-patient file recording medical, counselling and social history. It is important to mention who is the main caregiver and his relationship to the child, as well as the level of disclosure of the child's HIV status.
- To use child specific tools and activities for patient support (see OCB guideline). These activities facilitate health and treatment education, allow children to express their feelings, to develop life skills and to simply to have fun.

Disclosure counselling

"Disclosure of HIV positive status" is the term used to describe the process by which children learn about their HIV status. Children who know their diagnosis have better health outcomes as they generally feel more responsible and involved in the management of their treatment. When working with children under 12 years old, the recommendation is to go for progressive disclosure: a gradual process by which a child learns first (partial disclosure) about his health, about having an 'unnamed' infection and about his treatment. This process continues until he is ready for 'total disclosure' where he finally learns about his HIV status.

[h] *Patient Support for HIV infected children,* MSF-OCB, September 2008.

Who should disclose?

The disclosure process should be conducted by someone whom the child trusts and respects. Usually, this will be the caregiver. Counsellors should pro-actively prepare or assist the caregiver in the disclosure process and follow-up.

When to disclose?

A progressive disclosure started at an early age is ideal. It should at least begin when the child starts asking questions about himself, his health, or his regular clinic visits. The explanations given should be adapted to his cognitive development and his feelings. Partial disclosure should at least be done between 6-9 years. Total disclosure is to be done latest at 12 years of age. When the disclosure process is not started at 10, it is necessary to proactively work with the caregiver on possible reluctance to discuss the child's health condition directly, addressing the advantages of disclosure. In some countries the MoH also have recommendations on the maximum age to disclose.

During consultations, don't forget the child is in the room. If a private conversation is necessary, make a separate appointment with the caregiver. This is especially important when discussing disclosure. Children always understand more than is thought.

Never lie to the child!

Even when the child is very young, try to explain things in a simplified way. Lying or deceitfulness can often result in long term damage to the caregiver-child relation.

Adherence counselling

The counsellors have to prepare the child and the caregiver for lifelong ARV treatment. The child's developmental stage will influence the extent to which s/he can or will cooperate with medication administration. With young children, maintaining good treatment adherence will be the responsibility of the caregiver. He/she needs to understand the potential complexities in a drug regimen and assist the child with the drug administration. After close observation and coaching by the caregiver, older children/adolescents should feel responsible for managing their own health and understand the necessary aspects of treatment.

1- ART preparation

ART preparation refers to the preparatory work conducted with the child and the caregiver, prior to ARV initiation. It includes both an educational and a counselling component (for emotional and social preparation). This will be achieved through at least 2 sessions with the child and the caregiver. ART preparation is the ideal moment to also open up the discussion on disclosure of the child's HIV status. For children older than 6, partial disclosure should be started before initiation on ARV's.

All HIV infected children ≤ 5 years old should be started on ART as soon as possible irrespective of clinical stage or CD4. Counsellors should be flexible and communicate well with clinicians for these young children since ART initiation must not be delayed.

Patient education:

Children and caregivers should be provided with relevant education on the disease and the treatment, and understand what it means to commit to a lifetime treatment. The team should help caretakers practice medication administration, and should address the following issues:

– *Who will administer the medications?* It will be particularly important to determine who will be in charge of administering the drugs, what will happen if for some reason the responsible adult is not present (i.e. identify another fully informed adult in charge who will be able to help when the usual caregiver is not present). It is essential to emphasize the need for continuity in the care given at home ie the same adult responsible over time, the same adult accompanying the child to the consultations over time.
– *What medications will be given and how?* Children and caregivers must be able to confidently identify each medication, and know how it is to be stored, measured, and administered.
– *When will medications be given?* Antiretroviral medications should be given at the same time every day.

Emotional and social aspects:

The counsellor should assess the child and the caregiver's acceptance and readiness to start the treatment, and prepare them for it. He should also explore the emotional availability of parents and/or care givers, maintaining awareness about the quality of the relationship.

The risk of non-adherence can be reduced by reminding caregivers of children's need for ritual, and consistency, by warning them of potential side effects, and by preparing them for common problems such as refusing or spitting out medications.

2- Adherence follow-up session

The child should be seen by the counsellor during follow-up visits, especially at the beginning of the treatment. Patient education/counselling sessions are advised at least at D15, M1, M6 and M12. Indeed adherence during the first days and weeks of treatment can be critical to the long-term success of the regimen. It is important to assess adherence (a self-report method is recommended, eg. Morisky scale) and the understanding of the medication administration. Barriers to adherence should be also identified.

The main barriers to adherence include:
– *Barriers related to the caregiver:* frequently changing, absent or sick, elderly, illiterate, depressed, living far from the health facility, economically unstable.
– *Barrier related to the child:* level of disclosure, lack of understanding of disease/treatment, stigmatization, lack of self-esteem, depression.
– *Barriers related to treatment:* formulations not adapted for children: large volumes, bad taste, many pills, mixture of syrups and tablets, side effects, changing doses as child grows.
– *Barrier related to the health system:* distance, attitude of the staff, non-child friendly environment, stock ruptures.

A basic pill-taking tool for children, like the pill pathway, is useful to involve the child in the management of his treatment.

It is very important to promote trust, partnership, and an honest communication with children and their caregivers. Peer support can be invaluable for children, adolescent as well as parents; parents may learn as many practical tips from other parents as they do from the health care team. Support groups specifically for parents/caregivers of children under 6, or children/youth groups for disclosed children can be highly beneficial for reinforcing adherence, social skills and social support.

Part 2:
Prevention and management of co-infections and opportunistic infections

2.1 Cotrimoxazole prophylaxis

Cotrimoxazole (CTX) prophylaxis is recommended for ALL infants, children and adolescents living with HIV irrespective of clinical and immunological conditions[i].

It protects against pneumonia (especially PCP), cerebral toxoplasmosis, certain types of diarrhoea, malaria and severe bacterial infections (strep pneumoniae, haemophilus influenzae, salmonella, legionella, nocardia, methicillin sensitive staphylococcus aureus and many gram negative bacilli).

HIV-exposed infants should start CTX at 4 – 6 weeks of age and should be continued until HIV infection has been excluded by an age appropriate HIV test to establish final diagnosis (at least 6 weeks after cessation of breast feeding).

Table 8 - Simplified dosing of cotrimoxazole prophylaxis in children

Weight	Suspension 200/40 mg per 5 ml	Tablet (dispersible) 100/20 mg	Tablet (scored) 400/80 mg	Tablet (scored) 800/160 mg
3 – 5.9 kg	2.5 ml	1	-	-
6 – 9.9 kg	5 ml	2	0.5	-
10 – 13.9 kg	5 ml	2	0.5	-
14 – 19.9 kg	10 ml	4	1	0.5
20 – 24.9 kg	10 ml	4	1	0.5
25 – 34.9 kg	-	-	2	1

Contraindications to CTX

- Allergy to sulphonamides
- G6PD deficiency
- Concurrent sulfadoxine-pyrimethamine (SP) treatment of malaria
- Severe liver disease
- Severe renal insufficiency

Side effect management

Adverse events due to CTX are less frequent in children than in adults. The most common toxicities are rash and hematologic disturbances. Grade toxicities are comparable to those of adults except for haemoglobin values in infants during the first weeks of life.

[i] Refer to national guidelines for CTX recommendations in adults.

Adverse event	Classification	Features	Management
Skin Rash	Grade 1 or 2	Localized or diffuse maculo-papular/morbilliform rash Pruritis	Continue CTX. Symptomatic treatment (antihistamine) If no improvement in 1-2 weeks, discontinue CTX.
	Grade 3 or 4	Above ***PLUS*** *any of:* • Vesicles • Ulceration • Epidermolysis • Mucous membrane involvement • Fever	Stop CTX and any other suspected agents. Do not re challenge with CTX. Note clearly in clinical file.
Haematologic Disturbance	Grade 1 or 2	Hb* > 7.5 g/dl WBC > 1500/mm^3 Neutrophil count > 500/mm^3	Continue CTX. Repeat blood tests if clinically indicated.
	Grade 3 or 4	Hb* < 7.5 g/dl or WBC < 1500/mm^3 or Neutrophil count < 500/mm^3	Stop CTX. Assess other possible causes and treat. Do not re challenge with CTX if suspected cause. Note clearly in clinical file.

* Hb cut off applies to children > 60 days old

Whenever CTX must be discontinued due to toxicity, Dapsone 2 mg/kg/day can be used (max 100 mg/day).
Do not attempt desensitization to Cotrimoxazole in children.

2.2 Tuberculosis and isoniazid preventive therapy

Key points:

- In general, tuberculosis (TB) is under diagnosed in HIV exposed or infected children.
- Children under 3 years old are at particular risk of active TB disease and death.
- Screening children for TB symptoms at each contact with health services is essential.
- Isoniazid Preventive Therapy (IPT) is an important intervention for all HIV exposed or infected children who do not have active TB disease.
- In the majority of cases, the diagnosis of TB can be made based on clinical grounds. If available, CXR, microscopy or Xpert MTB/RIF can be useful.

2.2.1 TB screening and prevention

All children should be screened for TB at each contact with health services and within the community. TB screening is simple and can be done by any trained health care worker:

- Caregivers of children should be asked about *current cough, fever, poor weight gain* and *contact*[j] with a TB case.
- Adolescents should be asked about the presence of four symptoms: *current cough, fever, weight loss* and *night sweats*, and *contact* with a TB case.

Any child who has had contact with a TB case but has none of the screening symptoms should be considered eligible for IPT.
HIV exposed (as long as positive HIV status has not been ruled out) or infected children > 12 months of age with none of the screening symptoms should be considered for systematic IPT, even if there has been no TB contact.
Children who have one or more of the screening symptoms should be assessed for the possibility of active TB (refer to TB diagnostic algorithm in Appendix C.2)

Isoniazid preventive therapy (IPT)

Isoniazid prophylaxis is a very important intervention to reduce the risk of HIV exposed and infected children developing active TB. Prior to starting IPT, try to exclude active TB. If TB screening is negative or evaluation has not found active TB, *6 months of IPT* should be given to HIV exposed and infected children in the following 3 situations:

I. *Contacts*: all HIV-exposed and HIV-infected infants and children < 15 years of age, having had contact with any case of TB *PRIORITY*.

II. *Systematic*: all HIV-exposed and HIV-infected children between the ages of 12 months and 15 years, regardless of contact history, 6 months of IPT to be repeated every 3 years [k].

[j] Contact is defined as living in the same household, or in close and regular contact with any known or suspected TB case within the last 12 months.

[k] Exposed infants confirmed HIV negative (>18 months of age and/or not breastfed for >6 weeks) do not require repeat IPT unless a contact case.

III. *Post TB treatment*: all HIV-exposed and HIV-infected children < 15 years of age, 6 months of IPT immediately following the successful completion of TB treatment.

Dosing for Isoniazid:

– Newborns and children < 30 kg: 10 mg/kg (7-15 mg/kg/day)
– Children > 30 kg: 5 mg/kg (4-6 mg/kg/day)
– Maximum dose: 300 mg/day

Neonates born to a mother with active pulmonary TB (smear positive or negative) should receive at delivery a careful clinical assessment. If completely asymptomatic, 6 months of isoniazid prophylaxis should be given to the neonate. If any clinical signs of active TB are present, full TB treatment should be started. BCG vaccination should be deferred until after TB treatment or prophylaxis is complete, unless the child is confirmed to be HIV infected within this time, in which case, a BCG should not be administered.

Children on IPT should be followed up at least monthly and monitored for the development of TB symptoms. They should also receive 10 mg of pyridoxine (B6) daily. See Appendix C.1 for the dosing table and IPT monitoring tool for the follow up of children on IPT.

Notes:

– Giving IPT in HIV infected people does not increase risk of developing INH resistant TB. Due to the paucibacillary nature of young children with TB, if active TB is suspected after IPT has already been initiated, the risk of developing INH resistant is very low. Concerns regarding INH resistance should not be a barrier to providing IPT.
– TST does not have a role in determining which child should have IPT. It can be used though, if available, as part of an evaluation for active TB.

2.2.2 Diagnosis of TB in HIV infected children

Overall, the clinical presentation of TB in HIV infected children is similar to that in HIV uninfected children except that HIV infected children are more likely to be malnourished and have a negative TST.

Refer to Appendix C.2: Paediatric TB Diagnostic Algorithms and Chapter 5 of MSF *Tuberculosis* Guideline 2014 for full guidance.

Key elements for diagnosis:-

– Clinical history
– Contact with a known or suspected TB case
– Symptoms suggestive of TB:
  • Cough persistent for > 2 weeks and not improving
  • Unexplained fever for > 1 week
  • Unexplained weight loss or failure to thrive
  • Unexplained fatigue, lethargy or reduced playfulness

Full clinical examination

– Fever, undernutrition/low weight for age or height
– Signs of respiratory infection: abnormal auscultation or percussion may be present.

– Signs of severe respiratory infection: tachypnoea, cyanosis, hypoxemia SaO_2 < 90%, nasal flaring, chest indrawing, grunting and feeding difficulties in infants.

Refer to Table 9 for symptoms, signs and investigations for extra-pulmonary TB (EPTB).

Investigations

Currently available TB diagnostic tests are not adapted to confirm TB in young children. If X-rays, Xpert MTB/RIF or microscopy and culture are available, they should be used to support diagnosis. However, *if there is clinical suspicion of TB despite an apparently normal CXR, negative Xpert or negative smear, treat for TB*.

Sputum or other samples (see Table 9) can be taken for analysis by microscopy or Xpert MTB/RIF where available. Preferred analysis is by Xpert MTB/RIF (refer to MSF TB Guideline, WHO Xpert MTB/RIF guideline or TB advisor for details). For young children who cannot expectorate, sputum samples can be collected by sputum induction or gastric aspiration. However, these should only be done if proper facilities, trained staff and an Xpert or reference culture lab are available (poor sensitivity with microscopy alone).

CXR features consistent with TB include: upper lobe infiltrates, hilar adenopathy, pleural effusion and a miliary picture, although there is no radiological feature that can distinguish TB from other HIV associated lung conditions.

Assess response to broad spectrum antibiotics: a poor response to antibiotic therapy is highly suggestive of TB. But at the same time, *clinical improvement on antibiotics does not rule out TB*. In such cases, children should continue to be monitored for recurring symptoms. See Part 2, Chapter 5: *Respiratory conditions*, for recommendations for antibiotic regimens

Table 9 - Extra-pulmonary TB: signs, symptoms and sample taking
(NB: often pulmonary TB is also present in cases of EP TB)

Site	Description	Practical approach
Peripheral lymph nodes	• Non-painful, non inflamed lymphadenopathy (> 4 weeks, > 2 cm), • Softening and fistulising to become chronic • Most often in cervical region • Often associated with other TB manifestation sites	Fine needle (22G) aspiration
Miliary TB	• Generalized infection • Progressive deterioration over days to weeks • Non specific symptoms - high fever, headaches, weight loss • High risk of meningeal involvement in children (60-70%)	Chest X-ray and Lumbar puncture ***MEDICAL EMERGENCY***

Site	Description	Practical approach
TB meningitis	• Subacute, developing over days to weeks • Fever, irritability, poor feeding, headaches, behaviour change • Vomiting, neck stiffness and photophobia usually present • LP: often clear fluid, high lymphocytes, high protein (> 0.4 g/l or Pandy +), low glucose (< 60 mg/dl) • Often associated with miliary TB	Chest X-ray and Lumbar puncture ***MEDICAL EMERGENCY***
Pleural effusion	• Pleuritic chest pain, dyspnoea • Pleural fluid: straw coloured, protein > 30g/l (Rivalta +), lymphocytes + • More common in adolescents	Chest X-ray and Pleural tap
Abdominal TB	• Ascites (rule out other possible causes) • Puncture liquid: translucent, yellow, lymphocytes +, protein > 30 g/l (Rivalta +) • Abdominal mass (excluding hepato-splenomegaly), pain or diarrhoea • Usually fever > 2 weeks	Ultrasound and tap of ascitic fluid
Osteoarticular	• Slow onset (> 4 weeks) of monoarthritis with little or no pain • Usually hip, knee, elbows or wrists • Signs of joint destruction (clinical or radiological) • Often associated with pulmonary TB	X-ray, joint tap or synovial biopsy
Spinal TB (Pott's disease)	• Infection of vertebrae and disks leading to destruction and deformation of the spine • Pain less prominent than extent of radiological destruction • Deterioration of physical conditionI	X-ray
Pericardial TB	• Chest pain, dyspnoea, lower limb oedema or ascites, soft heart sounds	Chest X-ray, Cardiac US and pericardial tap

2.2.3 Tuberculosis treatment

Key points about TB treatment in children:

– Always use paediatric fixed dose combinations.
– Prednisolone (2 mg/kg/day) is of benefit in cases of TB meningitis and TB pericarditis.
– Discuss any case of suspected drug resistant TB in a child with TB advisor.

Refer to national or MSF *Tuberculosis* for the recommended TB regimens and drug dosing schedule for children.

Adjunctive Therapy for Co-infected Children

All children with TB/HIV should receive cotrimoxazole prophylaxis.[l]
Nutritional supplementation[l] is recommended in the first 2 months of TB treatment, unless they meet the criteria of severe acute malnutrition in which case they should receive therapeutic feeding as per MSF or national nutrition guidelines.
Co-infected children should routinely receive pyridoxine prophylaxis (10mg/day) as both INH and HIV increase the risk of peripheral neuropathy.

Antiretroviral treatment in children with TB/HIV

Children already on ART when starting TB treatment may need their ARV regimen adjusted for the duration of TB treatment. Refer to Table 10.

- Co-administration of rifampicin and nevirapine or LPV/r makes co-treatment in children < 3 years challenging. Triple NRTI (ABC/3TC/AZT) is preferred but the child must return to first-line ART after completion of TB treatment.
- In children > 3 years, efavirenz based regimen is preferred during TB treatment.
- If LPV/r is co-administered, superboosting with ritonavir is required.
- If there is no other solution than to provide NVP co-administered with TB treatment, ensure that the total dose of NVP is 200mg/m^2 twice a day.

Children who are not yet on ART, delay ART and start TB treatment immediately. Initiate ART as soon as TB drugs are tolerated but within 8 weeks of starting TB treatment. Refer to Table 10. The risk of Immune Reconstitution Inflammatory Syndrome (see Part 2, Chapter 3) and significant drug interactions with this approach is thought to be outweighed by the expected gains in mortality.

Due to the risk of hepatitis in the early stages of TB and ARV co-therapy, ALT should be checked at baseline, then as clinically indicated.

Table 10 - WHO recommended regimens for children and adolescents initiating ART while on TB treatment

Patient group	Preferred	Alternative
< 3 years	Triple NRTI (ABC/3TC/AZT)	Two NRTIs + NVP, ensuring that dose is 200mg/m^2.[a]
> 3 years	Two NRTIs + EFV	Triple NRTI (ABC/3TC/AZT)

[a] See NVP dosing already calculated to weight range in Appendix B table.

[l] National or WFP supported nutrition programs usually have specified rations and food products for TB patients. If not, discuss with your Nutrition advisor.

Table 11 - WHO recommended regimens for children and adolescents initiating TB treatment while receiving ART

Patient group	Age	Preferred	Alternative
Child on standard NNRTI-based regimen (two NRTIs + NVP or EFV)	< 3 years	Triple NRTI (ABC/3TC/AZT)	Continue NVP, ensuring that dose is 200mg/m^2.[a]
	> 3 years	If on EFV, continue. If on NVP, change to EFV.	Triple NRTI (ABC/3TC/AZT)
Child on standard PI-based regimen (two NRTIs + LPV/r)	< 3 years	Triple NRTI (ABC/3TC/AZT)	Boosted LPV/r adding RTV to achieve full therapeutic dose[b]. Or if not feasible, substitute with NVP, ensuring that dose is 200 mg/m^2.[a]
	> 3 years	Substitute with EFV	Continue LPV/r, by adding RTV to achieve full dose[b] or Triple NRTI (ABC/3TC/AZT)

[a] See NVP dosing already calculated to weight range in Appendix B table.

[b] Boosted LPV/r is an alternative especially for young children already on LPV/r because of previous NVP exposure. boosted LPV/r indicates additional boosting of LPV/r by adding ritonavir to reach mg equivalence ie ritonavir in a 1:1 ratio with lopinavir. In young children this can be difficult due to the bad taste of ritonavir syrup.

Ritonavir syrup is 80 mg/ml. Where larger volumes of syrup are required, the 100 mg ritonavir tablet may be an appropriate alternative.

Dosing tips for LPV/R

– For each ml of LPV/r syrup, add 0,75 ml of ritonavir syrup.
– For each tablet of LPV/r (100/25), add 1 ml of ritonavir syrup.
– For each tablet of LPV/r (200/50 mg), add 2 ml of ritonavir syrup.

Considerations at the end of TB treatment

The ART regimen adjustments made during TB treatment should be revised at the end of TB treatment to be in line with recommendations for non co-infected patients.

Important

- Wait until 2-4 weeks after the end of TB treatment before switching to a NVP containing regimen to ensure clearance of rifampicin and prevent any drug interaction.
- *If switching to NVP following a triple NRTI regimen: a lead in dose of NVP for 2 weeks is necessary.*

- *If switching to NVP following a LPV/R containing regimen:* maintaining LPV/r (stop additional ritonavir) for 4 weeks then stop LPV/r, and start NVP at lead in dose for 2 weeks, then increase to full dose NVP
- *If switching to NVP following an EFV containing regimen:* no 2 week lead in period is necessary. Start NVP at full dose.

Adverse effects of co-therapy with TB treatment and ART

Observing the timing between the start of each new medication and the onset of an adverse reaction can be a helpful way to identify the drug responsible. The grade tables for severity of drug toxicities can be found in Appendix E. Early diagnosis and management of mild adverse effects should be the goal, in order to prevent the development of more severe (grade 3 and 4) reactions.

Adverse effects	Likely ARV drug involved	Likely TB drug involved	Management
Peripheral Neuropathy *Early or late side effect*	D4T	Isoniazid	Pyridoxine: • Preventive therapy: 10 mg/ day • Treatment dose: 50 mg/day Consider alternative ARV if possible.
Hepatitis *Usually early side effect*	NVP EFV IP	Pyrazinamide Rifampicin Isoniazid	If symptomatic or ALAT toxicity of grade 3 or 4: STOP all drugs Once clinically resolved or ALAT < 2.5 × ULN, restart with TB therapy (refer to MSF *Tuberculosis* guidelines).
Gastrointestinal dysfunction Diarrhoea, abdominal pain *Early or late side effect*	All	All	Symptomatic management
Skin rash *Usually early side effect*	NVP EFV ABC (CTX)	Rifampicin Isoniazid Pyrazinamide	If grade 3 or 4 toxicity, STOP all drugs. Once resolved, reintroduce TB therapy first (refer to MSF *Tuberculosis* guidelines). *NVP and ABC can cause severe hypersensitivity reactions. In such cases, these drugs should not be restarted.

Adverse effects	Likely ARV drug involved	Likely TB drug involved	Management
Central nervous system dysfunction *Early or late side effect*	EFV	Isoniazid	Pyridoxine prevention and therapy (as above)
Anaemia *Usually early side effect*	AZT (CTX)	Rifampicin	Treat anaemia If grade 3 or 4 toxicity: • AZT suspected and refractory to treatment: use alternative NRTI. • CTX suspected and refractory to treatment: switch to dapsone.

2.3 Immune Reconstitution Inflammatory Syndrome (IRIS)

IRIS is a paradoxical reaction that can occur in patients with an underlying opportunistic infection and whose immunity is rapidly improving on ART. The patient usually presents clinically with either worsening symptoms of a known opportunistic infection, or the development of new symptoms suggesting a previously undiagnosed infection. It usually occurs within the first 8 weeks after ART initiation although it can manifest up to 6 months later.

In general, the following features should be present in order to diagnose IRIS:
- Underlying stage 3 or 4 conditions pre-ART,
- Low baseline CD4 count or percentage (usually less than 50 or < 10%),
- Onset within 6 months of starting ARVs, commonly within 8 weeks,
- Coincides with an improving immunity (extrapolated to a more than two fold CD4 increase in the first year),
- Transient acute events (e.g. respiratory tract infection, adverse drug reaction) have been either excluded or treated.

Common pathogens causing IRIS:
- TB
- MAC
- CMV
- *Cryptococcus neoformans*

} Clinical presentation will depend on causative and organ system colonized

- HCV or HBV
- Herpes simplex and herpes zoster

Management

- Continue ART unless very severe event.
- Treat underlying OI.
- Treat inflammatory syndrome:
  - Mild cases (common):
    NSAIDs (e.g. **Ibuprofen** PO: 30 mg/kg/day in 3 divided doses)
  - Severe cases (CNS symptoms, respiratory distress):
    prednisolone PO: 1 mg/kg BID for 7 days; then 1 mg/kg OD for 7 days, then 0.5 mg/kg OD for 7 days, then 0.25 mg/kg OD for 7 days; then stop.

2.4 Immunisation

Key points:

– The benefits of vaccinating HIV infected children, especially in a context with a high prevalence of vaccine-targeted diseases, are usually higher than associated risks.

– All HIV infected or exposed children should receive all EPI vaccines according to the recommended schedule (except BCG in children with confirmed HIV).

– Immunization is vital in HIV infected children up to 5 years of age. Therefore it is important to vaccinate them on time according to the EPI schedule, avoiding any unnecessary delays. All delayed or interrupted vaccination schedules must be completed as soon as possible. Seven contacts are needed to complete the entire protection

– Exceptions to the statement above are the following live attenuated vaccines (not applicable for Oral Polio Vaccine [OPV]):
  • BCG vaccine should not be given to children with confirmed HIV; or whose HIV infection status is unknown but who have signs or reported symptoms suggestive of HIV infection.
  • Measles and Yellow Fever vaccines should be postponed to those who are with a presumptive diagnosis of severe HIV disease or severely immune suppressed (CD4 < 20%).
  • Children who have been on ART for at least 3 months or CD4 count ≥ 20% should be vaccinated against measles. Also, they should be vaccinated against Yellow Fever if there is an outbreak situation.

– Always include information on vaccination in the clinical file of the child and systematically check that vaccination status is up to date.

Table 12 - Recommended EPI schedule for HIV infected or exposed children

Vaccine	Doses	Age (min interval between dose is 4 weeks)	Comments
BCG	1	At birth	*Contraindicated in children with confirmed HIV or clinical suspicion of HIV.* However, since HIV infection status is usually not known at birth, BCG should still be given at birth (or at least before 6 weeks of age) to infants in regions of high HIV/TB prevalence.
Hepatitis B	1	At birth	Within 24 hours
Polio	4	Dose 0: at birth up to 2 weeks Dose 1 to Dose 3: from 6 weeks	
DTP/Hib/HepB	3	From 6 weeks	

Vaccine	Doses	Age (min interval between dose is 4 weeks)	Comments
PCV	4	Dose 1 to Dose 3: from 6 weeks Booster: from 12 to 24 months	If child begins the scheme aged between 12 and 59 months: 2 doses should be administered (with minimum interval of 8 weeks between doses).
Measles	3	Dose 0: from 6 to 8 months Dose 1: from 9 to 11 months Dose 2: from 12 months	D0 dose is specific for exposed and HIV + infant as he has no or few mother's antibodies and is at higher risk to get measles. Avoid administration to those who are with a presumptive clinical diagnosis of severe HIV disease or in severely immune suppressed (CD4 < 20%).
Yellow fever	1	From 9 months	According to country EPI. It should not be administered to those who are with a presumptive diagnosis of severe HIV disease or severely immune suppressed (CD4 < 20%).
Meningo-A conjugated	1	From 12 months	Meningitis belt countries that have introduced the vaccine. Up to 29 years old.

Table 13 - Time schedule summary

Contact	Age	Vaccines
1	Birth	BCG + OPV0 + HepB (monovalent)
2	From 6 weeks	DTP/Hib/HepB1 + OPV1 + PCV1
3	From 10 weeks	DTP/Hib/HepB2 + OPV2 + PCV2
4	From 14 weeks	DTP/Hib/HepB3 + OPV3 + PCV3
5	From 6 to 8 months	Measles 0
6	From 9 months	Measles 1 + Yellow fever
7	From > 12 months	Measles 2 *(best between 15-18 months)* PCV Booster *(best between 12-18 months)* Meningo-A conjugated

2.5 Respiratory conditions

Condition	Causes	Clinical features	Management
Pneumonia ***At risk:*** *Any age* *Any CD4*	**Bacterial:** *Haemophilus influenza B*, Pneumococcus, Staphylococcus, Gram negatives Atypical (older age) **Viral:** RSV, CMV **Fungal:** PCP *Often presenting OI in young infants (see below)* Others - rare	**Acute onset of:** Cough Fever Fast breathing Coarse crackles often present on auscultation **Severe cases:** Cyanosis, hypoxemia (SaO_2 < 90%), nasal flaring, chest indrawing, grunting, tachypnoea, feeding difficulties in infants *Definition of tachypnoea:* Respiratory rate (RR) RR > 60 breath /min in children < 2 months RR > 50 breaths/min in children 2 to 11 months RR > 40 breaths/min in children 1 to 5 years **CXR:** Useful to differential bronchitis from pneumonia. May suggest TB, PCP or other pathologies. May identify an effusion/empyema.	**Non severe cases:** **Amoxicillin** PO: 100 mg/kg/day in 3 divided doses for 7 days *and consider PCP treatment*:* **cotrimoxazole** *PO: 40/8 mg/kg/dose 3×/day for 21 days* **Severe cases:** **ceftriaxone** IV or IM: 100 mg/kg OD +/- **cloxacillin** IV or IM: 100 mg/kg/day in 4 divided doses *(if S. aureus suspected)* *If improvement after 3-5 days of parenteral treatment, switch to oral drugs to complete 7-10 days of antibiotics.* *Refer to clinical guidelines for further details on antibiotics.* *and consider PCP treatment*:* **cotrimoxazole** *PO or IV(preferred): 40/8 mg/kg/dose 3×/day for 21 days* *+* **prednisolone** *PO: 1 mg/kg/dose 2×/day for 5 days, then 1 mg/kg OD for 5 days, then 0.5 mg/kg OD for 5 days* ** Presumptive PCP treatment for children < 1 year of age + older children with severe immune suppression and not on CTX prophylaxis. For all others, consider PCP if poor response to standard treatment after 48 hours.* **For non severe cases treated as outpatients:** advise carer to return with the child if no improvement after 48 hours of antibiotics. **For all children:** if poor response to treatment after 1 week, consider TB treatment.
Tuberculosis	**COMMON IN CHILDREN LIVING WITH HIV** **For detailed information and recommendations, refer to Part 2, Chapter 2, *Tuberculosis and isoniazid preventive therapy*.**		
Pnemocystis *Jiroveci Pneumonia* (PCP) *Peak age 2-6 months* *Associated with Low CD4*	*Pneumocystis jiroveci*	Respiratory distress – fast breathing, hypoxia Acute or sub acute onset Fever can be high but often afebrile Non productive cough Feeding difficulties in infants Chest usually clear on auscultation Hypoxemia **CXR:** Diffuse interstitial infiltration, hyperinflation, pneumothorax or normal (20%). Effusion very uncommon with PCP	Oxygen **cotrimoxazole** PO or IV: 40/8 mg/kg/dose 3×/day for 21 days + For severe cases: **prednisolone** PO: 1 mg/kg/dose 2×/day for 5 days, then 1 mg/kg OD for 5 days, then 0.5 mg/kg OD for 5 days Cotrimoxazole prophylaxis after treatment completion

Condition	Causes	Clinical features	Management
Lymphoid Interstitial Pneumonitis (LIP) *Children > 3 years old*	Not an OI Lympho-proliferative infiltrate	Slow onset: cough and dyspnoea, hypoxemia (SaO_2 < 92%) Often enlarged lymph nodes, spleen and chronic parotitis May find wheeze, clubbing, signs of right heart failure **CXR:** Bilateral reticulonodular infiltrate. Similar appearance to miliary TB – but more irregular distribution and clinically distinct: *child with LIP may look well, child with TB is usually more ill with fever and weight loss.*	Good response to ART Symptomatic management as needed as an adjunct to ART • Bronchodilators • Steroids may be useful. If no observed response after 1 month, discontinue by weaning gradually over 2 months.
Bronchiectasis	Result of previous lung disease	Chronic, recurrent cough with sputum production Clubbing **CXR:** Honeycombing' usually lower lobes	Broad spectrum antibiotics and symptomatic therapy (e.g. oxygen) during exacerbations Physiotherapy
Chronic suppurative otitis media	*Pseudomonas spp* *Proteus spp* *S. aureus*	Persistent discharge from ear for > 2 weeks Pain and fever absent if localised Ear drum perforation visible with otoscope Mastoiditis: painful swelling behind affected ear, fever Other possible complications: brain abscess, meningitis (refer to paediatric guidelines)	Regular gentle ear cleaning/irrigation – refer to paediatric guidelines Children > 1 year: **ciprofloxacin** ear drops (0.3%) – 2-3 drops twice daily until no more discharge (max 4 weeks) Mastoiditis: **ceftriaxone** IV: 40 mg/kg 2x/day + **clindamycin**: 10 mg/kg/dose 3x/day + **ciprofloxacin** PO: 15m g/kg/dose 2x/day for 15 days (covers *Pseudomonas*)

- Other respiratory infections: Mixed infections (common), MAC, Cryptococcosis, Penicilliosis or Meliodosis (latter two in older children in SE Asia).
- Other non-infectious causes: Cardiac failure (rapid breathing, elevated jugular venous pressure, absence of fever, CXR: cardiomegaly), Severe anaemia, Kaposi's Sarcoma.

2.6 Systemic conditions

Condition	Causes	Clinical features	Management
Sepsis *Important cause of mortality*	*Pneumococcus* *H. influenzae* Non typhoidal salmonella *Staphylococcus aureus* Gram-negative enterics (*E.coli* and *Klebsiella spp*)	Non specific signs depending on stage +/- fever or hypothermia +/- tachycardia or bradycardia +/- tachypnoea or bradypnoea **Signs of severity** • Severe respiratory distress, impaired consciousness, petechiae/purpura, signs of peritonitis, meningitis or cellulitis • *Shock* – 2 of following 4: cold peripheries, fast pulse, capillary refill > 2 secs, weak or absent pulse WBC may be high (sometimes low) Gram stain or culture from a sterile site may be positive (blood, CSF, urine). ***However, the diagnosis is usually CLINICAL.***	Treat shock if present (see paediatric guidelines). Test for malaria and treat if indicated. Oxygen if signs of respiratory distress. Keep SaO_2 > 90%. Insert IV line. If not possible to gain access, use intraosseous. Check blood glucose level/Treat hypoglycemia. Assess and maintain hydration – monitor urine output if possible. **Empirical antibiotic therapy** **ceftriaxone** IV or IM: 100 mg/kg OD for a minimum of 5 days *When no fever for at least one day, and tolerates feeding - treat orally with* **amoxi-clav** *80 mg/kg/day in 3 divided doses to complete 7-10 days of antibiotics.* *If no improvement after 48hrs, add second antibiotic (refer to paediatric guidelines).* *Consider* ***cotrimoxazole*** *in children under 1 year old with respiratory symptoms or in severely immunosuppressed older children not on CTX prophylaxis (see PCP treatment).* *Consider* ***cloxacillin*** *if suspicion of staphylococcal sepsis.*
Malaria	*P. falciparum* *P. vivax* *P. ovale* *P. malariae*	Usually: fever, lethargy, vomiting **However:** *In endemic areas, consider malaria in any unwell child.* Look for signs of severe malaria – refer to MSF *Clinical guidelines* for details. Diagnosis: rapid test, clinical or blood film	**REFER TO MSF *CLINICAL GUIDELINES*** *Note*: Treatment with Artemether/Lumefantrine is preferred for children on EFV or AZT due to possible increased risk of adverse effects with ASAQ.

Condition	Causes	Clinical features	Management
Mycobacterium avium complex **(MAC)** *Less commonly diagnosed in Africa* *Associated with low CD4*	*Mycobacterium avium complex*	**Symptoms:** Weight loss, fatigue, unremitting fever, chronic diarrhoea, wasting, abdominal pain **Examination:** Enlarged lymph nodes, hepatomegaly, anaemia, unresolving pulmonary infiltrate **Investigations:** AFB and culture from sterile site (blood, bone marrow, lymph node) Often not available, and takes >2 weeks for result Hb, WCC (anaemia, neutropaenia, thrombocytopaenia) Biochemistry (raised Alkaline Phosphatase, LDH and transaminases) **Diagnosis of exclusion:** Suspected TB (especially EPTB) not responding to TB treatment with supporting lab findings	**Antibiotic therapy** At least 2 drugs: **clarithromycin** or **azithromycin** plus **ethambutol** +/- **rifabutin** **clarithromycin** (preferred): 7.5-12.5 mg/kg/dose BID (max 500 mg). Use higher dose range if co-administered with EFV. **azithromycin** (less effective, but fewer drug interactions): 10-12 mg/kg OD (max 500 mg) **ethambutol**: 20 mg/kg OD **rifabutin** (if > 5 years): 10-20 mg/kg OD (max 300 mg) Patients should improve after 4-6 weeks on treatment. Treatment should last at least 12 months. Secondary prophylaxis is necessary with either **azithromycin** (5 mg/kg OD) or **clarithromycin** (7.5 mg/kg/dose BID) until CD4 is above severe immune-suppression level at two separate measurements at least 6 months apart. ART is indicated and should be initiated as soon as the clinical condition is stable on MAC treatment to minimize the risk of IRIS.

- Other important systemic conditions to consider: Miliary TB.

2.7 Neurological conditions

<table>
<tr><th>Condition</th><th>Causes</th><th>Clinical features</th><th>Management</th></tr>
<tr>
<td>Meningitis and Meningo-encephalitis</td>
<td>Bacteria:
In all children
Pneumococcus, Meningococcus, H. influenza B
In children < 2 months
E.coli, Group B Strep, Listeria
Mycobacteria:
tuberculosis
Viruses:
mumps, herpes zoster
Fungal:
Cryptococcus neoformans especially with low CD4</td>
<td>Fever, headache, lethargy, irritability, abnormal cry, poor feeding, vomiting, neck stiffness, convulsions, bulging fontanelle, coma

CSF findings (Note: these are ranges; exceptions occur in clinical practice)
<table>
<tr><th>Diagnosis</th><th>CSF aspect</th><th>WBC (µl)</th><th>Protein (mg/dl)</th><th>Glucose (mg/dl)</th></tr>
<tr><td>Normal</td><td>Clear</td><td>< 5</td><td>< 40</td><td>> 2/3 of blood glucose</td></tr>
<tr><td>Bacterial</td><td>Cloudy, Turbid</td><td>100-20000 mainly neutrophils</td><td>100-500 Pandy pos</td><td>Very low < 10</td></tr>
<tr><td>TB meningitis</td><td>Clair or yellowish AFB + (rare)</td><td>< 500 mainly lymphocytes</td><td>> 250 Pandy pos</td><td>Low < 45</td></tr>
<tr><td>Crypto</td><td>Clear Indian ink + +/- Crypto Ag +</td><td>< 800 mainly lymphocytes</td><td>20-500 Pandy neg</td><td>Low < 45</td></tr>
<tr><td>Viral meningitis</td><td>Clear</td><td>10-700 mainly lymphocytes</td><td>20-100 Pandy pos or neg</td><td>N</td></tr>
</table>
</td>
<td>Test for malaria and treat if indicated
Assess for shock.
Check blood glucose: if < 45 mg/dl give glucose 10% 5 ml/kg IV.

Bacterial meningitis
Children < 3 months: refer to Clinical guidelines
Children > 3 months: ceftriaxone IM or IV: 100 mg/kg OD for 10 days

TB meningitis
Refer to MSF Tuberculosis guideline.

Cryptococcal meningitis
amphotericin B IV: 1 mg/kg OD
+ fluconazole PO 6-12 mg/kg/dose OD for 14 days
(Caution in drug preparation and administration. Read and follow instructions carefully.)

then fluconazole alone PO 6-12 mg/kg/dose OD for 8-10 weeks

Serial CSF taps should be done if ↑ICP (headache, vomiting, visual disturbance) to keep pressure < 20 cmH2O. Taps - remove 1 ml/kg. Max 25 ml per puncture.

Secondary prophylaxis: fluconazole 3-5 mg/kg/dose OD for at least 12 months and at least 6 months over severe immune-suppression threshold</td>
</tr>
</table>

Condition	Causes	Clinical features	Management
HIV encephalopathy *Develops during first 2 years of life*	Direct HIV virus effect	***At least one of the following, progressing over two months in the absence of another illness:*** • Loss or failure to attain developmental milestones, loss of intellectual capacity • Microcephaly: head circumference < 5th percentile for age, or stagnation and failure of head circumference to grow • Motor deficits: symmetrical spastic paresis, increased reflexes (pyramidal tract motor deficit), gait disturbance or ataxia. Facial motor signs such as abnormal eye movements **CLINICAL DIAGNOSIS**	**ART** Suppresses viral replication and reduces the risk of CNS invasion by HIV. May reduce viral replication within the brain itself and lead to clinical improvement. **Physiotherapy** If available and clinically indicated **Pain management** If clinically indicated
Focal deficits	**Stroke** due to HIV associated vasculitis or coagulopathy **CNS tumour:** Lymphoma **Cerebral toxoplasmosis**	**Stroke** Sudden onset, no signs of raised intracranial pressure (ICP) **CNS tumour** Sudden or progressive onset with signs of raised ICP (severe headache, vomiting) and no improvement after at least 10 days of treatment for toxoplasmosis **Toxoplasmosis** Rare in children. May occur in severely immune suppressed children not on CTX. May or may not have signs of raised ICP.	**Stroke** Supportive treatment **CNS tumour** Supportive treatment including steroids if signs of raised ICP **Toxoplasmosis** **pyrimethamine** + **sulfadiazine** + **folic acid** for 6 weeks *or* **cotrimoxazole** high dose for 6 weeks (refer to *Clinical guidelines*) If signs of raised ICP: **prednisolone**, high dose, gradually weaned Treatment response is expected within 10 days. Secondary prophylaxis is needed. *In settings where neuroimaging is not available, consider empiric trial of CTX for all HIV children who present with a focal deficit, with or without raised ICP.*
Peripheral neuropathies	HIV virus Drugs (ARV, TB)	Paresthesia, pain, progressive weakness and loss of motor milestones	Adapt ART regimen to avoid causative drugs (eg switch D4T for AZT). If on Isoniazid, increase pyridoxine dose to 50 mg/day until symptoms resolve.

2.8 Gastrointestinal conditions

Condition	Common causes	Clinical features	Management
Oral thrush +/- Oesophagitis	Candida albicans	**Oral candidiasis** Creamy white lace-like patches inside the cheeks and on lips that do not scrape off easily (differentiate from milk residue). Can also appear as red patches and as angular cheilitis **Oesophageal candidiasis** > 90% of cases associated with oral thrush but can have oesophageal disease without oral signs Difficulty swallowing -often manifests as vomiting, painful swallowing, and retrosternal pain	**Oral candidiasis** **nystatin** PO: 100 000 IU/ml 4 ml 4 x/day for 2 weeks or **miconazole** gum patch: apply 1 patch/day to the gums for 7 days **Oesophageal candidiasis** **fluconazole** PO: 3-6 mg/kg/dose OD for 14-21 days Nutritional support and regular pain relief **Prevention** In recurrent cases of oesophageal candida: **fluconazole** prophylaxis 3 mg/kg/dose OD (max 200 mg) until CD4 count is restored.
Acute diarrhoea	**Watery diarrhoea:** Viruses, Cholera in high risk zones, *Salmonella*, Enterotoxigenic *E Coli*, *Giardia* or other infections (eg respiratory infections or malaria) **Bloody diarrhoea + fever** *Salmonella*, *Shigella*, Enteroinvasive or Enterohaemorraghic *E.Coli*, *Yersinia* **Bloody diarrhoea no fever** *Entameoba*, *Campylobacter*	More than 3 stools per day - bloody or watery (verified) Fever: can be present in both bacterial or viral infections Dehydration – assess severity: recent weight loss, reduced consciousness, sunken eyes, reduced skin tone, thirst	Rehydration: IV or intraosseous if in shock or unconscious. Otherwise, oral rehydration **Acute bloody diarrhoea** **azithromycin** PO: 20 mg/kg OD for 5 days or **ciprofloxacin** PO: 30 mg/kg/day in 2 divided doses for 7 days If amoebiasis suspected: **tinidazole** or **metronidazole** PO (see *Clinical guidelines*) If no blood or fever but suspicion of cholera or giardiasis, treat accordingly. **zinc** *(not necessary with Plumpy Nut)* < 6 months: 10 mg OD for 10 days 6 months- 5 years: 20mg OD for 10 days Provide nutritional support. No anti-diarrhoeal drugs in children (little benefit and may be harmful), especially in acute diarrhoea.

Condition	Common causes	Clinical features	Management
Persistent diarrhoea *> 14 days* or **Chronic diarrhoea** *> 28 days*	**Viruses** HIV, CMV **Bacteria** MAC **Protozoa** *Giardia, Entamoeba, Cryptosporidium, Isospora* **Helminths** Hookworm, Whipworm, Strongyloides	More than 3 stools per day - bloody or watery Dehydration – assess severity: recent weight loss, reduced consciousness, sunken eyes, reduced skin tone, thirst Malnutrition and wasting Stool analysis on three separate samples If available: WBC and CD4 Abdominal ultrasound: enlarged intra abdominal lymph nodes in MAC	Rehydration: IV or intraosseous if in shock or unconscious. Otherwise oral rehydration. *Chronic diarrhea has high associated mortality in HIV patients. Urgent ART is needed.* **If no pathogen identified, antibiotic trial:** **cotrimoxazole** PO: 40/8 mg/kg/dose 3x/day + **metronidazole** PO: 45 mg /kg/day in 3 divided doses for 7 days (or tinidazole) **If no response or suspicion of bacterial infection** (bloody stools, fever): **ciprofloxacin**: 30 mg/kg/day in 2 divided doses for 7 days **If *Isospora belli* confirmed by stool analysis:** **cotrimoxazole**: 80/16 mg/kg/day in 2 divided doses for 10 days, followed by 50/10 mg/kg/day in 2 divided doses for 3 weeks **If suspicion of helminthiasis:** **albendazole** PO Children > 6 months but < 10 kg: 200 mg OD for 3 days Children > 6 months: 400 mg OD for 3 days **If giardiasis:** **tinidazole** or **metronidazole**: refer to *Clinical guidelines* **zinc** *(not necessary with PPN)* < 6 months: 10 mg OD for 10 days 6 months - 5 years: 20 mg OD for 10 days Nutritional support Antidiarrhoeal drugs: *only if no antibiotic response, not for children < 2 yrs, max 10 days* **loperamide** Children 2 to 5 years: 3 mg/day in 3 divided doses Children 6 to 8 years: 4 mg/day in 2 doses Children > 8 years: 6 mg/day in 3 doses

Oral hairy leukoplakia, apthous ulcers, gum disease and tooth decay are also common. Oral hygiene is important to prevent and treat these conditions. Kaposi's sarcoma may present with mouth lesions.

2.9 Skin conditions

Condition	Common causes	Clinical features	Management
Varicella zoster *Chicken pox* *Peak 5-10 years*	Varicella zoster virus *Primary infection*	Prodromal symptoms for 2 days Then vesicular eruption extending rapidly all over body Pruritus and fever are common. Highly contagious from day 2 before the rash to day 7 after the rash. Often severe in immuno compromised children • Skin infections • Chronic skin lesions • Pneumonia • Encephalitis • Bacterial sepsis	**Uncomplicated varicella** **paracetamol** PO: 60 mg/kg/day in 3-4 divided doses +/- **ibuprofen** PO: 30 mg/kg/day in 3 divided doses If pruritus: apply locally **calamine** 3 times a day. **Complicated varicella** **If the child looks toxic:** fast breathing, eye involvement, lethargic or comatose **ampicillin** IV or IM: 100 mg/kg/day in 3 divided doses *plus* **cloxacillin** IV or IM: 75 mg/kg/day in 3 divided doses *plus* **aciclovir** IV: 15-30 mg/kg/day in 3 infusions (every 8 hours) for 7 days **In less severe cases:** **amoxicillin** PO: 100 mg/kg/day in 3 divided doses *plus* **cloxacillin** PO: 50 mg/kg/day in 2 divided doses
Herpes zoster *Shingles*	Varicella zoster virus *Reactivation*	Sensory prodrome in dermatomal area Then vesicular eruption May be disseminated (not limited to dermatome). Can cause varicella in non-immunised contacts.	Local treatment, refer to *Clinical guidelines*. For necrotic, extensive forms, eruption on the face, ophthalmic zoster, add **aciclovir** IV: 15-30 mg/kg/day in 3 divided doses for 7 days within 48 hours of the onset of lesions. Pain relief: **paracetamol** PO: 60 mg/kg/day in 3-4 divided doses +/- **ibuprofen** PO: 30 mg/kg/day in 3 divided doses +/- **codeine**: 3 mg/kg/day in 3 divided doses Post herpetic neuralgia: **carbamazepine**: 10 mg/kg/day in 2 divided doses (max 200 mg) for 10 days
Oral and oesophageal herpes	*Herpes simplex* virus	PPrimary infection: fever, mouth pain, oral ulcers and grouped vesicles, unable to feed, enlarged submandibular lymph nodes Reactivation usually less severe May have bacterial super infection. May become chronic in immuno-compromised children.	**paracetamol** PO: 60 mg/kg/day in 3-4 divided doses +/- **ibuprofen** PO: 30 mg/kg/day in 3 divided doses Nutritional support: frequent feedings, nasogastric tube if necessary If recurrent or extensive forms affecting oesophagus, add **aciclovir** PO within 96 hours following onset of lesions: Children < 2 years: 200 mg 5 times/day for 7 days Children > 2 years: 400 mg 5 times/day for 7 days

Condition	Common causes	Clinical features	Management
Warts	Human papilloma virus	Multiple papules Can be flat or raised Commonly hands, face feet and genitals	No effective topical therapy Usually resolves spontaneously or with improved immune status. Individual lesions can be excised if troublesome.
Superficial fungal infections	Candida albicans Dermatophytes	**Candidiasis** Wet, itchy red lesions in skin folds or genital area ('diaper rash') Can be severe in immuno-compromised children **Vaginitis** Itching, burning and white discharge **Dermatophytoses** Tinea of the scalp: scaly plaques often causing hair loss Tinea of the skin and feet: annular plaques with advancing red borders Nail infections are common and cause disfigurement.	**Candidiasis**: **miconazole** 2% cream twice daily or **clotrimazole** 1% cream for 7-10 days **Vaginitis**: **clotrimazole** pessary 200 mg nocte for 3 days. Fluconazole if severe. **Dermatophytoses**: Keep lesions clean and dry. Apply **Whitfields ointment** 3 times per day for 2-3 weeks. Oral Griseofulvin may be required for severe cases (refer to *Clinical guidelines*). Nail infections are difficult to treat; 12-18 months of oral treatment needed.
Molluscum contagiosum	*Molluscum contagiosum* virus	Numerous dome shaped papules Thick white content Central umbilication Often on the face but can be disseminated especially in immuno- compromised children. No associated systemic symptoms like fever, headache or lethargy. If these are present: *suspect Crypto-coccosis or Penicilliosis (in asia).*	No effective topical therapy Usually resolves spontaneously or with improved immune status. Individual lesions can be excised if troublesome.
Bacterial skin infections *Impetigo, folliculitis, abscesses, cellulitis*	*Staphylcoccus aureus* *Streptococci*	Can be disseminated. Usually non pruritic. **Impetigo** Crusty yellow and/or purulent, moist erosive skin lesions. Frequently around mouth and nose area **Others** Skin redness, swelling and tenderness +/- pus	Local treatment (impetigo): Keep clean and dry. Systemic treatment: **cloxacillin** PO: 50 mg/kg/day in 2 divided doses for 10 days or **erythromycin** PO: 30-50 mg/kg/day in 2-3 divided doses for 10 days Incision and drainage may be required for abscesses

Condition	Common causes	Clinical features	Management
Scabies	*Scabies sarcoptei* (mite)	Red papules and scales. Itch +++. Worse at night Usually in finger webs, underarms, waist, groin, feet and ankles. Sometimes on thighs and buttocks. Spares the face and scalp area. Burrows in finger web visible in typical cases Hyperkeratosis lesions in knees or buttocks (chronic cases) Frequently infected: impetigo Severe cases (Norwegian or 'crusted scabies'): Especially in immuno-compromised children Widespread scaly plaques, even on scalp, less prominent itch	**5% permethrin** is preferred (not for children < 2 months old) • One application with 8 hour contact time then washed off. • 2nd application 7 days later reduces the risk of failure. If permethrin is not available: **topical benzyl benzoate** *Note: this must be diluted for children - see Clinical guidelines for details.* If bacterial super infection: **cloxacillin** PO: 50 mg/kg/day in 2 divided doses for 10 days Screen all the family and contacts. Treat all household members at the same time. In severe cases: **ivermectin** (NOT children < 15 kg): 15-25 kg: 3 mg 25- 45 kg: 6 mg on an empty stomach Plus topical treatment as above Treatment may need to be repeated each week for 2-3weeks until clinical response.
Papular pruritic eruptions	*Cause not fully understood* *Likely related to insect bites*	Itchy skin eruption Usually symmetrical affecting extremities, but also the trunk Common with low CD4 counts	Antihistamines If in doubt, treat for scabies. Topical steroids - if no response to scabies treatment. Usually disappears after immune recovery on HAART.

Note: the management of Kaposi's sarcoma in children is not covered in this guideline. If there is a suspicion of Kaposi's sarcoma in a child, please contact your medical advisor.

Appendices

Appendix A. WHO clinical staging of HIV disease in children

Clinical Stage 1

- Asymptomatic
- Persistent generalized lymphadenopathy

Clinical Stage 2

- Unexplained persistent hepatosplenomegaly
- Papular pruritic eruptions
- Extensive wart virus infection
- Extensive *Molluscum contagiosum*
- Recurrent oral ulcerations
- Unexplained persistent parotid enlargement
- Lineal gingival erythema
- Herpes Zoster
- Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis)
- Fungal nail infection

Clinical Stage 3

- Unexplained moderate malnutrition not adequately responding to standard therapy
- Unexplained persistent diarrhoea (14 days or more)
- Unexplained persistent fever (above 37.5 intermittent or constant, for longer than one month)
- Persistent oral candidiasis (after first 6-8 weeks of life)
- Oral hairy leukoplakia
- Acute necrotizing ulcerative gingivitis/periodontitis
- Lymph node TB
- Pulmonary tuberculosis
- Severe recurrent bacterial pneumonia
- Symptomatic lymphoid interstitial pneumonitis (LIP)
- Chronic HIV-associated lung disease including bronchioectasis
- Unexplained anaemia (< 8 g/dl), neutropenia (< 500/mm^3) or chronic thrombocytopenia (< 50,000/mm^3)

Clinical Stage 4

- Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy
- *Pneumocystis* pneumonia
- Recurrent severe presumed bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis but excluding pneumonia)
- Chronic *Herpes simplex* infection; (orolabial or cutaneous of more than one month's duration or visceral at any site)
- Extrapulmonary tuberculosis

- Kaposi Sarcoma
- Oesophageal candidiasis (or candida of trachea, bronchi or lungs)
- Central nervous system toxoplasmosis (outside the neonatal period)
- HIV encephalopathy
- Cytomegalovirus (CMV) infection, retinitis or CMV infection affecting another organ, with onset at age over 1 month
- Extrapulmonary cryptococcosis including meningitis
- Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidioidomycosis, penicilliosis)
- Chronic cryptosporidiosis (with diarrhoea)
- Chronic isosporiasis
- Disseminated non-tuberculous mycobacteria infection
- Acquired HIV associated rectal fistula
- Cerebral or B cell non-Hodgkin lymphoma
- Progressive multifocal leukoencephalopathy
- HIV associated cardiomyopathy or nephropathy

For detailed explanations of each of these conditions, please refer to Annex D of the 2010 WHO guideline: *Antiretroviral therapy for HIV infection in infants and children: towards universal access*.

Appendix B. Paediatric ARV dosing table

Drug	Strength of tablet or liquid	3-5.9 kg	6-9.9 kg	10-13.9 kg	14-19.9 kg	20-24.9 kg	Strength Adult tablet	25-34.9 kg
AZT/3TC/NVP	60/30/50 mg tab (dispersible)	1 tab BD	1.5 tab BD	2 tab BD	2.5 tab BD	3 cp 2x/jour	300/150/200 mg tab	1 tab BD
D4T/3TC/NVP	6/30/50 mg tab (dispersible)	1 tab BD	1.5 tab BD	2 tab BD	2.5 tab BD	3 tab BD		4 tab BD
ABC/3TC/AZT	60/30/60 mg tab (dispersible)	1 tab BD	1.5 tab BD	2 tab BD	2.5 tab BD	3 tab BD	300/300/150 mg tab	1 tab BD
AZT/3TC	60/30 mg tab (dispersible)	1 tab BD	1.5 tab BD	2 tab BD	2.5 tab BD	3 tab BD	300/150 mg tab	1 tab BD
D4T/3TC	6/30 mg tab (dispersible)	1 tab BD	1.5 tab BD	2 tab BD	2.5 tab BD	3 tab BD	30/150 mg tab	1 tab BD
ABC/3TC[a]	60/30 mg tab (dispersible)	2 tab OD	3 tab OD	4 tab OD	5 tab OD	6 tab OD	600/300 mg tab	1 tab OD
3TC	Liquid 10 mg/ml	3 ml BD	4 ml BD	6 ml BD				
	30 mg tab (dispersible)	1 tab BD	1.5 tab BD	2 tab BD	2.5 tab BD	3 tab BD	150 mg tab	1 tab BD
AZT	Liquid 10 mg/ml	6 ml BD	9 ml BD	12 ml BD				
	60 mg tab (dispersible)	1 tab BD	1.5 tab BD	2 tab BD	2.5 tab BD	3 tab BD	300 mg tab	1 tab BD
ABC	Liquid 20 mg/ml	3 ml BD	4 ml BD	6 ml BD				
	60 mg tab (dispersible)	1 tab BD	1.5 tab BD	2 tab BD	2.5 tab BD	3 tab BD	300 mg tab	1 tab BD

Drug	Strength of tablet or liquid	3-5.9 kg	6-9.9 kg	10-13.9 kg	14-19.9 kg	20-24.9 kg	Strength Adult tablet	25-34.9 kg
NVP[b]	Liquid 10 mg/ml	5 ml BD	8 ml BD	10 ml BD				
	50 mg tab (dispersible)	1 tab BD	1.5 tab BD	2 tab BD	2.5 tab BD	3 tab BD	200 mg tab	1 tab BD
EFV	200 mg tab (scored)			1 tab OD	1.5 tab OD	1.5 tab OD	200 mg tab	2 tab OD
	600 mg tab (double-scored)[c]			1/3	1/2	2/3	600 mg tab	2/3
LPV/r[d]	Liquid 80/20 mg/ml	1 ml BD	1.5 ml BD	2 ml BD	2.5 ml BD	3 ml BD		
	100/25 mg tab			2 tab AM + 1 tab PMi	2 tab BD	2 tab BD	100/25 mg tab	3 tab BD
TDF	40 mg/scoop of oral powder			3			300 mg tab	1 tab (200 mg)[e] or 1 tab (300 mg) OD
	150 mg or 200 mg tab				1 tab (150 mg)	1 tab (200 mg)		

[a] The ABC 120 mg/3TC 60 mg formulation should be soon available. Refer to your HIV advisor.
[b] Dose for HIV treatment. Use NVP liquid formulation for PMTCT and see *PMTCT* guideline for dosing.
[c] The double-scored tablet has 2 score lines on one side of the tablet and one score line on the other side, enabling the tablet to be divided into thirds and halves as needed.
[d] LPV/r heat-stable tablet must be swallowed whole and not split or crushed. Liquid formulation requires cold chain for transport and storage.
[e] 200 mg TDF tablets should be used for weight 25-29.9 kg and 300 mg tablets for 30-34.9 kg.

FDC ATV/r exist only for adult formulation (300/100 mg). Paediatric ATV 150 mg/rtv 100 mg, ATV 200 mg/rtv 100 mg do not exist yet as FDC. This is the reason why we favor the use of LPV/r in children until pediatrics formulations of FDC ATV/r are available.
However in some particular cases (ie: side effect of Lpv/r, bad adherence to a twice a day regimen), it can be useful to use the ATV. Refer then to the dosage below:

Drug	Strength of tablet or liquid	3-5.9 kg	6-9.9 kg	10-13.9 kg	14-19.9 kg	20-35 kg	Strength Adult tablet	> 35 kg
ATV (to boost with ritonavir)	150 mg capsule 200 mg capsule				1 capsule 150 mg + 1 tab rtv 100 mg OD	1 capsule 200 mg + 1 tab rtv 100 mg OD	300/100 mg tab	tab OD

Dosing table for initial 2-week lead in period with once daily NVP based regimen

Drug	Strength of tablet or liquid	3-5.9 kg	6-9.9 kg	10-13.9 kg	14-19.9 kg	20-24.9 kg	Strength Adult tablet	25-34.9 kg
AZT/3TC/NVP	60/30/50 mg tab (dispersible)	1 tab OD + 1 tab OD	1.5 tab OD + 1.5 tab OD	2 tab OD + 2 tab OD	2.5 tab OD + 2.5 tab OD	3 tab OD + 3 tab OD	300/150/200 mg tab	1 tab OD + 1 tab OD
AZT/3TC	60/30 mg tab (dispersible)						300/150 mg tab	
D4T/3TC/NVP	6/30/50 mg tab (dispersible)	1 tab OD + 1 tab OD	1.5 tab OD + 1.5 tab OD	2 tab OD + 2 tab OD	2.5 tab OD + 2.5 tab OD	3 tab OD + 3 tab OD	30/150/200 mg tab	1 tab OD + 1 tab OD
D4T/3TC	6/30 mg tab (dispersible)						30/150 mg tab	

Notes:
– Use FDCs and dispersible tablets wherever possible.
– D4T should be phased out and as soon as an alternative NRTI is available, switch from d4T.

Appendix C.1. Isoniazid preventive therapy – *paediatric*

Name . . . . . Age . . . . .

ID number-child . . . . . ID number-mother . . . . .

TB IPT start date . . . . .

TB IPT end date . . . . .

Indication:

Systematic ☐ Contact* ☐ Post TB treatment prophylaxis ☐

See over for TB IPT recommendations

* Contact = living in the same household, or in close and regular contact with any known or suspected TB case, within the last 12 months

NB:
Before starting IPT, confirm that the child has NO POOR WEIGHT GAIN, NO CURRENT COUGH and NO FEVER.
IPT should not be given to children with active hepatitis or peripheral neuropathy.
Children on IPT should be clinically reviewed at least monthly.

TB IPT monthly follow up chart

Date	Weight (kg)	Weight loss Yes/no	Temp. > 38°C Yes/no	Cough Yes/no	Asymptomatic (A)[a] or Suspect active TB (S)[b]	Isoniazid dosage and quantity prescribed	B6 prescribed[c]	Date of next appointment	Clinician signature

[a] If any signs of isoniazid toxicity especially jaundice or peripheral neuropathy – refer for urgent medical review.
[b] If active TB is suspected, refer to the tuberculosis diagnostic tool.
[c] All children on TB IPT should receive 10 mg of B6.

IPT recommandations

Always ensure symptom screening is negative.

Systematic

All HIV-exposed and HIV-infected children between the ages of 12 months and 15 years, regardless of contact history: 6 months of IPT to be repeated every 3 years*.

Contact**

All HIV-exposed and HIV-infected children < 15 years of age, having had contact with any case of TB: 6 months of IPT.

Post TB treatment

All HIV-exposed and HIV-infected children < 15 years of age: 6 months of IPT immediately following the successful completion of TB treatment.

* Exposed infants confirmed HIV negative (> 18 months of age and/or not breastfed for > 6 weeks) do not require repeat IPT unless a contact case.

** Contact = living in the same household, or in close and regular contact with any known or suspected TB case, within the last 12 months.

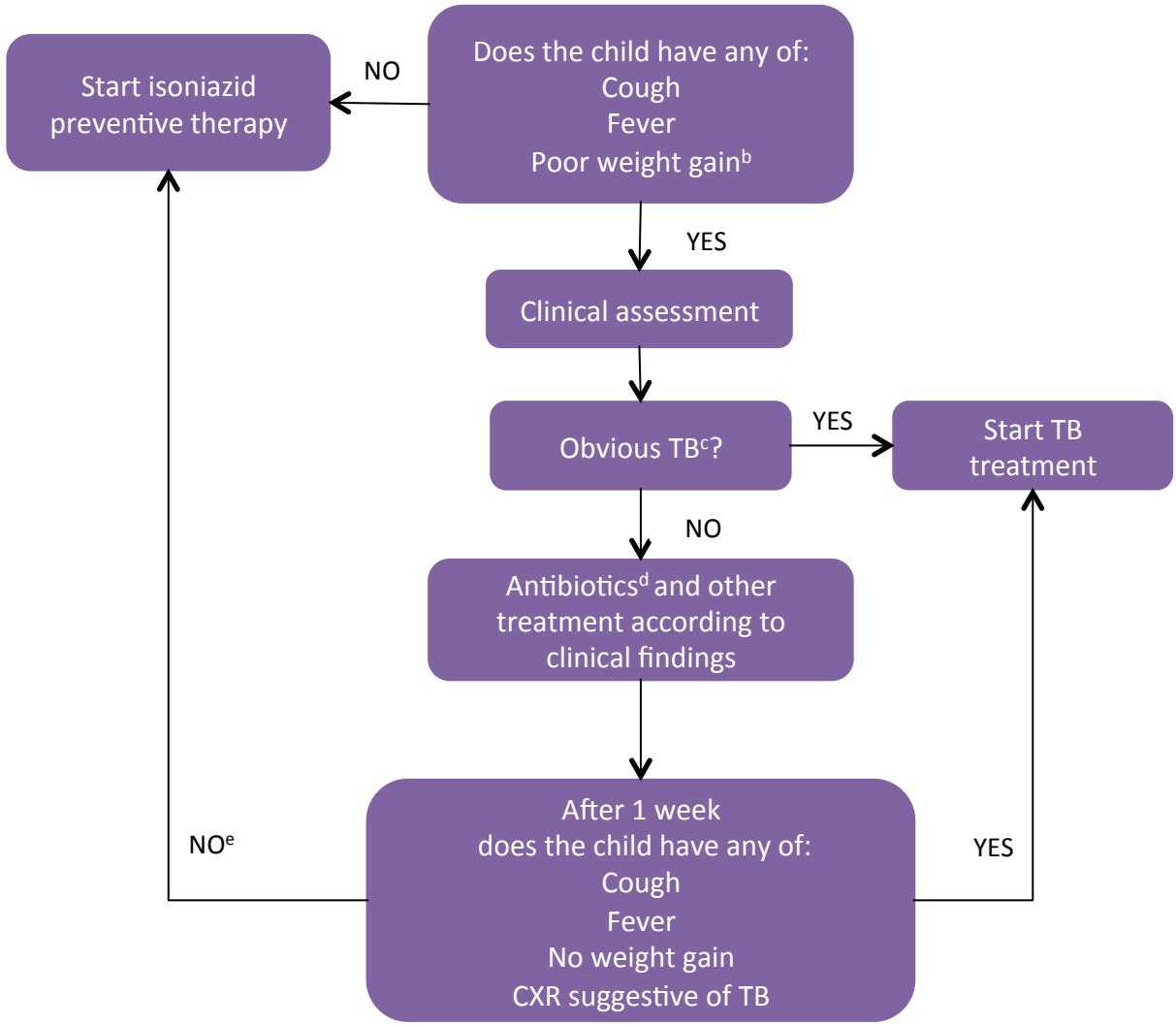
Isoniazid dosing in newborns and children (10 mg/kg)

Weight in kg	< 3.5	3.5 - 5	6 - 9	10 - 15	16 - 20	21 - 25	> 25
Tablet H 100 mg	-	1/2	1	1 1/2	2	2 1/2	3*
Syrup H 50 mg/5 ml	3 ml	5 ml	9 ml	-	-	-	-

* or 1 adult tablet

Appendix C.2. Paediatric TB diagnostic algorithms

Paediatric TB diagnostic algorithm 1:
HIV exposed or infected child with contact of a TB case[a]



[a] Contact: child living in the same household or in close and regular contact with any known or suspected TB case in the last 12 months.

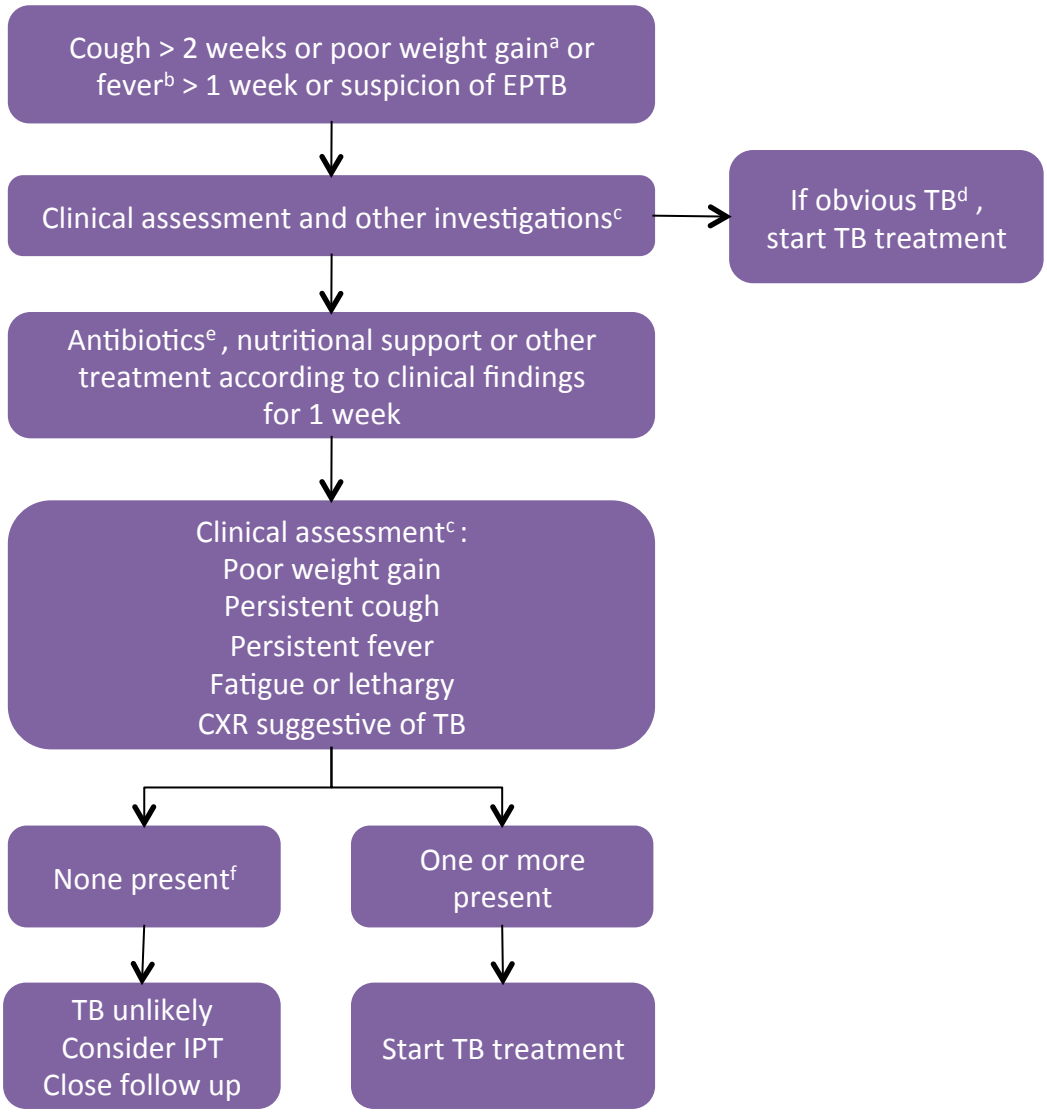
[b] Acute malnutrition or flattening of growth curve.

[c] Examples of "obvious TB" may include cases of Pott's disease, TB meningitis, TB adenitis with fistula formation, smear or Xpert MTB/RIF positive or highly suggestive CXR (eg. hilar lymphadenopathy, upper lobe infiltrates, miliary picture).

[d] Broad spectrum antibiotics: see *Respiratory conditions*, Part 2, Chapter 2.5.
Plus consider PCP treatment if respiratory symptoms. PCP treatment can be given presumptively to all children < 12 months, and any older child with severe immune suppression and not on CTX prophylaxis. For all others, it should be considered if there is poor response to standard treatment after 48 hours.

[e] Clinical response to a broad-spectrum antibiotic does not rule out TB. Carer should be informed to consult if symptoms re-occur.

Paediatric TB diagnostic algorithm 2:
HIV exposed or infected symptomatic child



a Acute malnutrition or growth curve flattening.

b Temperature > 38°C.

c Clinical assessment (including weight and nutritional status), bacteriological tests, and when relevant and available: X-ray (CXR), investigations for EPTB, TST.

d Smear microscopy positive or Xpert MTB/RIF positive, CXR showing suggestive lesions (eg. Hilar lymphadenopathy, upper lobe infiltrates, miliary picture), gibbus.

e Broad spectrum antibiotics: see *Respiratory conditions*, Part 2, Chapter 2.5.
Plus consider PCP treatment if respiratory symptoms. PCP treatment can be given presumptively to all children < 12 months, and any older child with severe immune suppression and not on CTX prophylaxis. For all others, it should be considered if there is poor response to standard treatment after 48 hours.

f Clinical response to a broad-spectrum antibiotic does not rule out TB. Carer should be informed to consult if symptoms re-occur.

Appendix D. HIV infant diagnosis by DNA-PCR using Dried Blood Spot (DBS)

The first HIV DNA PCR test done is referred to as DBS1 and the second confirmation test, done to exclude possible procedures errors, is DBS2. DBS1 can be done as early as at birth, but is often timed with the first post-natal visit or DTP1 vaccination at 4 - 6 weeks of age.
DBS2 should be done preferably within 4 weeks of DBS1 and should be sent to the same laboratory.
Alternative: DBS1 and DBS2 could be collected at the same time: While DBS1 is sent for HIV DNA-PCR analysis, DBS2 is stored at MSF project site. If the DBS1 result is positive, DBS2 can be sent for confirmation of result.

Note:
The optimal timing for DBS1 is currently still under discussion. The earlier a child is diagnosed, the earlier ART can be commenced, and some countries are moving towards testing DBS1 at/or around birth. Testing at birth will detect approximately 70% of early infections (defined as *in utero* and peri-partum HIV infection). A second test needs to be done at around 6-10 weeks for all those who tested negative at birth in order to pick up those infected during delivery.

Result Interpretation

- If DBS1 is NEGATIVE: Report the result as "HIV-negative.
- If the first result (DBS1) is POSITIVE: Start ART as soon as possible and collect a second sample for confirmation.
- If the second result (DBS2) is also POSITIVE: Report final result as "HIV-positive".
- If the second result (DBS2) is negative: This is a discordant result. Refer to your laboratory and HIV advisor to follow specific strategy.

Result DBS1	Result DBS2	Final Result
negatif	not applicable	NEGATIF
positif	positif	POSITIF
positif	negatif	Discordant *Refer to lab advisor*

Notes:
- All children with a negative HIV DNA PCR result should be re-tested using antibody-based tests (e.g. Rapid Diagnostic Tests) to confirm a final diagnosis after 18 months, unless they never breastfed[a].
- In projects which do not have the capacity to do so, earlier discharge between 12-15 months may be considered if a negative HIV test is obtained and the infant has not breastfed during the past 6 weeks[b].
- The likelihood of a false positive result decreases when clear clinical indications of HIV infection are present.
- The likelihood of a false negative result increases when there are clear clinical indications of an HIV infection:
  If a child tested negative once but has new symptoms compatible with HIV disease, testing must be repeated.

[a] Children remain at risk of HIV infection as long as they are breastfed.
[b] Ref: final decision should be made following WHO testing advice 2010.

– The likelihood of false positive increases with a well-functioning PMTCT program (as HIV prevalence in infants decreases, predictive positive value of the test decreases as well and false positive results increase).
– On each site, the lab-in-charge should monitor and report quarterly the HIV DNA-PCR discordance percentage to the medical coordinator and to the MSF section lab advisor.

Collection, storage and transportation of DBS samples

Caution: there is a high risk of cross contamination from capillary blood sampling to laboratory testing if proper procedures are not followed.

1. Equipment

– ELAEPAPF903 PAPER, SAMPLE SUPPORT, 903 Protein saver card
– ELAEPAPF9RA (903 protein saver card) RACK for drying w/o velcro
– ELAEBAGP1S- (903 card) BAG, plastic, impervious to gas, zip lock
– SLASDESS1S- (903 card) DESICCANT for gaz impermeable plast.bag
– ELAEHUMI1C- HUMIDITY INDICATOR CARD (Tropack) 30 to 50%
– Rip-resistant envelope

2. Method: collection and storage of DBS

a. Label card with appropriate identification number and date.
b. Apply 1 drop or 50-75 µl of whole blood to each circle, and fill the 5 circles (at least 4 circles).
c. Placing the card on the drying rack, let the card completely air dry (between 2-3 hours and overnight depending of the ambient humidity), in a clean, dust-free and insect-free area.
d. Complete patient information in the appropriate laboratory register (identification number, age, date of blood collection).
e. Once dry, place the card in a low gas-permeable zip-lock bag with desiccant and humidity card. The cards are either placed individually in a zip-lock bag or placed individually in a glassine bag and packed by 5 maximum in the zip-lock bag. Press as much as possible the air out of the bag and seal it shut.
f. Keep packed DBS (in sealed plastic bags) in a dry place at room temperature until transportation to the external laboratory.
g. Check the humidity cards weekly: if the card is pink (humidity > 30%) remove the desiccant bag and store with 6 packets of new desiccant bags in the sealable bag.

3. Transportation

– Place zip-lock bags containing DBS in a rip-resistant envelope with the necessary documents.
– DBS are not considered infectious material regarding international regulations. It is possible to transport them by normal post at room temperature.

Appendix E. Severity grading of selected clinical and laboratory toxicities
(most commonly seen with recommended antiretroviral drugs for children)

Parameter	Mild *(grade 1)*	Moderate *(grade 2)*	Severe *(grade 3)*	Severe and potentially life-threatening *(grade 4)*
General guidance on estimating severity grade				
Characterization of symptoms and general guidance on management	Symptoms causing no or minimal interference with usual social and functional activities[a]: no therapy needed, monitor	Symptoms causing greater than minimal interference with usual social and functional activities: may require minimal intervention and monitoring	Symptoms causing inability to perform usual social and functional activities: requires medical care and possible hospitalization	Symptoms causing inability to perform basic self-care functions[c]: requires medical or operative intervention to prevent permanent impairment, persistent disability or death
Haematology ***(standard international units are listed in italics)***				
Absolute neutrophil count	750 - < 1000/mm^3 *0.75 x 10^9 - < 1 x 10^9/l*	500 - 749/mm^3 *0.5 x 10^9 - 0.749 x 10^9/l*	250 - 500/mm^3 *0.25 x 10^9 - 0.5 x 10^9/l*	< 250/mm^3 *< 0.250 x 10^9/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 attributable to anaemia (e.g. cardiac failure), refractory to supportive therapy
Platelets	100 000 - < 125 000/mm^3 *100 x 10^9 - 125 x 10^9/l*	50 000 - < 100 000/mm^3 *50 x 10^9 - < 100 x 10^9/l*	25 000 - < 50 000/mm^3 *25 x 10^9 - < 50 x 10^9/l*	< 25 000/mm^3 *< 25 x 10^9/l* or bleeding
Gastrointestinal				
Biochimie				
ALT (SGPT)	1.25 - 2.5 x ULN	2.6 - 5.0 x ULN	5.1 - 10.0 x ULN	> 10.0 x ULN
AST (SGOT)	1.25 - 2.5 x ULN	2.6 - 5.0 x ULN	5.1 - 10.0 x ULN	> 10.0 x ULN

Parameter	Mild *(grade 1)*	Moderate *(grade 2)*	Severe *(grade 3)*	Severe and potentially life-threatening *(grade 4)*
Bilirubin (>2 weeks of age)	1.1 - 1.5 x ULN	1.6 - 2.5 x ULN	2.6 - 5.0 x ULN	> 5.0 x ULN
Lipase	1.1 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 5.0 x ULN	> 5.0 x ULN
Pancreatic amylase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.0 x ULN
Clinical				
Diarrhoea ≥ 1 year of age	Transient or intermittent episodes of unformed stools OR increase of ≤ 3 stools over baseline per day	Persistent episodes of unformed to watery stools OR increase of 4–6 stools over baseline per day	Grossly bloody diarrhoea OR increase of ≥ 7 stools per day OR intravenous fluid replacement indicated	Life-threatening consequences (e.g. hypotensive shock)
< 1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR hypotensive shock
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR aggressive rehydration indicated (e.g. intravenous fluids)	Persistent nausea with no or minimal oral intake resulting in dehydration with aggressive rehydration indicated
Pancreatitis	Not applicable	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 indi-cated (e.g. intravenous fluids)	Life-threatening consequences (e.g. hypotensive shock)
Allergic/Dermatological				
Acute systemic allergic reaction	Localized urticaria (weals) lasting a few hours	Localized urticaria with medical intervention indicated OR mild angio-oedema	Generalized urticaria OR angio-oedema with medical intervention indicated OR symptomatic mild bronchospasm	Acute anaphylaxis OR life-threatening bronchospasm or laryngeal oedema

Parameter	Mild *(grade 1)*	Moderate *(grade 2)*	Severe *(grade 3)*	Severe and potentially life-threatening *(grade 4)*
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR target lesions	Diffuse macular, maculo-papular, 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 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 minimal 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]
Other laboratory parameters ***(standard international units are listed in italics)***				
Cholesterol (fasting, paediatric < 18 years old)	170 - < 200 mg/dl *4.40 - 5.15 mmol/l*	200 - 300 mg/dl *5.10 - 7.77 mmol/l*	> 300 mg/dl *> 7.77 mmol/l*	Not applicable
Serum 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*

Parameter	Mild *(grade 1)*	Moderate *(grade 2)*	Severe *(grade 3)*	Severe and potentially life-threatening *(grade 4)*
Serum 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)	Not applicable	500 - < 751 mg/dl *5.65 - < 8.49 mmol/l*	751 - 1 200 mg/dl *8.49 - 13.56 mmol/l*	*> 1 200 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 paediatric adverse events, Bethesda, Maryland, USA; December 2004.

[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 appropriate to their age and culture (e.g. social interactions, play activities, learning tasks).

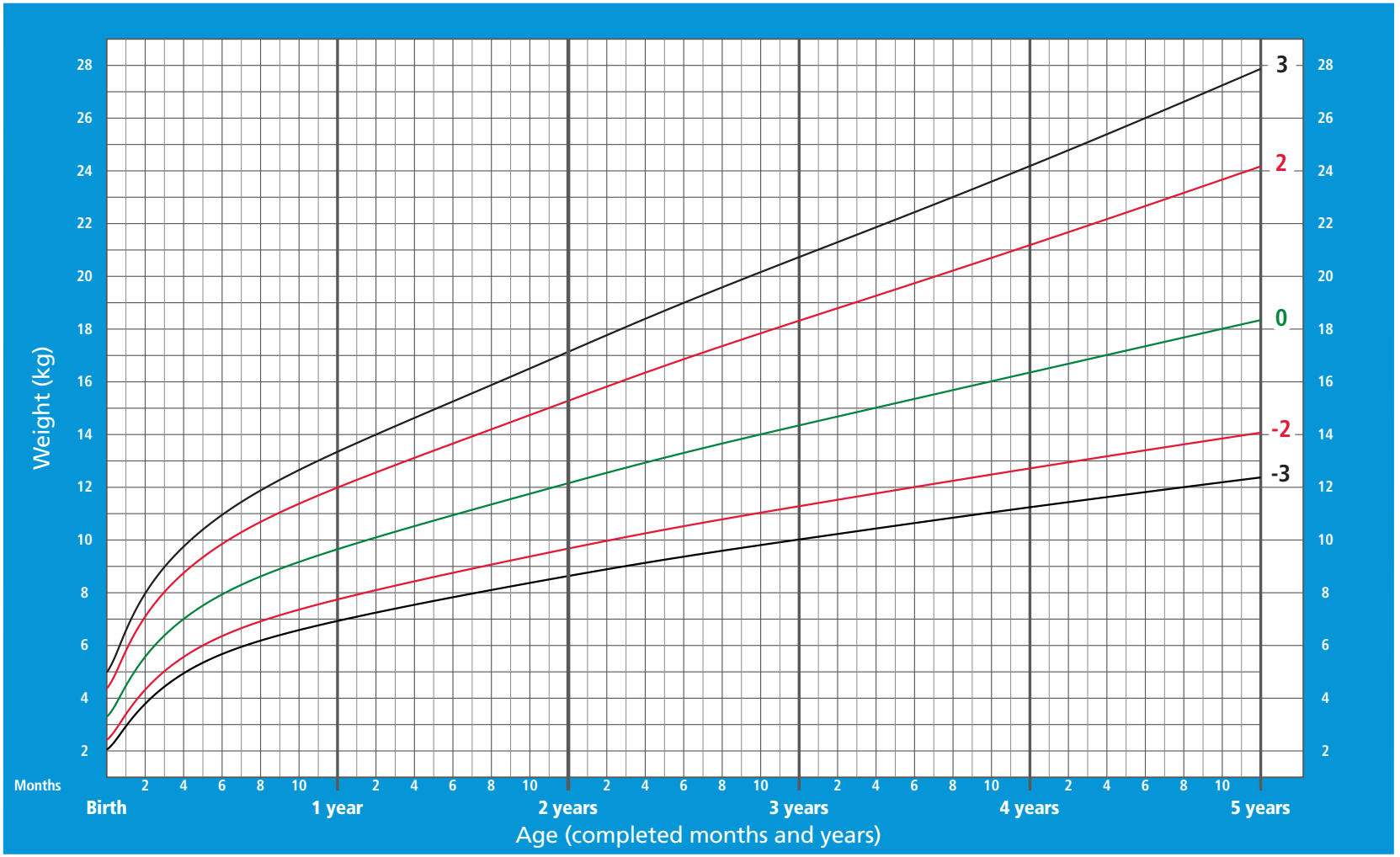
[c] Activities that are appropriate to age and culture (e.g. feeding self with culturally appropriate eating implement, walking or using hands).

Appendix F.1. WHO growth charts– Weight/Age (boys and girls)

Weight-for-age BOYS

Birth to 5 years (z-scores)

World Health Organization

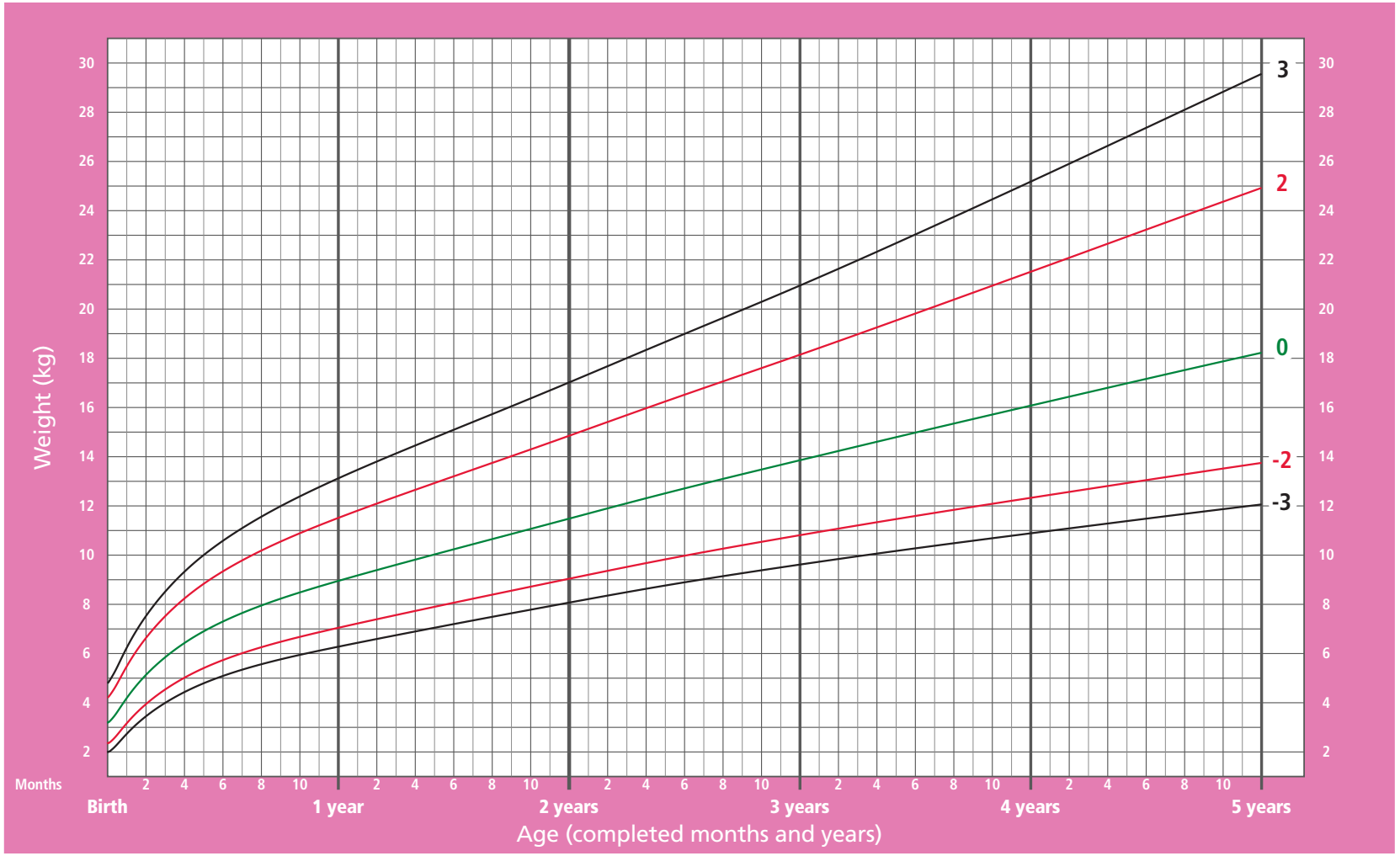


WHO Child Growth Standards

Weight-for-age GIRLS

Birth to 5 years (z-scores)

World Health Organization



WHO Child Growth Standards

Appendix F.2. Normal child development

Age	Milestone	Normal age variations
1 month	Looks at faces Brings head up at 45° when pulled seated	0 to 2 months
2 months	Social smile in response Sits head steady	2 to 4 months
4 months	Roll over Grabs and holds objects	4 to 6 months
6 months	Sits by itself	6 to 9 months
9 months	Pulls itself standing up with support	9 to 12 months
12 months	Walks Plays with examiner Puts objects in a cup First words	10 to 18 months
2 years	Speech understandable Scribbles	2 to 4 years
3 years	Hops, plays ball Dresses alone Draws a three part man	3 to 4 years
5 years	Social games Invents stories Copies (letters, drawings)	5 to 6 years

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