HIV/AIDS Programme
Strengthening health services to fight HIV/AIDS

ANTIRETROVIRAL THERAPY FOR HIV INFECTION IN INFANTS AND CHILDREN: TOWARDS UNIVERSAL ACCESS

Recommendations for a public health approach

2010 revision

World Health Organization

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ACRONYMS AND ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
AFB	acid-fast bacilli
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
a.m.	ante meridiem (denotes morning)
ANC	antenatal care
ART	antiretroviral therapy
ARV	antiretroviral (drug)
AST	aspartate aminotransferase
ATV	atazanavir
AUC	area under curve
AZT	zidovudine (also known as ZDV)
BAL	bronchoalveolar lavage
BCG	bacille Calmette – Guérin (vaccine)
BSA	body surface area
CD4+	T-lymphocyte bearing CD4 receptor
%CD4+	percent CD4+
CDC	Centers for Disease Control and Prevention
CHAP	Children with HIV Antibody Prophylaxis (clinical trial)
CMV	cytomegalovirus
CNS	central nervous system
CPK	creatinine phosphokinase
CRAG	cryptococcal antigen
CSF	cerebrospinal fluid
CTX	co-trimoxazole
d4T	stavudine
DART	Development of Antiretroviral Therapy (in Africa)
DBS	dried blood spot
ddI	didanosine
DMPA	depot medroxyprogesterone acetate
DNA	deoxyribonucleic acid
DOT	directly observed therapy
EC	enteric-coated
EFV	efavirenz
EIA	enzyme immunoassay
EML	Essential Medicines List
ELISA	enzyme-linked immunosorbent assay
ETV	etravirine
EU	European Union
EWI	early warning indicator
FDC	fixed-dose combination
FDC	fixed-dose combination
FPV	fos-amprenavir
FTC	emtricitabine
Grade	grading of recommendations assessment, development and evaluation
HAART	highly active antiretroviral therapy
HDL	high-density lipoprotein
Hgb	haemoglobin
HGC	hard gel capsule
HIV	human immunodeficiency virus
HIVDR	HIV drug resistance
HIVNET	HIV Network for Prevention Trials
HIVResNet	Global HIV Drug Resistance Network
HSV	herpes simplex virus
IDV	indinavir
IMCI	integrated management of childhood illness
INH	isoniazid
IPT	isoniazid preventive therapy
IRIS	immune reconstitution

	inflammatory syndrome
LDH	lactate dehydrogenase
LGE	lineal gingival erythema
LIP	lymphocytic interstitial pneumonia
LPV	lopinavir
LTB	laryngotracheal bronchitis
MCH	maternal-child health
MDR	multidrug resistant
MTCT	mother-to-child transmission (of HIV)
MUAC	mid-upper arm circumference
NAT	nucleic acid amplification test
NFV	nelfinavir
NNRTI	non-nucleoside reverse transcriptase inhibitor
NPA	nasopharyngeal aspirate
NRTI	nucleoside reverse transcriptase inhibitor
NSAID	non-steroidal anti-inflammatory drug
NVP	nevirapine
OI	opportunistic infection
PCP	Pneumocystis pneumonia
PCR	polymerase chain reaction
PENTA	Paediatric European Network for Treatment of AIDS
PGL	persistent generalized lymphadenopathy
PI	protease inhibitor
p.m.	post meridiem (denotes afternoon)
PMTCT	prevention of mother-to-child transmission (of HIV)
/r	low-dose ritonavir
RCT	randomized controlled trial
RDA	recommended daily allowance
REE	resting energy expenditure
RNA	ribonucleic acid
RT	reverse transcriptase
RTI	reverse transcriptase inhibitor
RTV	ritonavir
RUTF	ready-to-use therapeutic feeds
SD	standard deviation
sd-NVP	single-dose nevirapine
SQV	saquinavir
T20	enfurvirtide
TAM	thymidine analogue mutation
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
TEN	toxic epidermal necrolysis
TLC	total lymphocyte count
TPV	tipranavir
TRG	Technical Reference Group on Paediatric HIV Care and Treatment
TST	tuberculin skin test
ULN	upper limit of normal
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
Up24 Ag	ultrasensitive p24 antigen
URTI	upper respiratory tract infection
USAID	United States Agency for International Development
WBC	white blood cell count
WHO	World Health Organization
XDR	extensively drug resistant

EXECUTIVE SUMMARY

Tremendous progress has been made over the past few years in diagnosing and treating infants and children with human immunodeficiency virus (HIV) infection. However, much remains to be done to effectively scale-up and sustain prevention efforts and treatment services for all in need. The most efficient and cost-effective way to tackle paediatric HIV globally is to reduce mother-to-child transmission (MTCT). In 2008, an estimated 45% of pregnant women living with HIV received antiretrovirals (ARVs) to prevent transmission of HIV to their children. However, every day, there are nearly 1 200 new infections in children less than 15 years of age, more than 90% of them occurring in the developing world and most being the result of transmission from mother to child.

HIV-infected infants frequently present with clinical symptoms in the first year of life. Without effective treatment, an estimated one third of infected infants will have died by one year of age, and about half will have died by two years of age. While progress has been made in preventing new HIV infections in infants and children, greater efforts are needed to scale-up these effective preventive interventions as well as services for care and treatment.

The 2009 progress report *Towards universal access: scaling up priority HIV/AIDS interventions in the health sector*, documents the progress made by countries in scaling up antiretroviral therapy (ART) for children. In 2008, over 275 000 children received ART, up from 127 000 in 2006. This is 38% of those in need using the previous 2006 recommendations for ART initiation in children. Given the new guidance contained in this document, estimates of the numbers of infants and children who qualify for ART will have to be revised.

HIV-infected infants and children now survive to adolescence and adulthood, and the challenges of providing HIV care are evolving into the challenges of providing both acute and chronic, lifelong care. Despite the high risk of early mortality in HIV-infected infants and children, the average age at initiation of therapy in children in resource-limited settings remains high.

Significant obstacles remain to scaling up paediatric care, including limited screening for HIV, a lack of affordable, simple diagnostic testing technologies for children less than 18 months of age, a lack of human resources with the capacity to provide the care that is required, insufficient advocacy and understanding that ART is efficacious in children, limited experience with simplified, standardized treatment guidelines, and limited availability of affordable and practical paediatric ARV formulations. Health-care systems remain unable to meet the demands of national paediatric ART coverage. Consequently, far too few children have been started on ART in resource-limited settings. Moreover, the need to treat an increasing number of HIV-infected children highlights the primary importance of preventing transmission of the virus from mother to child in the first place.

The WHO guidelines *Antiretroviral therapy for HIV infection in infants and children* are based on a public health approach to HIV care. Updated in 2010, these guidelines are harmonized with the treatment guidelines adopted for adults, pregnant women, and for prevention of mother- to- child transmission (PMTCT).

The present guidelines are part of WHO's commitment to achieve universal access to the prevention, care and treatment of HIV infection in infants and children.

Summary of changes

Earlier, more accurate diagnosis of HIV

- Establishing HIV exposure status at birth or soon after birth
- Testing of infants by 4 – 6 weeks of age if HIV-exposed using virological assays
- New standards for the quality of serological and virological assays

Earlier initiation of ART

- Infants and children <2 years of age: Start ART immediately upon diagnosis
- Children ≥2 years and <5 years of age: ≤25% CD4 or CD4 count of ≤750 cells/mm^3
- Children ≥5 years of age: CD4 count of ≤350 cells/mm^3

Simplified antiretrovirals for use in first-line and second-line therapy

- Continued encouragement for use of fixed-dose combinations (FDCs)
- Protease inhibitors for infants with NNRTI exposure
- Recommended preferred standard regimens

What to expect in the first six months of therapy

- Expected signs and symptoms of initial therapy

Promoting attention to nutrition for children on ART

- The importance of nutritional assessment and the nutritional requirements of infants and children on ART

More strategic monitoring for antiretroviral efficacy and toxicity

- While laboratory monitoring should not be a barrier to initiating ART, with improved laboratory monitoring, children are likely to have better results on ART, better management of adverse reactions and, possibly, develop less resistance.
- Simple guide to routine clinical follow-up.
- A phased-in approach to the use of viral load testing which, if feasible, will improve the identification of treatment failure.

Strengthening adherence

- Although a lack of evidence precludes recommendations, important principles promoting improved adherence are described.

List of recommendations

Establishing a diagnosis of HIV infection in infants and children

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

<18 months of age – used as a screening assay to determine HIV exposure
>18 months of age – used as a diagnostic assay

2. It is strongly recommended that HIV virological assays used for the purpose of clinical diagnostic testing (usually at or after 6 weeks of age) have a sensitivity of at least 95% (ideally greater than 98%), and specificity of 98% or more, under quality-assured, standardized and validated laboratory conditions.
3. It is strongly recommended that HIV virological testing be used to diagnose HIV infection in infants and children less than 18 months of age.
4. In infants and children undergoing virological testing, the following assays (and respective specimen types) are strongly recommended for use:
   HIV DNA on whole blood specimen or dried blood spots (DBS)
   HIV RNA on plasma or DBS
   ultrasensitive p24 antigen (Up24 Ag) on plasma or DBS
5. It is strongly recommended that all HIV-exposed infants have HIV virological testing at 4 to 6 weeks of age or at the earliest opportunity thereafter.
6. In infants with an initial positive virological test result, it is strongly recommended that ART be started without delay and, at the same time, a second specimen be collected to confirm the initial positive virological test result. Do not delay ART. In infected infants immediate initiation of ART saves lives and commencement of ART should not be delayed while waiting for the results of the confirmatory test. (See recommendation 13 if virological testing is not available).
7. It is strongly recommended that test results from virological testing in infants be returned to the clinic and child/mother/carer as soon as possible, but at the very latest within four weeks of specimen collection. Positive test results should be fast-tracked to the mother – baby pair as soon as possible to enable prompt initiation of ART.
8. It is strongly recommended that all infants with unknown or uncertain HIV exposure being seen in health-care facilities at or around birth or at the first postnatal visit (usually 4 – 6 weeks), or other child health visit, have their HIV exposure status ascertained.
9. It is strongly recommended that well, HIV-exposed infants undergo HIV serological testing at around 9 months of age (or at the time of the last immunization visit). Those who have reactive serological assays at 9 months should have a virological test to identify infected infants who need ART.
10. It is strongly recommended that infants with signs or symptoms suggestive of HIV infection undergo HIV serological testing and, if positive (reactive), virological testing.
11. In breastfeeding infants or children, it is strongly recommended that breastfeeding is not discontinued in order to perform any kind of diagnostic HIV test.
12. It is strongly recommended that children aged 18 months or older, with suspected HIV infection or HIV exposure, have HIV serological testing performed according to the standard diagnostic HIV serological testing algorithm used in adults.
13. In sick infants in whom HIV infection is being considered as an underlying cause of symptoms and signs, and virological testing is not available, HIV serological testing and use of the clinical algorithm for presumptive clinical diagnosis of HIV infection is strongly recommended.

When to start antiretroviral therapy in infants and children

Infants

1. Initiate ART for all HIV-infected infants diagnosed in the first year of life, irrespective of CD4 count or WHO clinical stage.

Children

2. Initiate ART for all HIV-infected children between 12 and 24 months of age irrespective of CD4 count or WHO clinical stage.
3. Initiate ART for all HIV-infected children between 24 and 59 months of age with CD4 count of ≤750 cells/mm^3 or %CD4+ ≤25, whichever is lower, irrespective of WHO clinical stage.
4. Initiate ART for all HIV-infected children more than 5 years of age with a CD4 count of ≤350 cells/mm^3 (as in adults), irrespective of WHO clinical stage.
5. Initiate ART for all HIV-infected children with WHO clinical stages 3 and 4, irrespective of CD4 count.
6. Initiate ART for any child less than 18 months of age who has been given a presumptive clinical diagnosis of HIV infection.

What to start – recommended first-line ART regimens for infants and children

Infants

1. For infants not exposed to ARVs, start ART with nevirapine (NVP) + 2 nucleoside reverse transcriptase inhibitors (NRTIs).
2. 2. For infants exposed to maternal or infant NVP or other NNRTIs used for maternal treatment or PMTCT, start ART with lopinavir/ritonavir (LPV/r) + 2 NRTIs.
3. For infants whose exposure to ARVs is unknown, start ART with NVP + 2 NRTIs.

Children

4. For children between 12 and 24 months of age exposed to maternal or infant NVP or other NNRTIs used for maternal treatment or PMTCT, start ART with lopinavir/ritonavir (LPV/r) + 2 NRTIs.
5. For children between 12 and 24 months of age not exposed to NNRTIs, start ART with NVP + 2 NRTIs.
6. For children more than 24 months and less than 3 years of age start ART with NVP + 2 NRTIs.
7. For children 3 years of age and older, start ART with NVP or efavirenz (EFV)-containing regimen + 2 NRTIs.
8. For infants and children, the nucleoside backbone for an ART regimen should be one of the following, in preferential order:
   Lamivudine (3TC) + zidovudine (AZT) or 3TC + abacavir (ABC) or 3TC + stavudine (d4T)

Infants and children with specific conditions

9. For children more than 3 years of age with tuberculosis (TB), the preferred regimen is EFV + 2 NRTIs.
10. For infants and children less than 3 years of age with TB, the preferred regimens are NVP + 2 NRTIs or a triple nucleoside regimen.
11. For a child or adolescent with severe anaemia (<7.5 g/dl) or severe neutropenia (<0.5/mm^3), the preferred regimen is NVP + 2 NRTIs (avoid AZT).
12. For adolescents more than 12 years of age with hepatitis B, the preferred regimen is tenofovir (TDF) + emtricitabine (FTC) or 3TC + NNRTI.

Clinical and laboratory monitoring

CD4 monitoring

1. CD4 should be measured at the time of diagnosis of HIV infection, and every 6 months thereafter. Monitor with increasing frequency as CD4 count approaches the threshold for starting ART.
2. CD4 should be measured prior to initiating ART.
3. CD4 should be measured every 6 months after initiating ART.
4. Measure CD4 if new clinical staging events develop, including growth faltering and neuro-developmental delay.
5. Where capacity for CD4 measurement is limited, target the use of CD4 monitoring to assess the significance of clinical events.

Viral load monitoring

6. Viral Load determination is desirable, but not essential, prior to initiating ART.
7. Viral Load should be assessed to confirm clinical or immunological failure where possible, prior to switching a treatment regimen.

Routine clinical and laboratory monitoring

8. Baseline haemoglobin level (and white cell count, if available) should be determined at initiation of ART.
9. For infants and children, measure haemoglobin at week 8 after initiation of AZT-containing regimens, or more frequently if symptoms indicate.
10. Growth, development and nutrition should be monitored monthly.
11. Laboratory monitoring for toxicity should be symptom directed.

First-line regimen treatment failure; when to switch regimens

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

2. Clinical failure is defined as the appearance or reappearance of WHO clinical stage 3 or stage 4 events after at least 24 weeks on ART in a treatment-adherent child.
3. Immunological failure is defined as developing or returning to the following age-related immunological thresholds after at least 24 weeks on ART, in a treatment-adherent child:
   - CD4 count of <200 cells/mm^3 or %CD4+ <10 for a child ≥2 years to <5 years of age
   - CD4 count of <100 cells/mm^3 for a child 5 years of age or older.
4. Virological failure is defined as a persistent viral load above 5 000 RNA copies/ml, after at least 24 weeks on ART, in a treatment-adherent child.

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

1. After failure on a first-line NNRTI-based regimen, a boosted PI plus 2 NRTIs are recommended for second-line ART.
2. LPV/r is the preferred boosted PI for a second-line ART regimen after failure on a first-line NNRTI-based regimen.
3. After failure on a first-line regimen of AZT or d4T + 3TC, ABC + 3TC is the preferred NRTI backbone option for second-line ART; ABC + ddI is an alternative.
4. After failure on a first-line regimen of ABC + 3TC, AZT + 3TC is the preferred NRTI backbone option for second-line ART; AZT + ddI is an alternative.

Considerations for infants and children with tuberculosis and HIV

Isoniazid preventive therapy

1. All HIV-infected infants and children exposed to TB through household contacts, but with no evidence of active disease, should begin isoniazid preventive therapy (IPT).
2. Children living with HIV (older than 12 months of age and including those previously treated for TB), who are not likely to have active TB, and are not known to be exposed to TB, should receive 6 months of IPT as part of a comprehensive package of HIV care.
3. Infants living with HIV, who are unlikely to have active TB and are not known to have been exposed to TB, should not receive IPT as part of a comprehensive package of HIV care.
4. The recommended dose of isoniazid (INH) for preventive therapy in HIV coinfection is 10 mg/kg/daily for 6 months (maximum 300 mg/day).

Infants and children diagnosed with TB and HIV

5. Any child with active TB disease should begin TB treatment immediately, and start ART as soon as tolerated in the first 8 weeks of TB therapy, irrespective of CD4 count and clinical stage.
6. The preferred first-line ARV regimen for infants and children less than 3 years of age, who are taking a rifampicin-containing regimen for TB, is 2 NRTIs + NVP or a triple NRTI regimen.
7. The preferred first-line ARV regimen for children more than 3 years of age who are taking a rifampicin-containing regimen for TB is 2 NRTIs + EFV.

8. The preferred first-line ARV regimen for infants and children less than 2 years of age, who have been exposed to NVP and are taking a rifampicin-containing regimen for TB is a triple NRTI regimen.

HIV-infected infants and children who develop TB on ART

9. For all HIV-infected children, anti-TB therapy should be started immediately upon the diagnosis of TB; ART should continue.
10. Make adjustments to ART regimens as needed to decrease the potential for toxicities and drug interactions:
    - If on a regimen of 2 NRTIs + NVP, substitute EFV for NVP if child is 3 years in age
    - If on a regimen of 2 NRTIs + NVP and substitution with EFV is not possible, ensure NVP is dosed at the maximum dose of 200 mg/m^2 per dose twice daily
    - If on a regimen of LPV/r, consider adding RTV to a 1:1 ratio of LPV: RTV to achieve the full therapeutic dose of LPV.

Considerations for the nutrition for HIV-infected infants and children

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

Adherence to ART

1. Pill boxes/calendars/diaries or other practical tools should be used to support adherence.

1. INTRODUCTION

Worldwide, in 2008, an estimated 430 000 new HIV infections occurred in infants and children, of which 90% were acquired through MTCT. Of the 430 000 new infections, between 280 000 and 360 000 were acquired during labour and in the peri-partum period. Of the remaining new infections, the majority were acquired during breastfeeding.

In 2008, nearly 276 000 children worldwide received ART, up from 127 300 in 2006 [1, 2]. This represents an estimated 38% of all children in need of ART using the 2006 criteria for treatment initiation. With the new recommendations contained in this document, these need estimates will have to be revised. HIV-infected infants and children now survive to adolescence and adulthood, and the challenges of providing HIV care are evolving into the challenges of providing both acute and chronic, lifelong care. Despite the high risk of early mortality in HIV-infected children, the average age at initiation of therapy in children in resource-limited settings remains high.

For example, in a cohort of more than 2 400 HIV-infected children in West Africa, the average age for starting ART was 4.9 years [3]. Data emerging since the publication of the 2006 World Health Organization (WHO) recommendations for ART in infants and children [4] suggest that early initiation of ART is life-saving [5]. Infants who acquire HIV during pregnancy and around the time of delivery progress rapidly to AIDS or death in the first few months of life. All infants should have their HIV-exposure status determined at or around the time of birth. And exposed infants should have access to early diagnosis, the necessary prerequisite to early initiation of ART. Currently, only an estimated 15% of HIV-exposed infants receive a diagnostic test in the first two months of life.

WHO guidelines for the use of ART in infants and children are based on a public health approach to HIV care [6]. Updated in 2010, these guidelines are harmonized with the treatment guidelines adopted for adults, pregnant women, and for prevention of mother- to- child transmission (PMTCT) (http://www.who.int/hiv/pub/guidelines/en).

Annex E details ARV dosing information.

This information may be updated between publications.
Readers are advised to consult the website for the most up-to-date information.
http://www.who.int/hiv/topics/paediatric/en/index.html

2. OBJECTIVES OF THESE GUIDELINES

These treatment guidelines serve as a framework for selecting the most potent and feasible first-line and second-line ART regimens for the care of HIV-infected infants and children.

These guidelines address the diagnosis of HIV infection and consider ART in different situations, e.g. where infants and children are coinfected with HIV and TB, or have been exposed to ARVs, either for PMTCT or because of breastfeeding from an HIV-infected mother on ART. In addition, these guidelines address the importance of nutrition in the HIV-infected child and of recognizing the severity of malnutrition, especially in relation to the provision of ART. Adherence to therapy and resistance to ARVs are discussed. A section on ART in adolescents briefly outlines key issues related to treatment and care for this age group.

WHO recognizes the need to strengthen health systems with a view to maximizing the quality and long-term benefits of ART. Improved access to HIV diagnostic testing for infants and children is necessary to save lives. The inability to diagnose HIV infection as early as possible in infants and children severely limits access to ART and its timely initiation. Reliable access to immunological assays for assessing CD4 levels in children is crucial for guiding the initiation of treatment and for optimizing the maintenance of ART.

These guidelines are intended primarily for use by treatment advisory boards, national AIDS programme managers and other senior policy-makers who are involved in the planning of national and international HIV care strategies for infants and children in resource-limited countries. Elements of the guidelines such as the simplified dosing guidance (Annex E) are also designed for clinical implementation in the field.

3. DEVELOPMENT OF THESE GUIDELINES

Since 2004, when the first guidance on ART for infants and children became available, diagnosis and treatment of HIV has advanced considerably. The WHO Technical Reference Group on Paediatric HIV/ART Care (TRG),[i] initially constituted in 2005 to develop recommendations for scaling up paediatric HIV care and treatment, reconvened in April 2008 to review new data and evidence on the use of ART in infants. The TRG met again in December 2009 to review the paediatric recommendations related to those areas recently updated in the WHO guidance on Antiretroviral therapy for HIV infection in adults and adolescents [7], the *WHO recommendations on the diagnosis of HIV infection in infants and children* [8], and the recommendations adopted in 2010 for the prevention and management of tuberculosis.

3.1 Process of guideline development

Beginning in 2006, a subgroup of the TRG initially identified key questions for review. Preliminary work included the preparation of systematic reviews and Grading of Recommendations Assessment, Development and Evaluation (GRADE) profiles for:

- when to test infants for HIV infection
- when to initiate ART for infants and children
- what treatment regimens to begin for infants and children.

The TRG also revised recommendations and articulated basic principles based on targeted reviews and, where possible, GRADE profiles, for:

- clinical and laboratory monitoring of infants and children on ART
- when to switch treatment regimens
- treatment and management of HIV-infected infants and children coinfected with TB
- nutritional assessment and requirements of infants and children on ART
- approaches to encouraging and supporting adherence to ART.

Search strategies employed in the systematic reviews, meta-analyses and GRADE profiles, which were conducted by the Cochrane HIV/AIDS group, followed the methodology described in *The Cochrane handbook for systematic reviews of interventions* (Version 5.0.2; last updated September 2009 (http://www.cochrane-handbook.org/).

In reviews where data were not amenable to meta-analysis and/or GRADE profiles, systematic searches, using relevant key words and search strings, were conducted of electronic databases (Medline/Pubmed, Embase, CENTRAL), conference databases (Aegis, AIDSearch, NLM Gateway and hand searches) and clinical trial registers (http://clinicaltrials.gov/www.controlled-trials.com, www.pactr.org).

The TRG reviewed compiled evidence profiles for each proposed recommendation according to WHO's process for the development of guidelines, including consideration of the quality of available evidence, assessment of risks and benefits, acceptability, feasibility and costs. The group achieved consensus for the final recommendations [9-11]. The evidence documentation prepared for these

(i) A list of TRG members is provided in Annex A.

guidelines is available on the 2010 ART guidelines for infants and children evidence map webpage (http://www.who.int/hiv/topics/paediatric/en/index.html).

The criteria used to assess the quality of this evidence and the terminology used to rank the quality of evidence is described in Table 2. Where minimal evidence is available, recommendations are based on the reference group's opinions as to what constitutes best practice. The recommendations made in this document are graded as "strong" or "conditional", terminology which is defined in Table 2. Where it has not been possible to make recommendations, the reference group has indicated, where appropriate, the urgent need for research. It should be noted that where recommendations are made based on very low or low quality of evidence, further research is critical to better inform the recommendations being made.

Working groups were formed for each of the key topic areas, each one led by experts from the TRG. Peer review was conducted through these individual working groups (or subgroups). These working groups networked with the broader community of experts in paediatric HIV medicine in order to assemble current scientific and practical perspectives on the issues pertinent to the development of these guidelines. One of the working groups, the Paediatric ARV Working Group, met several times in person and by conference call in order to review up-to-date data on the pharmacology of paediatric ARVs and then compile the updated Annex E. Another of the working groups, a TRG subgroup, addressed TB in HIV-infected infants and children and participated in developing recommendations for the prevention and management of TB for these guidelines.

Following the consultations, revised guidelines were drafted and submitted to the TRG and the working groups for final review. All responses were considered and addressed in the final draft. Disagreements were resolved by consensus discussion either at meetings or electronically.

The proposed recommendations were considered using a risk – benefit analysis tool consisting of a table exploring the following domains: existing and proposed recommendations, evidence for the outcomes deemed critical (mortality, disease progression and serious adverse reactions), risks and benefits of implementing the recommendation, acceptability, costs, feasibility, suggested ranking of recommendation (strong or conditional), gaps and research needs. The groups placed particular emphasis on the critical need to maintain equity, access and coverage.

3.2 Understanding WHO evidence-based recommendations

Each recommendation in this guideline is assessed as being strong or conditional, based on the GRADE evidence profile. The GRADE approach includes estimations of the balance between risks and benefits, acceptability (values and preferences), cost and feasibility. Values and preferences may differ in regard to desired outcomes or there may be uncertainty about whether the intervention represents a wise use of resources. Despite clear benefits, it may not be feasible to implement a proposed recommendation in some settings.

3.2.1 Quality of evidence and summary scores

GRADE profiles assess the quality of available evidence and ascribe a summary score to the assessed quality. Well designed, randomized, controlled clinical trials attract the highest summary score. A high summary score should indicate that the estimates of effect (desirable or undesirable)

available from the evidence are close to the actual effects of interest. It is not always possible to prepare GRADE profiles for all interventions.

Table 1: GRADE approach to ranking the quality of a body of evidence

High	=	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	=	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	=	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very low	=	Any estimate of effect is very uncertain.

3.2.2 Strength of recommendations

Following an assessment of the quality of the evidence, an assessment of the strength of the recommendation can be made. The higher the quality of evidence (GRADE summary score), the more likely a strong recommendation can be made. The assessed strength of a recommendation depends on the potential impact of the recommendation. Table 2 explains the criteria for strength of a recommendation.

Table 2: Assessment of the strength of a recommendation

Strength of recommendation	Rationale
Strong	The panel is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects.
Conditional	The panel concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects. However: The recommendation is only applicable to a specific group, population or setting or New evidence may result in changing the balance of risk to benefit or The benefits may not warrant the cost or resource requirements in all settings
No recommendation possible	Further research is required before any recommendation can be made

See Annex B for further information.

3.3 Declarations of Interest

All experts contributing to and attending each of the guideline meetings completed declarations of interest forms. All declarations made were reviewed by the WHO Secretariat and then discussed within the assembled working groups. These discussions covered the circumstances of the relationship between each declaring participant and the pharmaceutical company or organization, the amount of funds or value of products received, and the potential conflict of research or other bias or favour. None of these declarations was interpreted by the WHO Secretariat or the TRG to warrant true or perceived conflicts of interest. Dr E. Abrams has received research support from five pharmaceutical companies and served on an advisory board of one pharmaceutical company; Dr E. Capparelli has served as a consultant for seven pharmaceutical companies; Professor M. Cotton has received speaking fees from a pharmaceutical company; Professor D. Gibb receives medications and subsidy for trials that are part of PENTA; Dr C. Giaquinto received research grants for PENTA, and speaker's fees and some expenses for conference participation from seven pharmaceutical companies.

The work of revising these guidelines was coordinated by the WHO Department of HIV/AIDS Antiretroviral, Treatment and HIV Care Unit. Funding for this work has been generously provided by the Joint United Nations Programme on HIV/AIDS Unified Budget and Workplan (UNAIDS UBW); WHO's Core Voluntary Contribution; United States Agency for International Development (USAID); the US Centers for Disease Control and Prevention (CDC) and the European Union (EU).

In the current guidelines'update, one of the noticeable effects of using GRADE is that the text includes the terminology of the various grading processes that have been used since 2004. In the coming years, each of the recommendations included in this text will be updated and presented in a consistent manner, in accordance with GRADE. A full review of these guidelines is scheduled to begin in 2012, with interim reviews conducted as new evidence becomes available.

The institutions that contributed to the development of these guidelines were the Institut de Santé Publique, Epidémiologie et Développment (France); Liverpool Medical School (UK); Mailman School of Public Health, Columbia University (USA); South African Medical Research Council – South African Cochrane Centre (South Africa); University of California, San Francisco – Cochrane Collaborative Review group on HIV/AIDS (USA); University of New South Wales (Australia); the US Centers for Disease Control and Prevention (CDC); Clinton Foundation HIV/AIDS Initiative; the Global Fund to Fight AIDS, Tuberculosis and Malaria; National Institute for Child Health and Human Development (USA); Paediatric European Network for Treatment of AIDS (Italy and UK); UNAIDS; and United Nations Children's Fund (UNICEF). (Individual group members, contributors and reviewers are named in Annex A.)

3.4 Implementation

These guidelines will be disseminated as a paper-based handbook, electronically and on the WHO website.

Regional and subregional meetings are planned to adapt these guidelines to local needs and to facilitate implementation.

An evaluation process is being developed to assess the use of these guidelines among end-users.

4. ESTABLISHING A DIAGNOSIS OF HIV INFECTION IN INFANTS AND CHILDREN

4.1 Recommendations

1. It is strongly recommended that HIV serological assays used for the purpose of clinical diagnostic testing have a minimum sensitivity of 99% and specificity of 98% under quality-assured, standardized and validated laboratory conditions.
   <18 months of age – used as a screening assay to determine HIV exposure
   >18 months of age – used as a diagnostic assay
   (Strong recommendation, moderate quality of evidence)
2. It is strongly recommended that HIV virological assays used for the purpose of clinical diagnostic testing (usually at or after 6 weeks of age) have a sensitivity of at least 95% and ideally greater than 98%, and specificity of 98% or more under quality-assured, standardized and validated laboratory conditions.
   (Strong recommendation, moderate quality of evidence)
3. It is strongly recommended that HIV virological testing be used to diagnose HIV infection in infants and children less than 18 months of age.
   (Strong recommendation, high quality of evidence)
4. In infants and children undergoing virological testing, the following assays (and respective specimen types) are strongly recommended for use: HIV DNA on whole blood specimen or DBS, HIV RNA on plasma or DBS, Up24 Ag on plasma or DBS.
   (Strong recommendation, high quality of evidence)
5. It is strongly recommended that all HIV-exposed infants have HIV virological testing at 4 – 6 weeks of age or at the earliest opportunity thereafter.
   (Strong recommendation, high quality of evidence)
6. In infants with an initial positive virological test result, it is strongly recommended that ART be started without delay and, at the same time, a second specimen be collected to confirm the initial positive virological test result. Do not delay ART. In infected infants immediate initiation of ART saves lives and commencement of ART should not be delayed while waiting for the results of the confirmatory test.
   (Strong recommendation, high quality of evidence)
7. It is strongly recommended that test results from virological testing in infants be returned to the clinic and child/mother/carer as soon as possible, but at the very latest within four weeks of specimen collection. Positive test results should be fast-tracked to the mother – baby pair as soon as possible to enable prompt initiation of ART.
   (Strong recommendation, high quality of evidence)
8. It is strongly recommended that all infants with unknown or uncertain HIV exposure being seen in health-care facilities at or around birth or at the first postnatal visit (usually 4 – 6 weeks), or other child health visit, have their HIV exposure status ascertained.
   (Strong recommendation, high quality of evidence)
9. It is strongly recommended that well HIV-exposed infants undergo HIV serological testing at around 9 months of age (or at the time of the last immunization visit). Those who have reactive

serological assays at 9 months should have a virological test to identify infected infants who need ART.
(Strong recommendation, low quality of evidence)

10. It is strongly recommended that infants with signs or symptoms suggestive of HIV infection undergo HIV serological testing and, if positive (reactive), virological testing.
(Strong recommendation, low quality of evidence)

11. In breastfeeding infants or children, it is strongly recommended that breastfeeding is not discontinued in order to perform any kind of diagnostic HIV test.
(Strong recommendation, high quality of evidence)

12. It is strongly recommended that children 18 months of age or older, with suspected HIV infection or HIV exposure, have HIV serological testing performed according to the standard diagnostic HIV serological testing algorithm used in adults.
(Strong recommendation, high quality of evidence)

13. In sick infants in whom HIV infection is being considered as an underlying cause of symptoms and signs, and virological testing is not available, HIV serological testing and use of the clinical algorithm for presumptive clinical diagnosis of HIV infection is strongly recommended.
(Strong recommendation, low quality of evidence)

The revised recommendations require national programmes to review their HIV testing algorithms and ensure that clinical care pathways are updated to reflect these revised diagnostic approaches for infants and children. Also, they require immunization and maternal and neonatal/child health services to develop the capacity to provide diagnostic testing for infants and children.

Published data confirming dramatic survival benefits for infants started on ART as early as possible after the diagnosis of HIV [5, 12] prompted a review of the WHO paediatric treatment guidelines. In June 2008, new guidance was issued recommending prompt initiation of ART in infants diagnosed with HIV infection. In order to identify those infants who will need immediate ART, early confirmation of HIV infection is required, thus WHO recommendations on the diagnosis of HIV infection in infants and children were published in 2010 [8].

4.2 Background

Infants and children can be infected with HIV during pregnancy, during delivery and post partum, through breastfeeding, or through sexual or parenteral exposure. Infants infected *in utero* usually have detectable HIV on virological testing at birth. Infants infected at or around delivery usually have undetectable HIV on virological testing at birth, and may take a short time (e.g. 1 – 2 weeks) before the virus is detectable by virological assays.

Data from studies in resource-limited settings confirm that, for infants who acquire HIV before or around delivery, disease progression occurs very rapidly in the first few months of life, often leading to death [3]. In recent studies in South Africa, up to 80% of infected infants, who were well at 6 weeks, progressed to become eligible to start ART by 6 – 12 months of age [5, 13]. Therefore, early determi-

nation of HIV exposure and definitive diagnosis is critical to allow early initiation of potentially life-saving ART [5, 14].

HIV serological testing (antibody testing) can diagnose infection in adults and children more than 18 months of age. Because of the passage of maternal HIV antibodies across the placenta to the baby, a positive HIV serological test in infancy does not confirm HIV infection in the infant, but does indicate maternal HIV infection and exposure of the infant. HIV serological tests used for clinical diagnostic testing should have a minimum sensitivity of 99% and specificity of 98%, under standardized and validated laboratory conditions [15]. In order to diagnose HIV infection definitively in infants less than 18 months of age, assays that detect the virus or its components (i.e. virological tests) are required.

Virological tests that can be used in infants and children include: assays to detect HIV DNA, assays to detect HIV RNA, and ultrasensitive assays to detect p24 antigen (Up24 Ag) [16].

Assays to detect HIV DNA or HIV RNA or both (collectively known as nucleic acid amplification tests [NAT]) are commercially available using a variety of manual and automated platforms. NAT tests have become cheaper and easier to standardize, and provide several advantages for the early diagnosis of HIV infection in children and for monitoring the effectiveness of ART [17]. HIV virological assays used for the purpose of clinical diagnostic testing should have a sensitivity of at least 95% and a specificity of 98% or more under quality-assured, standardized and validated laboratory conditions.

The sensitivity of virological tests depends in part on the timing of the test. Because a significant proportion of HIV infection occurs in the peripartum period, all virological tests are less sensitive in detecting infection on specimens obtained at birth. HIV DNA and RNA are not detected in early blood specimens but usually become detectable at or after 1 – 2 weeks of age [16]. In infants with in utero HIV infection, HIV DNA and RNA can be detected in peripheral blood specimens obtained within 48 hours of birth.

HIV DNA assays have good accuracy in whole blood and DBS in most circumstances. HIV RNA assays have good accuracy in plasma and DBS, as do the Up24 Ag assays. Only the newer immune complex-dissociated ultrasensitive version of the p24 antigen assays should be used [16].

False-positive and false-negative results can occur with virological testing, and it is necessary to confirm positive test results.[i] Confirmatory testing may stretch already constrained health-care systems, but ensuring accuracy with confirmatory tests reduces the risk of unnecessarily starting uninfected infants on lifelong ART.

DBS specimens are easiest to collect, store and process; they do not require venepuncture as they can be obtained by using blood from a finger-stick or heel-stick. They carry a smaller biohazard risk than liquid samples, are stable at room temperature for prolonged periods and are easier to transport, allowing for centralized laboratory testing. Specimens from DBS can be used for detecting HIV DNA, HIV RNA, or Up24 Ag [16]. The use of DBS is very practical for testing HIV-exposed infants in lower-level health facilities, and should be more widely implemented in order to improve access to diagnostic testing in a range of resource-limited settings.

(i) In infants with a first positive virological test result, start ART without delay and at the same time collect a second specimen to confirm the initial positive virological test result.

In children aged 18 months or more, HIV serological tests, including rapid serological tests (either rapid HIV tests or laboratory-based HIV enzyme immunoassays [EIAs], or a combination of both), can be reliably used to diagnose HIV infection definitively in the same manner as they are used in adults. HIV serological testing can also be used in infants with unknown maternal HIV status to screen for HIV exposure and to identify infants who have seroreverted and are likely to be uninfected [8].

National programmes in charge of PMTCT and the provision of ART should strive to ensure that diagnostic protocols are in place for systematic testing of HIV-exposed infants and children, and symptomatic infants and children where HIV is suspected. The identification and follow-up of infants born to women known to be HIV infected is a necessary first step in infant diagnosis. National programmes may choose to identify health-care settings (e.g. perinatal, immunization and well child clinics) where routine HIV serological testing of all infants with unknown HIV exposure can be performed. This is especially important where high rates of HIV exposure are anticipated but have not previously been identified for various reasons (e.g. low coverage of maternal antenatal care [ANC] testing, lack of testing facilities and other infrastructure, or where testing was not previously accepted by the community) [18].

It needs to be emphasized that infants and children less than 18 months of age who are known or suspected to have been exposed to HIV should be closely monitored and should benefit early in life from child survival interventions (notably for diarrhoea and pneumonia), co-trimoxazole prophylaxis [19] and potentially ART, even where virological testing is not available for the definitive diagnosis of HIV infection.

Children may or may not have a living parent or identified legal guardian, and issues of consent, competency to consent, disclosure, confidentiality and counselling have to be considered. National policies need to be clear in their recommendations on how to provide HIV testing services to infants and children, and programmes should ensure that tools and resources provide clear specific guidance on counselling, informed consent (from child, parent and/or caregiver) and disclosure of HIV test results [20-21]. If HIV infection is diagnosed in a young child or infant, the mother herself is usually HIV-infected, and partners and other siblings may also be infected. Appropriate counselling and support should therefore be provided to families when testing for HIV in children.

4.3 The determination of HIV infection in infants and children

The term "infant" refers specifically to a child less than 12 months of age.

All infants should have their HIV exposure status established at their first contact with the health system, at or around birth, but always before 6 weeks of age.[ii] This may be ascertained in one of the following ways.

1. Preferably, by determining whether the HIV status of the mother has been assessed in this pregnancy through review of records, or maternal or caregiver questioning.
2. If maternal HIV testing has not been done or the HIV status of the mother remains unclear for the duration of the pregnancy, then by performing an HIV serological test on the mother after obtaining informed consent.

(ii) Countries may choose to identify circumstances or settings where this recommendation may need modification, based on HIV prevalence.

3. If the mother is unavailable or does not consent to maternal HIV testing, then by recommending HIV serological testing of the infant to detect HIV exposure. Maternal or guardian consent is required for such testing.

For infants less than 6 weeks of age with unknown HIV exposure and in settings where the HIV epidemic is generalized (i.e. >1% prevalence in women attending ANC), maternal and child health (MCH) programmes are strongly recommended to provide HIV serological testing to mothers or their infants in order to establish exposure status.[iii,iv]

Virological testing should be conducted at 4 – 6 weeks of age for infants known to be exposed to HIV, or at the earliest possible opportunity thereafter. Virological testing at 4 – 6 weeks of age will identify more than 95% of infants infected *in utero* and intrapartum [22-25]. Some flexibility in implementing this recommendation may be required, based on current national or local postpartum and infant follow-up practices. However, delaying testing beyond this time delays diagnosis and puts HIV-infected infants at risk for disease progression and death. Results from virological testing in infants must be returned to the clinic and child/mother/carer as soon as possible, but at the very latest within four weeks of specimen collection. Positive test results should be fast-tracked to the mother-baby pair as soon as possible to enable prompt initiation of ART.

Well, HIV-exposed infants either who have not had a virological test or have had an earlier negative virological test, are recommended to have HIV serological testing at around nine months of age (or at the time of the last immunization visit). Those who have reactive serological assays at nine months should have a virological test to identify infected infants who need ART.

Positive virological testing in an infant at any age is considered indicative of HIV infection for purposes of clinical management, and ART is indicated (see Chapter 5). A repeat test on a separate specimen should be performed to confirm the initial positive test. The reliability of the laboratory (determined by standard quality assessment) is fundamental to ensure reliable test results [16].

Urgent HIV diagnostic testing is recommended for any infant presenting to health facilities with signs, symptoms or medical conditions that could indicate HIV infection. In this situation, infants should initially be tested using HIV serological testing, and those with detectable HIV antibodies should have virological testing.

For children 12 – 18 months of age, diagnosis using virological testing is recommended. However, in resource-limited settings where access to virological testing is limited, it is recommended that, for this age group, virological tests are performed only after positive serological testing.

A definitive diagnosis of HIV infection in children aged 18 months or more (with known or unknown HIV exposure) can be made with HIV serological tests, including rapid serological tests following standard testing algorithms used for adults (see Annex J). The confirmation of a positive serological test result should follow standard national testing algorithms and, at a minimum, should involve du-

(iii) Countries may wish to determine prevalence thresholds and other circumstances where this recommendation should be followed.

(iv) Nationally or internationally approved rapid HIV serological tests may be used.

plicate testing using a different HIV serological test [8]. The use of rapid serological tests for diagnosis has the advantage that the results become available at the time of the clinic visit.

For children aged 18 months or more with signs and symptoms suggestive of HIV infection, WHO strongly recommends the use of HIV serological testing in accordance with national protocols. Some clinical conditions are very unusual without concomitant HIV infection (e.g. Pneumocystis pneumonia, oesophageal candidiasis, lymphoid interstitial pneumonitis, Kaposi sarcoma and cryptococcal meningitis). The diagnosis of these conditions suggests HIV infection and indicates the need to perform HIV serological testing.

4.4 Diagnosing HIV infection in breastfeeding infants and children

A breastfeeding infant or child is at risk for acquiring HIV infection throughout the entire breastfeeding period. Breastfeeding should not be stopped in order to perform any kind of diagnostic HIV test. A positive virological test results should be considered to reflect HIV infection, and the usual confirmatory algorithms followed. However, interpreting negative results is difficult. A six-week window period after the complete cessation of breastfeeding is advised before testing; only then can negative virological test results be assumed to reliably indicate HIV infection status. This applies to breastfeeding infants and children of all ages.

4.5 Diagnosing HIV infection where mother or infant has received ARV drugs for PMTCT

Existing data indicate that all types of virological testing can be used from six weeks of age even if the mother is breastfeeding the child and on ART. Mothers should not discontinue the use of ART and should not discontinue breastfeeding for the purposes of testing for HIV.

4.6 Presumptive diagnosis of severe HIV disease in HIV-exposed infants and children less than 18 months of age

No single clinical diagnostic algorithm has proved highly sensitive or specific for the diagnosis of HIV infection. Clinical algorithms vary in their sensitivity and specificity [26-28], especially with respect to the age of the child. In particular, they are less reliable in infants [29]. HIV serological testing (especially rapid testing) and increased access to early virological testing must be made available to help clinicians implement improved diagnostic algorithms.

However, where access to virological testing is not yet available, a presumptive diagnosis of severe HIV disease can be made in infants and children who are less than 18 months of age with a positive serological HIV test (in either the mother or child), and who have specific symptoms suggestive of HIV infection (see section 5.6). An infant or child who meets these criteria has severe HIV disease and needs immediate ART. HIV serological testing should be repeated at 18 months of age to confirm HIV infection in the child. It should be emphasized that WHO clinical staging of HIV disease can only be employed where HIV infection has been established.

Table 3: Summary of testing methods for infants and children[a, b]

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

Testing method/ assay	Specimen type/ modality	Purpose	Paediatric population for testing	Comments
HIV DNA	Whole blood/ liquid	Diagnostic	Infants and children	Confirm reactive result with a second virological test.
HIV DNA	Whole blood/ DBS	Diagnostic	Infants and children	Confirm reactive result with a second virological test.
HIV RNA	Plasma/liquid	Diagnostic	Infants and children	Exercise caution in interpreting negative results if infant is established on ART. Confirm reactive result with a second virological test.
HIV RNA	Whole blood/ DBS	Diagnostic	Infants and children	Exercise caution in interpreting negative results if infant is established on ART. Confirm reactive result with a second virological test.
Up24 Ag	Plasma/liquid	Diagnostic	Infants and children	Use other virological test in regions where subtype D is common or if infant is already on ART. Confirm reactive result with second virological test.
Up24 Ag	Whole blood/ DBS	Diagnostic	Infants and children	Use other virological test in regions where subtype D is common or if infant is already on ART. Confirm reactive result with second virological test.

[a] In children less than 18 months of age, HIV infection is diagnosed based on:
– positive virological test for HIV or its components (HIV RNA or HIV DNA or Up24 Ag)
– confirmed by a second virological test obtained from a separate determination taken more than four weeks after birth.

[b] Virological testing for infants requires that test results be returned to the clinic and the child/mother/caregiver as soon as possible and, at the latest, within four weeks of specimen collection. Positive results should be fast-tracked to the mother – baby pair as soon as possible to enable prompt initiation of ART.

5. WHEN TO START ANTIRETROVIRAL THERAPY IN INFANTS AND CHILDREN

5.1 Recommendations

5.1.1 Infants

1. Initiate ART for all HIV-infected infants diagnosed in the first year of life, irrespective of CD4 count or WHO clinical stage.
   (Strong recommendation, moderate quality of evidence)

5.1.2 Children

2. Initiate ART for all HIV-infected children between 12 and 24 months of age irrespective of CD4 count or WHO clinical stage.
   (Conditional recommendation, very low quality of evidence)
3. Initiate ART for all HIV-infected children between 24 and 59 months of age with CD4 count ≤750 cells/mm^3 or %CD4+ ≤25, whichever is lower, irrespective of WHO clinical stage.
   (Strong recommendation, very low quality of evidence)
4. Initiate ART for all HIV-infected children more than 5 years of age with CD4 count ≤350 cells/mm^3 (as in adults), irrespective of WHO clinical stage.
   (Strong recommendation, moderate quality of evidence)
5. Initiate ART for all HIV-infected children with WHO HIV clinical stages 3 and 4, irrespective of CD4 count.
   (Strong recommendation, low quality of evidence)
6. Initiate ART for any child less than 18 months of age who has been given a presumptive clinical diagnosis of HIV infection.
   (Strong recommendation, low quality of evidence)

Current research demonstrates that the initiation of ART early in infancy and childhood dramatically reduces the risk of death and disease progression [5, 12]. Without effective treatment, an estimated one third of infected infants will have died by one year of age, and about half will have died by two years of age [30, 31]. Given these data, WHO has updated the recommendations on when to begin ART.

Table 4: Explanation of age terminology used in these recommendations

Term		Definition
Infant	=	<12 months of age
Under 12 months of age	=	<12 months of age
12 months of age or older	=	≥12 months of age
Age 5 and over	=	>59 months of age

Starting ART in infants is recommended when HIV infection is diagnosed [5]. For children 24 months of age and older, determining when to initiate ART relies on clinical and/or immunological assess-

ment [32, 33]. For children aged 12 to 24 months, the guidelines make a conditional recommendation to initiate ART irrespective of CD4 count or WHO clinical stage. National authorities need to consider whether implementing this recommendation is likely to lead to better health outcomes for most HIV-infected children. Despite the lack of high quality evidence, the guideline panel felt that the benefits of adopting this approach outweigh the risks – especially where access to CD4 testing is limited and rates of child mortality are high.

Deciding when to start ART should also consider the child's social environment, including the identification of a clearly defined caregiver who understands the prognosis of HIV and the implications of ART (i.e. lifelong therapy, consequences of non-adherence, and the administration, toxicities and storage of drugs). Also, identifying a secondary (back-up), informed caregiver is advised. Access to adequate nutrition (see Chapter 14) and support for families is equally important. Informing older children of their diagnosis of HIV improves adherence. Disclosure to family members may improve adherence and should be encouraged [34-36]. Informing children and disclosing their HIV status to them is a process best performed with support from skilled health professionals (see Chapter 16).

5.2 When to initiate ART in HIV-infected infants

All infants with confirmed HIV infection should be started on ART, irrespective of the clinical or immunological stage.

Where viral testing is not available, infants less than 12 months of age with clinically diagnosed, presumptive severe HIV infection should start ART as soon as possible. Confirmation of HIV infection should be obtained as soon as possible.

By two years of age, over half of HIV-infected children will die in the absence of treatment [30, 31, 37, 38]. Recent studies demonstrated that more than 80% of infected infants become eligible to start ART before six months of age when using the 2006 clinical and/or immunological criteria for the initiation of treatment [13]. Starting asymptomatic infants on ART as soon as possible after diagnosis leads to a reduction in mortality compared with those in whom treatment initiation is delayed until immunological decline or clinical symptoms develop [5].

5.3 When to initiate ART in HIV-infected children 12 months of age and older

For children aged 12 to 24 months, these guidelines offer a conditional recommendation to initiate ART irrespective of immunological or clinical stage. Although no randomized trials support this recommendation, a number of studies have shown that the estimated risk of mortality is significantly higher for HIV-infected children under 2 years of age [31, 39, 40]. Furthermore, a systematic review contrasting disease progression in HIV-infected children in sub-Saharan Africa and the USA and Europe demonstrates that mortality rates in the first two years of life are higher for African children, and that for any given CD4 count or viral load (VL) African cohorts have worse health outcomes [41].

Based on these considerations the guideline panel concluded that where access to immunological testing is limited, and the burden of paediatric HIV disease is high, simplifying eligibility criteria for

initiation of ART may significantly improve health outcomes for HIV-infected children. National programmes need to determine how best to implement this recommendation, and whether to advocate universal treatment for all <24 months or focus on universal treatment for infants <12 months and apply clinical and immunological criteria for children between 12 and 24 months.

For all children 24 months or older, clinical and immunological thresholds should be used to identify those who need to start ART.

5.4 Clinical criteria to start ART

The WHO *clinical staging of HIV/AIDS for children with established HIV infection* (see Annex C) is consistent with the adult clinical classification system (Table 5). Clinical staging should be used once HIV infection has been confirmed (i.e. once there is serological and/or virological evidence of HIV infection).

Table 5. WHO classification of HIV-associated clinical disease*

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

* Annexes C and D provides further details on staging events and criteria for recognizing them.

A preliminary analysis of the revised WHO staging, based on clinical signs at baseline and disease history, in children enrolled in the Children with HIV Antibiotic Prophylaxis (CHAP) trial [42] showed that clinical staging in children not on ART is predictive of mortality risk[i] [43]. The clinical stage is therefore useful to identify when to start ART (Table 5). However, clinical staging is not as useful in infants and children less than two years of age.

Asymptomatic or mildly symptomatic HIV-infected children (i.e. those with clinical stages 1 and 2 disease) should be considered for ART when immunological values fall near the described threshold values. A drop below threshold values should be avoided.

Treatment with a potent and efficient ARV regimen improves clinical status and effectively reverses the clinical stage. It is recognized, however, that reliance solely on clinical criteria may inappropriately delay the initiation of ART.

5.5 Immunological criteria to start ART

The immunological parameters of the HIV-infected child of 24 months of age and older should be measured in order to assess the severity of HIV-related immunodeficiency and to guide decision-

(i) Confirmed weight-for-age and haemoglobin levels were also predictive of mortality in HIV-infected children. The timing of the initiation of ART in relation to interventions to prevent or treat malnutrition and anaemia requires further study.

making on the initiation of ART. The results of CD4 measurement should be used in conjunction with clinical assessment.

The CD4 threshold for starting treatment in 2 to 5-year-olds has changed.

All children 2 to 5 years of age with %CD4+ ≤25 or CD4 absolute count of ≤750 cells/mm^3 are eligible for ART (Table 6).

CD4 levels in healthy infants who are not infected with HIV are considerably higher than those observed in uninfected adults, and slowly decline to adult values by the age of about five to six years of age. Absolute CD4 count is naturally less constant and more age-dependent than percent CD4+ (%CD4+) in younger children (i.e. <5 years). Therefore, it is not possible to define a single threshold for when to start ART. CD4 measurements are valuable for making decisions about starting therapy and WHO encourages national programmes to increase access to CD4 measurement technologies.

Serial measurements are more informative than individual values and also reflect trends over time. Where possible, these measurements should compare the same parameter; i.e. either absolute CD4 count or, in children less than 5 years of age, percent CD4+. As with clinical status, immunological recovery occurs with successful ART; thus, CD4 measurements are useful for monitoring response to treatment.

The CD4 levels that identify thresholds for when to start ART are derived from longitudinal data on HIV-infected infants and children and, except in children less than 24 months of age, correspond to a 12-month mortality risk of up to 5% [39]. It should be noted that the younger the child, the less predictive the %CD4+ or absolute CD4 count of mortality. In infants and children less than two years of age, there is a high risk of death, even at a high CD4 levels (e.g. >1 500 cells/mm^3 or %CD4+ >25). The available CD4 data for children are based on studies mostly from resource-rich countries.

For children five years and older, it is recommended that thresholds used for adults to initiate ART are used to simplify programme approaches.

Table 6 summarizes the recommendations for initiating ART in HIV-infected infants and children according to the clinical stage and the availability of immunological markers (revised in 2010).

Table 6: Recommendations for initiating ART in infants and children; revised in 2010

Age	Infants and children <24 months of age[a,b]	≥24 months of age to 59 months of age	Five years of age or older
%CD4+	All[c]	≤25	NA
Absolute CD4	All[c]	≤750 cells/mm^3	≤350 cells/mm^3 (As in adults)

[a] All HIV-infected infants should receive ART due to the rapid rate of disease progression.

[b] Countries with reliable access to CD4 monitoring may choose to apply clinical and immunological criteria for initiation of ART in children aged 12 – 23 months.

[c] In children with absolute lymphopaenia, the CD4 percentage (%CD4+) may be falsely elevated.

The predictive value of total lymphocyte count (TLC) for mortality is not reliable, especially for younger infants, and it is therefore not recommended to use TLC to guide decisions on starting ART.

Determination of viral load (e.g. using plasma HIV-1 RNA levels) is not considered a prerequisite to starting ART. Because of the cost and complexity of viral load testing, currently, WHO does not require its routine use to assist with decisions on when to start therapy, to determine adherence, or to recognize treatment failure in resource-limited settings. It is hoped, however, that increasingly feasible and affordable methods of determining viral load will become available.

Table 7: Recommendations for initiating ART in HIV-infected infants and children according to clinical stage and immunological markers

	Clinical stage	Immunological
<24 months	Treat all	
>24 months	Stage 4[a]	Treat all[b]
	Stage 3[a]	Treat all
	Stage 2	Treat if CD4 below age-adjusted threshold Don't treat if no CD4 available:
	Stage 1	

[a] Stabilize any opportunistic infection (OI) before initiating ART.

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

5.6 Criteria for starting ART in infants and children less than 18 months with a presumptive diagnosis of severe HIV disease

Where access to virological testing is not yet available, WHO has developed criteria for making a presumptive diagnosis of severe HIV disease in children less than 18 months of age, in order to allow initiation of potentially life-saving ART. Any presenting acute illnesses should be managed first followed by prompt initiation of antiretroviral therapy.

In infants and children who have been started on ART on the basis of a presumptive diagnosis of severe HIV disease, treatment should be closely monitored and confirmation of HIV infection should be obtained as soon as possible using age-appropriate testing methods. Additionally, HIV serological testing should be performed at 18 months of age to confirm definitive HIV infection status in the child. Decisions on further treatment should be adjusted at that time in accordance with the results. ART should be stopped in infants and children only where HIV infection can be confidently ruled out and when such children are no longer exposed to HIV (i.e. through breastfeeding from an HIV-infected mother).

The initiation of ART on the basis of a presumptive diagnosis of severe HIV disease is not recommended for use by providers who are not appropriately trained in HIV care or the administration of ART. Presumptive diagnosis of severe HIV disease should not be used in children aged 18 months and older as antibody testing establishes their HIV infection status.

Table 8 lists the criteria for a presumptive clinical diagnosis.

Table 8: Criteria for presumptive diagnosis of severe HIV disease in infants and children <18 months of age where viral testing is not available

A presumptive diagnosis of severe HIV disease should be made if:	
1. The child is confirmed as being HIV antibody-positive **AND**	2a. The infant is symptomatic with two or more of the following: • oral thrush • severe pneumonia • severe sepsis **OR** 2b. A diagnosis of any AIDS-indicator condition(s) a can be made
Other findings that support the diagnosis of severe HIV disease in an HIV-seropositive infant include: – Recent HIV-related maternal death or advanced HIV disease – Child's %CD4+ <20%	
Confirm the diagnosis of HIV infection as soon as possible.	

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

As per the IMCI definition:

Oral thrush: Creamy white-to-yellow soft small plaques on red or normally coloured mucosa which can often be scraped off (pseudomembranous), or red patches on the tongue, palate or lining of mouth, usually painful or tender.

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

Severe sepsis: Fever or low body temperature in a young infant with any severe sign, e.g. fast breathing, chest indrawing, bulging fontanelle, lethargy, reduced movement, not feeding or sucking breast milk, convulsions.

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

6. WHAT TO START – RECOMMENDED FIRST-LINE ARV REGIMENS FOR INFANTS AND CHILDREN

6.1 Recommendations

6.1.1 Infants

1. For infants not exposed to ARVs, start ART with nevirapine (NVP) + 2 nucleoside reverse transcriptase inhibitors (NRTIs).
   (Strong recommendation, moderate quality of evidence)
2. For infants exposed to maternal or infant NVP or other NNRTIs used for maternal treatment or PMTCT, start ART with lopinavir/ritonavir (LPV/r) + 2 NRTIs.
   (Strong recommendation, moderate quality of evidence)
3. For infants whose exposure to ARVs is unknown, start ART with NVP + 2 NRTIs.
   (Conditional recommendation, low quality of evidence)

6.1.2 Children

4. For children between 12 and 24 months of age exposed to maternal or infant NVP or other NNRTIs used for maternal treatment or PMTCT, start ART with lopinavir/ritonavir (LPV/r) + 2 NRTIs
   (Conditional recommendation, low quality of evidence)
5. For children between 12 and 24 months of age, not exposed to NNRTIs, start ART with NVP + 2 NRTIs.
   (Strong recommendation, moderate quality of evidence)
6. For children more than 24 months and less than 3 years of age, start ART with NVP + 2 NRTIs.
   (Strong recommendation, moderate quality of evidence)
7. For children 3 years of age and above, start ART with an NVP or efavirenz (EFV)-containing regimen + 2 NRTIs.
   (Strong recommendation, moderate quality of evidence)
8. For infants and children, the nucleoside backbone for an ART regimen should be one of the following, in preferential order:
   - Lamivudine (3TC) + zidovudine (AZT)
   - 3TC + abacavir (ABC)
   - 3TC + stavudine (d4T)

   (Conditional recommendation, low quality of evidence)

6.1.3 Infants and children with specific conditions

9. For children >3 years of age with TB, the preferred regimen is EFV + 2 NRTIs.
   (Conditional recommendation, very low quality of evidence)
10. For infants and children less than 3 years of age with TB, the preferred regimens are NVP + 2 NRTIs or a triple nucleoside regimen.
    (Conditional recommendation, very low quality of evidence)
11. For a child or adolescent with severe anaemia (<7.5 g/dl) or severe neutropenia (<500 cells/mm^3), the preferred regimen is NVP + 2 NRTIs (avoid AZT).
    (Conditional recommendation, very low quality of evidence)

12. For adolescents >12 years of age with hepatitis B, the preferred regimen is tenofovir disoproxil fumarate (TDF) + emtricitabine (FTC) or 3TC + NNRTI.
(Conditional recommendation, very low quality of evidence)

6.2 Antiretroviral treatment using a public health approach

Countries are encouraged to use a public health approach to support and facilitate wider access to ART [6]. Among the key tenets of this approach are standardization and simplification of ART regimens. Therefore, it is suggested that countries select a limited number of first-line regimens and suitable second-line regimens, recognizing that children who cannot tolerate or who fail the first-line and second-line regimens may require input from more experienced physicians. The use of three ARV medications is the current standard treatment for HIV infection, in order to achieve the best possible suppression of viral replication and to arrest the progression of HIV disease. It is important to maximize the durability and efficacy of any first-line regimen by incorporating approaches to support adherence.

Box 1: Standard regimen for first-line ART
2 NRTIs + 1 NNRTI

NRTI/NNRTI-based regimens are efficacious and generally less expensive. In addition, generic formulations may be available, and a cold chain is not required.

Table 9: Examples of NRTIs and NNRTIs

NRTIs include		
Thymidine analogue: zidovudine (AZT) stavudine (d4T)	Cytidine analogue: lamivudine (3TC)	Guanosine analogue: abacavir (ABC)
NNRTIs include		
	efavirenz (EFV) nevirapine (NVP)	

When appropriate ARV regimens are being selected for the national formulary, the following programme-level factors should be taken into consideration:

- ability to treat all ages
- suitability of drug formulation, particularly for dosing in infants, young children
- ease of dispensing for pharmacists and caregivers
- licensing approval by national drug regulatory authorities for the product and the recommended dose
- toxicity profile
- laboratory monitoring requirement

- potential for maintenance of future treatment options
- possibility of infant exposure to maternal ART or preventive ARV regimens, which could result in drug resistance
- issues of adherence
- prevalent coexisting conditions (e.g. coinfections, malnutrition, malaria, TB, hepatitis B and hepatitis C)
- availability and cost-effectiveness
- capacity of drug procurement and supply systems.

The choice of an appropriate ARV regimen may be further influenced by:

- access to a limited number of ARVs in forms suitable for the treatment of infants and young children (see special considerations below);
- limited health service infrastructures (including human resources);
- the presence of varied HIV types (e.g. HIV-2).

6.3 Considerations for drug formulations and doses for infants and children

Quality-assured[i] ARV drugs in fixed-dose combinations (FDCs)[ii] or blister co-packs[iii] were previously used for adults and older children but have recently become available for use by young children. Once-daily dosing has become available for some adult ARV combinations and further simplifies drug regimens. The advantages of FDCs and once-daily dosing include improved adherence which, in turn, limits the emergence of drug resistance. FDCs also simplify ARV storage and distribution logistics.

WHO strongly encourages the continued development of new formulations specifically for infants and children.

Syrups, solutions and sprinkles may remain necessary for treating infants and very young children who cannot swallow tablets or capsules, but they have shortcomings including limited availability, high cost, storage difficulties, reduced shelf-life, sometines high alcohol content and poor palatability. As children become older, it is preferable to give solid formulations. See the report of the WHO Paediatric Antiretroviral Working Group on ARV formulations for children at http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html) [44]. For most ARVs, capsules and tablets are available in sufficiently low doses to enable accurate dosing for children. Some drugs, however, do not have solid formulations in doses appropriate for paediatric use. The pharmacokinetic profile of some but not all crushed tablets or sprinkled capsule contents have been evaluated.

Using tablets that must be cut can result in underdosing or overdosing, particularly if the tablets are unscored, and this may increase the risk of resistance or toxicity. Some solid formulations do not

(i) In the context of this document, quality-assured medicines assembled in FDCs include individual products deemed to meet international standards of quality, safety and efficacy. For WHO's work on the prequalification of ARVs, see http://www.who.int/hiv/amds/en/

(ii) FDCs include two or more active pharmacological products in the same pill, capsule, granules, tablet or oral liquid.

(iii) A blister co-pack is a plastic or aluminium blister containing two or more pills, capsules or tablets.

have even distribution of drug throughout the tablet. However, while suboptimal, cutting adult-dose solid formulation ARVs may be considered when no alternatives are available. When cutting unscored tablets, the use of tablet cutters is preferred. Unscored tablets should not be cut to fractions below one half. Pharmacokinetic studies have confirmed that for younger children the use of single-drug liquid formulations is better than splitting adult FDCs [45].

Dosing in children is usually based on either weight or body surface area [46]. As these change with growth, drug doses must be adjusted in order to avoid the risk of underdosing. Standardization is important and it is recommended that health-care workers be provided with tables of simplified drug doses for administration. Such tables may vary with the local availability of ARV drugs and formulations. WHO has developed prototype weight-band based dosing tables, as well as tools to assist countries with the standardization and calculation of drug doses[iv] (*see* Annex E). A range of fixed-dose formulations for children are available including d4T/3TC/NVP, AZT/3TC/NVP and ABC/3TC.

6.4 Choice of a first-line regimen

Studies of many different potent ARV regimens in children have demonstrated that similar improvements to those obtained in adults are seen in morbidity, mortality and surrogate markers [38, 47-52].

6.4.1 Infants and children <24 months

The recommended first-line regimen for infants and children <24 months with no prior exposure to maternal or infant NNRTIs, or whose exposure to maternal or infant ARVs is unknown, is to start standard NVP-containing triple therapy.

Box 2: Preferred regimen for NVP-naive infants or children <24 months with no known prior exposure to NVP
NVP + 3TC + AZT

Two NRTIs are combined with NVP as the NNRTI (Box 2). Reverse transcriptase inhibitor drugs prevent HIV replication by inhibition of the action of reverse transcriptase, the enzyme that HIV uses to make a DNA copy of its RNA. EFV is not currently recommended for use in children less than 3 years of age due to lack of information on appropriate dosing.

Data from a recent meta-analysis and from observational studies confirm that HIV-infected infants exposed to NNRTIs through infant prophylaxis or maternal treatment or prophylaxis have demonstrable viral resistance [53, 54]. An observational study [53] and a recent RCT [55] demonstrate that response to NVP-containing first-line treatment regimens may be compromised in infants and older children who acquire HIV despite intrapartum or peripartum exposure to NVP. Therefore, for HIV-infected infants and children under 24 months of age with a history of exposure to NVP or other NNRTIs used for maternal

(iv) A generic excel-based spreadsheet tool to assist in the development of dosing tables is available on the WHO website at http://www.who.int/hiv/paediatric/generictool/en/

treatment or PMTCT, a PI-based triple ART regimen is recommended. Where PIs are not available, affordable or feasible, NVP-based therapy is recommended [56] (see Annex J, Figure 5).

Box 3: Preferred initial regimen for NNRTI-exposed infants or children <24 months

LPV/r + 3TC + AZT

While the guidelines panel felt the evidence and risk – benefit analysis warranted the above recommendation to be strong, they also recognized that in many resource-limited settings, LPV/r is not available, affordable or, due to cold chain requirements, not feasible for use. It is also acknowledged that the use of LPV/r in a first-line regimen may compromise the potential to construct a potent second-line regimen.

6.4.2 Children ≥24 months

The recommended first-line regimen for HIV-infected children ≥24 months of age, is two NRTIs plus one NNRTI (Box 1). There are two exceptions: the use of EFV should be avoided in adolescent girls (due to the teratogenic potential of EFV in the first trimester of pregnancy) and in children less than 3 years of age (due to lack of appropriate dosing information in this age group). (See Table 10 for a summary of recommended first-line ART regimens for infants and children.)

The use of a triple NRTI regimen (i.e. [AZT or d4T] + 3TC + ABC) can be considered as an option for initial therapy in special circumstances (see Box 4). Of concern is the somewhat lower virological potency of this regimen compared with a two-class triple-drug combination in adult studies [57-60]. Currently, a triple NRTI regimen is only recommended in children less than three years of age who are receiving treatment for TB, a situation where NVP may not be an optimal choice because of drug interactions with rifampicin (see Chapter 13). This regimen could be considered for adolescents who may become pregnant, or adolescents with anticipated or documented poor adherence (see Chapter 15).

Box 4: Recommended alternative ARV regimen for infants and children to simplify management of toxicity, comorbidity and drug – drug interaction

AZT or d4T[a] + 3TC[b] + ABC

[a] AZT should not be given in combination with d4T.

[b] FTC can be used instead of 3TC in children more than 3 months of age.

6.5 Choice of NRTIs

NRTI drugs recommended for children are described below.

Lamivudine (3TC) is a potent NRTI with an excellent record of efficacy, safety and tolerability in HIV-infected children, and is a core component of the dual NRTI backbone of triple therapy. It is usually given twice daily in children and has been incorporated into a number of FDCs. Once-daily dosing is possible in older children.

Emtricitabine (FTC) is a newer NRTI that has recently been included in WHO's recommended first-line regimens for adults as an option and is also available for use in children; it can be given once daily. FTC is structurally related to 3TC and shares its resistance profile [61]. Where available, it can be used in children more than three months of age as an alternative to 3TC [62].

Stavudine (d4T) initially is better tolerated than AZT and does not require haemoglobin or laboratory monitoring. However, among the NRTIs, d4T has been most often associated with lipoatrophy and lactic acidosis [63]. In addition, peripheral neuropathy, elevated hepatic transaminases and pancreatitis have been observed.

Zidovudine (AZT) is generally well tolerated in children but has been associated with metabolic complications, although to a lesser extent than d4T. Initial drug-related side-effects are more frequent with AZT and the drug can cause severe anaemia and neutropenia; haematological monitoring is advised [64]. This is particularly important in areas where malaria is endemic or where malnutrition is common and anaemia is highly prevalent in young children. Large volumes of AZT liquid formulation are often poorly tolerated, and FDCs containing AZT are now available for children. In the event of intolerance, ABC or d4T can be substituted for AZT, except in cases of suspected lactic acidosis, where ABC is preferred.

Abacavir (ABC) is an alternative NRTI in first-line therapy. Data from clinical trials indicate a similar safety profile in children to that in adults, with very little haematological toxicity [65]. However, two large clinical trials found an association between ABC and myocardial infarction in adults [66, 67] but a meta-analysis from 54 clinical trials of ABC and another more recent clinical trial did not find this predisposition to cardiovascular diseases [68, 69]. Therefore, NRTI combinations containing ABC provide a good NRTI backbone for use with NNRTIs or as part of a triple nucleoside regimen. Of all the NRTI drugs, ABC has the least effect on mitochondrial DNA [70] and would be the preferred substitute for d4T or AZT in children developing lactic acidosis. However, in studies in Europe and the United States, ABC is associated with a potentially fatal hypersensitivity reaction in about 3% of children [71]. The frequency of ABC hypersensitivity in other regions is not known. In infants and children suspected of having a hypersensitivity reaction, ABC should be stopped and never restarted (see Annex F). Children starting ABC and/or their caregivers should be advised about the risk of hypersensitivity and the need to consult their care provider immediately if signs or symptoms of hypersensitivity occur.

Tenofovir (TDF) is included as an option for first-line regimens in adults. In adults, TDF is generally well tolerated [72] although there are numerous reports of renal insufficiency [73-75]. Because of limited paediatric safety data (especially the potential for effects on bone mineralization), the use of TDF in younger children is not yet recommended. A study in 16 HIV-infected children (age range 6.4 – 17.9 years) comparing TDF and d4T after 12 months of treatment reported that TDF did not impair bone mineral accrual and resulted in a good immunological response to ART [76]. However, a study using TDF as part of salvage therapy in children (age range 8.3 – 16.2 years) demonstrated a 6% decrease in bone density in 30% of children after 48 weeks of TDF [77]. Subsequent research has shown similar results [78], suggesting that TDF may be of limited use in prepubertal children. Additional clinical trials in ART-naive children as young as 2 years are ongoing.

Didanosine (ddI) is an adenosine nucleoside analogue NRTI. Its use is usually reserved for second-line regimens (see Chapter 12).

6.5.1 Choosing between NRTIs for first-line

The decision to use d4T, AZT or ABC in the first-line regimen needs to be made at the country level on the basis of local considerations, but it is recommended that at least two of these NRTIs be available to allow the substitution of one drug for the other should there be toxicity.

Fewer laboratory monitoring requirements may be a good reason to favour d4T over AZT as the chosen NRTI component, in particular, during the rapid scale-up of programmes. However, there is a long term risk of toxicity, particularly lipoatrophy in children treated with d4T-containing regimens. The use of d4T is being reduced in adults because d4T toxicity is frequently irreversible. D4T toxicity relates to the intracellular accumulation of the drug and its metabolites, and the subsequent poisoning of mitochondrial function. This explains why d4T toxicity develops gradually, over a longer time frame than toxicity to other ARVs. In children, however, d4T clearance is enhanced and intracellular levels are typically lower than in adults. Children can and do develop d4T toxicity but it is reported less often than in adults [64, 79-81].

Unlike d4T, AZT toxicity is increased in children compared with adults, with a high proportion developing anaemia over the first few months of therapy. However, in the long term, AZT is much better tolerated than d4T and is preferred over d4T despite the problem of anaemia and the relatively higher cost.

These guidelines introduce ABC as a preferred NRTI for first-line therapy. The choice of first-line NRTIs impacts second-line ART. Both AZT and d4T are thymidine analogues with very similar resistance profiles. Failure of AZT or d4T therapy results in the accumulation of thymidine analogue mutations (TAMs). The longer a child stays on a failing d4T- or AZT-based regimen, the more TAMs accumulate. Multiple TAMs reduce susceptibility to ABC, and thus may impact the success of future second-line therapy. By contrast, resistance to ABC does not result in resistance to thymidine analogues and one important advantage of ABC as a first-line drug is that both AZT and d4T will remain active in second-line.

There are limited options for paediatric treatment but all of these first-line choices are now available as generic, child-friendly FDCs. These guidelines recommend a preferential order of NRTIs to be used in first-line regimens, with AZT preferred over ABC, and ABC preferred over d4T. This recommendation seeks to balance toxicity, cost and practicality. National programmes should take into account the comparative short and long-term toxicities, as well as the relative risks and benefits to determine the optimal choice of NRTI for use in first-line therapy. Because of proven antagonism, d4T and AZT should never be used together [82, 83].

6.6 Choice of NNRTIs

NNRTI-based regimens are now the most widely prescribed combinations for initial therapy. They are potent, i.e. they rapidly reduce viral load, but are inactive with respect to HIV-2 and group O of HIV-1. In addition, a single mutation can induce cross-class resistance to the currently available NNRTIs. The NNRTIs EFV and NVP have both demonstrated clinical efficacy when administered in appropriate combination regimens in children. However, differences in toxicity profile, the potential for interac-

tion with other treatments, a lack of dosing information for EFV in young children and cost are factors that need to be taken into consideration when choosing an NNRTI [84-91].

Efavirenz (EFV) is not currently recommended for use in children less than three years of age because there is no established dosing. EFV is primarily associated with toxicities related to the central nervous system (CNS), teratogenicity and rash. Rash is more frequent in children than in adults, is generally mild, and usually does not require discontinuation of therapy. The CNS symptoms typically abate after 10 – 14 days in the majority of patients; observational studies have revealed transient CNS disturbance in 26 – 36% of children receiving EFV [52, 91]. EFV should be avoided in children with a history of severe psychiatric illness, where there is a potential for pregnancy (unless effective contraception can be assured) and during the first trimester of pregnancy. In these situations, NVP may be the better choice (*see* below). EFV is preferred as the NNRTI of choice in children more than three years of age with TB/HIV coinfection [92] (see Chapter 13).

Nevirapine (NVP) should be given only in combination with other ARVs, except when used for prophylaxis to reduce the risk of perinatal HIV transmission. NVP has a higher incidence of rash than other ARVs. NVP-related rash may be severe and life-threatening, including Stevens – Johnson syndrome and, as noted below, NVP is associated with a rare but potentially life-threatening risk of hepatotoxicity. In these situations, NVP should be permanently discontinued and not restarted (see Chapter 9 and Annex F). This makes the drug less suitable for treating children who are on other hepatotoxic medications, or drugs that can cause rash. There are limited data on the use of NVP in children coinfected with HIV and hepatitis B. NVP is currently the only NNRTI that can be used in infants. In addition, NVP is a component of all the three-drug FDCs currently available.

NVP may be the preferred choice in adolescent girls when there is potential for pregnancy or during the first trimester of pregnancy when EFV should be avoided because of its potential teratogenic effect. While there have been reports of possible NVP-associated hepatotoxicity or serious rash, a review of NVP safety in pregnant women with CD4 between 250-350 cells/mm^3 has not confirmed an increased risk of any serious adverse events, leading to the conclusion that the benefits of using NVP in pregnancy outweigh the risks [21]. Careful monitoring is none-the-less warranted for initiation of ART in adolescent, HIV-infected pregnant girls.

Limited data indicate that both EFV and NVP may interact with estrogen-based contraceptive pills. Because exposure to EFV should be avoided in the first trimester of pregnancy, it is recommended that sexually active adolescent girls receiving EFV consistently use barrier methods to prevent pregnancy in addition to or instead of oral contraceptives. Studies are in progress to evaluate interactions between injectable depot medroxyprogesterone acetate (DMPA) and selected PIs and NNRTIs. Despite initial pharmacokinetic studies suggesting some compromise of contraceptive efficacy, a large clinical study evaluated potential interactions between DMPA and selected PI and NNRTI drugs, and did not find significant clinical interactions [93-96].

Etravirine (ETV) is a new NNRTI that maintains activity against HIV with some NNRTI resistance mutations It is well tolerated in adults. A paediatric 25 mg tablet is in clinical trials.

Annex E provides more detailed information on dosing, preparations, storage and special instructions on the administration of the above-listed drugs.

6.7 Use of PIs in initial therapy

The efficacy of PIs in ARV-naïve children has been demonstrated, but in order to preserve a potent new class for second-line regimens, PIs usually are not used in first-line therapy. However, for infants and children <24 months who have been exposed to NVP or other NNRTIs, either directly or via maternal treatment before labour, during delivery or when breastfeeding, the PI LPV/r is now recommended as part of a first-line regimen.

PIs prevent viral replication by inhibiting the activity of an enzyme called protease that is used by HIV to cleave proteins required in the assembly of new virus particles. The PIs in use for children include LPV, RTV, nelfinavir (NFV), atazanavir (ATV), fos-amprenavir (FPV), darunavir (DRV) [97] and additional new PIs that are currently available to treat adults. RTV is exceptional as it inhibits the liver enzyme that normally metabolizes PIs. It is not used for its own antiviral activity but remains widely used in low doses to boost the effects of other PIs. LPV/r is the only PI available to date in a co-formulation and has been used extensively in children.

Further more detailed information on currently available PIs is available in in Chapter 12.

Annex E details ARV dosing information.

This information may be updated between publications.
Readers are advised to consult the website for the most up-to-date information.
http://www.who.int/hiv/topics/paediatric/en/index.html

6.8 Summary of Chapter 6 – First Line ARV Regimens

Table 10: Summary of preferred first-line ARV regimens for infants and children

Patient group	Standard first-line regimen
INFANTS	
Infant or child <24 months not exposed to ARVs	NVP + 2 NRTI
Infant or child <24 months exposed to NNRTI	LPV/r + 2 NRTI
Infant or child <24 months with unknown ARV exposure	NVP + 2 NRTI
CHILDREN	
Children 24 months to 3 years	NVP + 2 NRTI
Children >3 years	NVP or EFV + 2 NRTI

Box 5: Nevirapine-based regimens
Nevirapine + AZT/3TC (preferred) **OR** **Nevirapine + ABC/3TC** **OR** **Nevirapine + d4T/3TC**

Box 6: Efavirenz-based regimens
Efavirenz + AZT/3TC (preferred) **OR** **Efavirenz + ABC/3TC** **OR** **Efavirenz + d4T/3TC**

Box 7: Protease inhibitor-based regimens
Lopinavir/ritonavir + AZT/3TC (preferred) **OR** **Lopinavir/ritonavir + ABC/3TC** **OR** **Lopinavir/ritonavir + d4T/3TC**

Table 11: Preferred first-line regimens for specific situations

Situation	Preferred first-line regimen
CONCOMITANT CONDITIONS	
Child or adolescent with severe anaemia	NVP + 2 NRTIs (avoid AZT)
Child <3 years with TB treatment	NVP + 2 NRTIs OR 3 NRTIs: AZT or d4T + (3TC + ABC)
Child >3 years or adolescent with TB treatment	EFV + 2 NRTIs OR 3 NRTIs: AZT or d4T + (3TC + ABC)
Adolescent with hepatitis B	TDF + FTC or 3TC + NNRTI*

* EFV should not be initiated in the first trimester of pregnancy or prescribed to women with the potential to become pregnant, unless effective contraceptive use is assured.

7.1 Recommendations

7.1.1 CD4 monitoring

1. CD4 should be measured at the time of diagnosis of HIV infection, and every 6 months thereafter. Monitor with increasing frequency as CD4 count approaches threshold for starting ART.
   (Strong recommendation, very low quality of evidence)
2. CD4 should be measured prior to initiating ART.
   (Strong recommendation, very low quality of evidence)
3. CD4 should be measured every 6 months after initiating ART.
   (Conditional recommendation, very low quality of evidence)
4. Measure CD4 if new clinical staging events[i] develop, including growth faltering and neurodevelopmental delay.
   (Strong recommendation, very low quality of evidence)
5. Where capacity for CD4 measurement is limited, target the use of CD4 monitoring to assess the significance of clinical events.
   (Conditional recommendation, very low quality of evidence)

7.1.2 Viral load monitoring

6. VL determination is desirable, but not essential, prior to initiating ART.
   (Strong recommendation, moderate quality of evidence)
7. VL should be assessed to confirm clinical or immunological failure where possible, prior to switching treatment regimen.
   (Conditional recommendation, very low quality of evidence)

7.1.3 Routine clinical and laboratory monitoring

8. Baseline haemoglobin level (and white cell count, if available) should be assessed at initiation of ART.
   (Conditional recommendation low quality evidence)
9. For infants and children, measure haemoglobin at week 8 after initiation of AZT-containing regimens, or more frequently if symptoms indicate.
   (Conditional recommendation, very low quality of evidence)
10. Growth, development and nutrition should be monitored monthly.
    (Strong recommendation, low quality of evidence)
11. Laboratory monitoring for toxicity should be symptom directed.
    (Strong recommendation, very low quality of evidence)

(i) Staging events are changes in health status that result in a change in the child's stage of HIV, as per WHO guidelines. See Annexes C and D.

7.2 Principle

The inability to perform laboratory monitoring, notably for CD4 or viral load, should not prevent children from receiving ART.

7.3 Background

Clinical and laboratory assessments should be performed at baseline (i.e. at entry into HIV care) for children who have entered care but are not yet eligible for ART, and at initiation of and while on ART.

In resource-limited settings, WHO recommends that clinical parameters be used in conjunction with laboratory assessment, where available, for monitoring of children with HIV who are on ART. The inability to perform laboratory monitoring, notably for CD4 or viral load, should not prevent children from receiving ART. It is highly desirable that each country establish a laboratory monitoring protocol in order to improve the efficacy of therapeutic interventions and to ensure the maximum level of safety when delivering ARV drugs [98-100].

7.4 Baseline clinical and laboratory assessments

The baseline evaluation of HIV-infected infants and children includes clinical assessment and basic laboratory tests, where available. One of the objectives of this initial assessment is evaluation for the presence of active opportunistic infections (OIs). This visit to the clinic also serves as an opportunity to provide counselling and support for children and/or caregivers regarding disclosure of their HIV status to others, nutrition and secondary prevention, as well as for identifying any other specific needs.

Box 8: Baseline clinical assessment for children

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

- weight, height, head circumference and other measures of growth
- clinical staging of HIV disease (Annex C)
- developmental status
- screening for malaria, TB disease, and exposure to TB
- identification of concomitant medical conditions (e.g. hepatitis B or C infection, TB, other coinfections or OIs, pregnancy in adolescent girls)
- details of concomitant medications, including co-trimoxazole and traditional or herbal therapies
- nutritional status, including assessment of the quality and quantity of intake
- for those eligible for ART, assessment of the child's and caregiver's preparedness for therapy.

Box 9: Baseline laboratory assessment for children

- confirmation of HIV infection using virological or antibody testing
- measurement of %CD4+ (preferable for children <5 years) or absolute CD4 cell count where available
- haemoglobin measurement where AZT-containing first-line regimens are being used
- white blood cell count (WBC), if available
- pregnancy test, if indicated from the history, for sexually active adolescent girls
- hepatitis B and C status, where available
- VL, where available

7.5 Routine monitoring of children who are not yet eligible for ART

Because of the rapid rate of disease progression in infants and young children, more frequent clinical and laboratory monitoring is indicated for them than for adults. The clinical evaluation of HIV-infected children who are not yet eligible for ART should be performed every three to six months, at a minimum, and should include the same parameters as are used in the baseline evaluation. CD4 monitoring should be performed every six months; the results of CD4 measurement are useful in determining whether the child has become eligible for treatment and/or co-trimoxazole prophylaxis. Clinical evaluation and CD4 measurements should be obtained more frequently as the clinical or immunological threshold for initiating ART approaches, and at initiation of ART (see Table 12). Routine monitoring of viral load is not essential where capacity and resources are constrained and WHO does not recommend specific virological thresholds for initiating treatment.

Percent CD4 is preferred for children less than 5 years of age rather than absolute CD4 count. However, the inability to perform laboratory monitoring, notably for CD4 or viral load, should not prevent children from receiving ART.

7.6 Routine monitoring of children on ART

Once an infant or child is on ART, the frequency of clinical monitoring will depend on their response to ART. At a minimum, after starting ART, follow-up visits should occur:

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

See Annex J Figure 7 for a description of the routine follow-up visits for infants and children on ART.

Routine clinical assessment should include addressing the child's and/or caregiver's understanding of and adherence to therapy, along with their need for additional support. Key signs of an infant's and child's response to ART include:

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

Observation of the child's responses to therapy should include vigilance for symptoms of potential drug toxicities or treatment failure (i.e. reassessment of WHO clinical stage).

Laboratory assessment of CD4 values is desirable at a minimum of six months after the initiation of ART, and every six months thereafter. More frequent CD4 monitoring is indicated in cases of new or recurrent clinical staging events, growth faltering or neurodevelopmental delay. Where capacity for measuring CD4 is limited, monitoring should be targeted to the assessment of clinical events. Routine monitoring for viral load is not essential where capacity and resources are constrained; however, viral load should be used whenever possible to confirm suspected clinical or immunological failure. Where available, viral load should be assessed at six months after initiation of ART for infants on NNRTI-based regimens who are known to have been exposed to NNRTIs intrapartum or through breastfeeding. Failure to suppress the viral load to below 5 000 copies/ml in an adherent child at this time warrants switching to a PI-based regimen (see Chapter 11).

Table 12: Laboratory parameters for monitoring infants and children at baseline, before and during ART

Laboratory tests for diagnosis and monitoring	Baseline (at entry into care)	At initiation of first-line or second-line ART regimen	Every six months	As required or symptom-directed
HIV diagnostic testing	✔			
Haemoglobin[a]	✔	✔		✔
WBC and differential count				✔
%CD4+ or absolute CD4 cell count[b]	✔	✔	✔	✔
Pregnancy testing in adolescent girls		✔[c]		✔[d]
Full chemistry (including, but not restricted to, liver enzymes, renal function, glucose, lipids, amylase, lipase and serum electrolytes)[e]				✔
HIV VL measurement[f, g]				✔
OI screening (where possible)	✔			✔

[a] Haemoglobin monitoring at week 8 after initiation of ART is recommended if AZT is used.

[b] HIV-infected children not yet eligible for ART should be monitored with CD4 count every six months. For infants and children who develop new or recurrent WHO stage 2 or 3 events, or whose CD4 count approaches threshold values, the frequency of CD4 measurement can be increased.%CD4+ is preferred in children <5 years of age.

[c] Pregnancy testing may be needed for adolescent girls prior to initiating a regimen containing EFV.

[d] For pregnant adolescent girls, provide prophylaxis or combination ART to those who are in need of it for their own health and/or to prevent vertical transmission. (See WHO PMTCT Guidelines, 2010) [102]

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

[f] At present, VL measurement is not a prerequisite for initiation or regular monitoring of ART in resource-limited settings. VL can be used to diagnose HIV infection, and to confirm clinical or immunological failure prior to switching treatment regimen.

[g] VL should be assessed in infants on NNRTI-based regimens who are known to have been exposed to NNRTIs intrapartum or through breastfeeding.

Laboratory assessment of the child's response to treatment and monitoring of adverse reactions should be directed by clinical symptoms (see Annexes F and G), though. some routine monitoring tests are advisable in accordance with the use of specific drugs. In infants and children initiated on AZT-containing regimens, haemoglobin should be measured 8 weeks after starting ART or more frequently if symptoms indicate. Liver function tests (LFT i.e. liver enzymes) are recommended during the first few months of treatment in infants and children receiving NVP who have any signs of hepatitis or hepatotoxicity, who are coinfected with hepatitis viruses, or who are on hepatotoxic medications. Based on data in adults on ART, routine monitoring of LFTs is unlikely to be cost-effective [101].

7.7 Laboratory capacity for routine monitoring

Laboratory protocols for monitoring the safety and efficacy of ART are important. However, WHO recognizes that the same laboratory infrastructures may not be available at all levels of the health-care system. Therefore, WHO has tiered its laboratory monitoring recommendations to primary health-care centres (level 1), district hospitals (level 2) and regional referral centres (level 3) in order to facilitate HIV care and treatment in a variety of settings. Standard quality assessment of laboratories at all levels is important for ensuring reliability. Existing tools for addressing laboratory capacity and quality include the following:

- WHO laboratory recommendations by level are given in Annex I and at http://www.who.int/hiv/amds/WHOLabRecommendationBylevelFinal.pdf
- WHO consultation on technical and operational recommendations for scale-up of laboratory services and monitoring HIV antiretroviral therapy in resource-limited settings http://www.who.int/hiv/pub/meetingreports/scaleup/en/
- Diagnostics and laboratory technology (DLT) website http://www.who.int/diagnostics_laboratory/en/

8. WHAT TO EXPECT IN THE FIRST SIX MONTHS OF THERAPY

8.1 Principles

- In most children, CD4 cell counts rise with the initiation of ART and immune recovery.
- Complications observed in the first few weeks following the initiation of ART are more common in children with severe immunodeficiency.
- In a child with advanced HIV disease, the lack of initial improvement does not necessarily reflect a poor response to ART.

8.2 Background

The first six months on ART are critical. Clinical and immunological improvement is expected but drug toxicities and/or immune reconstitution inflammatory syndrome (IRIS) may emerge. Some children fail to respond as expected or may even exhibit clinical deterioration during this time. Complications in the first few weeks following the initiation of ART are seen most commonly when therapy is started in children with severe immunodeficiency. Apparent failure to improve in a child with advanced HIV disease does not necessarily reflect a poor response to ART; it takes time for HIV viral replication to be controlled by ART and for the child's immune system to recover. It also takes time for the catabolism associated with HIV infection to be reversed, particularly in children with significant HIV-associated wasting. Additionally, as a child with advanced disease recovers immune function, exacerbation of previously subclinical coexisting infections (e.g. TB) may occur, resulting in apparent clinical deterioration. This is not attributable to failure of therapy but rather to its success and the resulting immune reconstitution. It is important to allow sufficient time on therapy before judging the effectiveness of a regimen and to consider the possibility of IRIS in children with worsening disease in the first few months of ART. Supporting adherence during this period is critical and, in such cases, switching of ARV regimen would be inappropriate.

8.3 CD4 recovery

In most children, CD4 cell counts rise with the initiation of therapy and immune recovery. Generally, CD4 levels increase over the course of the first year of treatment, reach a plateau and then continue to rise further over the second year [47]. However, in some children, severe immunosuppression may persist. The lower the CD4 levels at the start of ART, the slower the recovery. At the same time, persistent failure to see a CD4 response should alert the clinician to potential adherence problems or non-response to ART. In this case, viral load determination can be useful.

8.4 Early ARV toxicity

First-line drug toxicities fall into two categories: early toxicity, usually presenting in the first few weeks to months of therapy, and late toxicity. Hypersensitivity reactions may be difficult to distinguish from acute clinical events such as malaria, and from the many manifestations of IRIS. Chapters 9 and 10 provide more detail on identifying and managing toxicity.

8.5 Mortality on ART

While ART significantly decreases mortality overall, death rates are high in the first six months after initiation of ART, particularly when children start ART with stage 4 clinical events, severe immunosuppression, severe malnutrition or very low haemoglobin [3, 103].

8.6 Immune reconstitution inflammatory syndrome

Immune reconstitution inflammatory syndrome (IRIS) is a spectrum of clinical signs and symptoms thought to be associated with immune recovery brought about by a response to antiretroviral treatment [104, 105]. While most HIV-infected children experience rapid benefit from ART, some undergo clinical deterioration. This is the result of either the unmasking of latent or subclincial infection or the reactivation of previously diagnosed, and often treated, conditions (infectious or non-infectious), sometimes termed "paradoxical" IRIS [104, 106-108].

There are limited data on IRIS in infants and children and the causes are not clearly understood. The onset of IRIS in children most often occurs within the first weeks to months following the initiation of ART and is seen most often in children who initiate ART with very low %CD4+ levels (<15%) [106, 109].

The most common OI associated with IRIS in children is TB, but those on treatment for Pneumocystis pneumonia (PCP) or cryptosporidiosis, or who have herpes simplex virus (HSV), fungal, parasitic or other infections may also develop IRIS [110, 111]. Where BCG immunization of infants and children is routine, BCG-associated IRIS (localized and systemic) is frequently observed [109, 112] (see Chapter 13).

Most cases of paradoxical IRIS resolve spontaneously, or can be managed with non-steroidal anti-inflammatory drugs, although some episodes of IRIS can be severe and even lead to death [113]. Unmasking IRIS generally requires treatment of the OI and concomitant anti-inflammatory therapy. In clinical settings where IRIS is suspected, it is often difficult to exclude other acute infectious illnesses and it may be necessary to start empiric antiinfective therapy in addition to specific treatment for IRIS. Occasionally IRIS becomes progressively worse and may require a short course of treatment with corticosteroids and rarely, a temporary discontinuation of ART [106]. The same ART regimen should be restarted once IRIS has improved.

9. ARV DRUG TOXICITY

9.1 Principles

- More attention should be paid to pharmacovigilance surveillance in paediatric populations.
- Toxicities can be monitored clinically. Routine laboratory monitoring, although desirable, is not essential.
- Moderate or severe toxicities may require substitution of a drug, but do not require discontinuation of all ART.
- Severe life-threatening toxicity requires discontinuation of all ARV drugs and the initiation of appropriate supportive therapy until the child is stabilized and the toxicity is resolved.
- Regardless of their severity, adverse reactions may affect adherence to therapy; the child and caregivers should be familiar with potential side-effects, and with signs of toxicities that are serious and require immediate contact with the provider.

9.2 Background

Antiretroviral agents can be responsible for a wide range of toxicities, from low-grade intolerance that may be self-limiting, to life-threatening side-effects. Differentiating between complications of HIV disease and ART toxicity (also known as adverse reactions) is sometimes difficult. Alternative explanations for an observed toxicity could include a concurrent infectious process (e.g. common childhood illnesses, including hepatitis A in a child with symptoms of hepatitis, or malaria in a child with severe anaemia), or a reaction to medications other than ARVs (e.g. isoniazid-induced hepatitis in a child on treatment for TB or a rash induced by co-trimoxazole). Non drug-related clinical events or adverse reactions that are not caused by an ARV drug do not require ARV drugs to be changed.

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 [114]. However, some toxicities are less common in children than in adults (e.g. NVP-related symptomatic hepatotoxicity is rare in children), while others are more commonly reported in children than adults (e.g. EFV-related rash or TDF-related loss of bone density). Most children on ART are from middle- or low-income settings, where pharmacovigilance systems may not be developed and adverse reactions may be underreported. More attention should be paid to pharmacovigilance and post-marketing surveillance in paediatric populations.

Drug-related adverse reactions while on ART can occur immediately (soon after a drug has been administered), early (within the first days or weeks of treatment) or late (after months or more of treatment). Adverse reactions can vary in severity from mild to severe to life-threatening and may be specific to the drug or generic to the class of drugs in use. (See Box 10 for guiding principles in the management of ARV drug toxicity.)

9.3 Toxicities

The most common toxicities include the following:

Haematological: drug-induced bone-marrow suppression, most commonly seen with AZT (anaemia, neutropenia and, more rarely, thrombocytopenia).

Mitochondrial dysfunction: primarily seen with the NRTI drugs and include lactic acidosis, hepatic toxicity, pancreatitis and peripheral neuropathy. The NRTIs differ in their ability to affect mitochondrial function: d4T and ddI are worse than AZT; 3TC and ABC have the least toxicity of all.

Lipodystrophy and other metabolic abnormalities: primarily seen with d4T and the PI class, and to a lesser degree with other NRTI drugs. Abnormalities include fat maldistribution and body habitus changes, hyperlipidaemia, hyperglycaemia, insulin resistance, diabetes mellitus, osteopaenia, osteoporosis and osteonecrosis.

Allergic reactions: including skin rashes and hypersensitivity reactions. These are more common with the NNRTI drugs, but also seen with certain NRTI drugs, such as ABC.

Because of the risk of potentially life-threatening hepatotoxicity associated with NVP, hepatic dysfunction of any etiology in a child on NVP requires careful consideration of whether NVP should be discontinued.

9.4 Monitoring toxicity

Toxicity can be monitored clinically, based on child/guardian reporting and physical examination, and can also be assessed by a limited number of laboratory tests, depending on the ART regimen being used and the capacity of the health-care setting. Routine laboratory monitoring, although desirable, is not essential and it is recognized that it may not be available in all situations (see Annex J, Figure 8 for the management of ARV drug toxicity).

The decision to substitute[i] a new ARV depends on the severity of the adverse reaction (Box 10). Substitution of one drug for another is recommended in the context of recognized individual drug toxicities (see Chapter 10).

9.5 Discontinuation and drug substitution

As a general principle:

Mild toxicities do not require discontinuation of therapy or drug substitution, and symptomatic treatment may be given (e.g. antihistamines for a mild rash).

Moderate or severe toxicities may require substitution with a drug in the same ARV class but with a different toxicity profile, or with a drug in a different class, but do not require discontinuation of all ART.

Severe life-threatening toxicities require discontinuation of all ARV drugs, and the initiation of appropriate supportive therapy until the patient is stabilized and the toxicity is resolved (see Annex F).

NNRTIs have a longer half-life than NRTIs, and stopping all first-line drugs simultaneously may result in exposure to sub-therapeutic levels of the NNRTI and subsequently to the development of NNRTI resistance. However, if a child has a life-threatening toxicity, all ARV drugs should be stopped simultaneously until the patient is stabilized.

(i) Substitution is the exchange of one drug in a (first-line regimen) for another first-line drug due to toxicity; this is different from switching a an entire regimen because of treatment failure.

Clinical examination may identify toxicities that are not life-threatening and that appear months to years after therapy has been started, such as lipodystrophy. In such cases, referral for management to higher-level health facilities or for consultation with an HIV expert is recommended.

9.6 Considerations for adherence

Regardless of their severity, adverse reactions may affect adherence to therapy. A proactive approach to managing toxicity is recommended. Discussing the potential side-effects of the ART regimen before initiation of therapy and during the early stages of treatment with the child and his or her caregivers, as well as offering support during minor and moderate adverse reactions, can increase the likelihood of adherence to therapy (see Chapter 16). Many ARV drug toxicities are time-limited and resolve spontaneously even when the same ART regimen is continued. The child and caregivers should be familiar with the signs of toxicities that are serious and require immediate return to the health facility. This is particularly important for toxicities that can be life-threatening, including the NVP-associated Stevens – Johnson syndrome, drug-induced hepatitis, lactic acidosis, pancreatitis, or ABC-associated hypersensitivity. (See Figure 8 for management of ARV drug toxicity)

Box 10: Guiding principles for the management of ARV drug toxicity

1. Determine the seriousness of the toxicity.
2. Evaluate concurrent medications and establish whether the toxicity may be attributable to an ARV drug or drugs, or to a non-ARV medication taken at the same time.
3. Consider other disease processes (e.g. viral hepatitis in a child on ARV drugs who develops jaundice). Not all problems that arise during treatment are caused by ARV drugs.
4. Manage the adverse reaction according to its severity (see Annex G).
5. In general:
   a. *Severe life-threatening reactions:* Immediately discontinue all ARV drugs, manage the medical event (i.e. provide symptomatic and supportive therapy) and reintroduce ARV drugs using a modified regimen (i.e. with an ARV substitution for the offending drug) when the patient is stabilized. [a]
   b. *Severe reactions:* Substitute the offending drug without stopping ART. [a]
   c. *Moderate reactions:* Consider continuation of ART as long as feasible. If the patient does not improve on symptomatic therapy, consider single-drug substitution.[a]
   d. *Mild reactions:* Reassure child and caregiver that while the reaction may be bothersome, it does not require a change in therapy; Provide counselling and support to mitigate adverse reactions.
6. Stress the maintenance of adherence despite toxicity for mild and moderate reactions.

[a] Refer to Table 13 for substitution options.

10. SUBSTITUTING DRUGS BECAUSE OF TOXICITY IN INFANTS AND CHILDREN

10.1 Principles

- Drug substitutions should be limited to situations where toxicity is severe or life-threatening, as there are few ARV options for children in resource-limited settings.
- If toxicity is related to an identifiable drug in a regimen, the offending drug can generally be replaced with another drug from the same class that does not have the same adverse effect.

Given the limited number of ARV drug options available in resource-limited settings, drug substitutions should only be considered when the toxicity is severe or life-threatening (see Annex G). Table 13 lists the usual ARV substitution options for adverse reactions among the recommended combination first-line regimens. If toxicity is severe and seems clearly related to a specific drug, the offending drug can generally be replaced with another from the same class that does not share the same type of toxicity, (e.g. substitution of d4T for AZT in the setting of anaemia or NVP for EFV when there is CNS toxicity).

For some life-threatening toxicities, it may not be possible to identify an optimal substitute drug. For example, with NVP-associated Stevens – Johnson syndrome, most clinicians would avoid substituting another NNRTI drug (EFV) because of the potential for class-specific toxicity. This would require a change to either a triple NRTI regimen (i.e. substituting ABC, for NVP), or substituting a PI for NVP, thereby introducing a drug class usually reserved for second-line regimens.

Table 13: Severe toxicities of ARVs in infants and children, and potential drug substitutions

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

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

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

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

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

[d] The introduction of the PI class of drugs in first-line regimens leads to limitations in the choice of drugs in the event of treatment failure (see Chapter 12).

[e] Lactic acidosis is least commonly associated with ABC, therefore ABC should replace AZT or d4T whenever lactic acidosis occurs.

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

[g] Substitution of d4T often may not reverse lipoatrophy.

[h] Exclude malaria in areas where malaria is endemic. Severe anaemia is defined as Hb <7.5 g/dl.

[i] Defined as neutrophil count <500 cells/mm^3

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

[k] E.g. persistent hallucinations or psychosis

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

11. FIRST-LINE REGIMEN TREATMENT FAILURE; WHEN TO SWITCH REGIMENS

11.1 Recommendations

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

   (Conditional recommendation, very low quality of evidence)
2. Clinical failure is defined as the appearance or reappearance of WHO clinical stage 3 or stage 4 events after at least 24 weeks on ART in a treatment-adherent child.
   (Conditional recommendation, very low quality of evidence)
3. Immunological failure is defined as developing or returning to the following age-related immunological thresholds after at least 24 weeks on ART, in a treatment-adherent child:
   - CD4 count of <200 cells/mm^3 or %CD4+ <10 for a child ≥2 years to <5 years of age
   - CD4 count of <100 cells/mm^3 for a child 5 years of age or older.

   (Conditional recommendation, very low quality of evidence)
4. Virological failure is recognized as a persistent VL above 5000 RNA copies/ml, after at least 24 weeks on ART, in a treatment-adherent child.
   (Conditional recommendation, very low quality of evidence)

11.2 Principles

- Assessment of adherence, and support to ensure adherence, are always required where treatment failure is suspected.
- Immunological or virological confirmation of clinically diagnosed treatment failure is advised wherever possible.
- National programmes need to provide standard second-line regimens that are expected to be potent and well tolerated, and based upon the first-line regimen provided.
- Continuation of ART is likely to result in health benefits even when treatment failure is suspected.
- Second-line regimens usually have a greater pill burden, are more expensive and more demanding for the child to adhere to compared with first-line regimens.
- Premature switching to second-line ART is therefore likely to be more costly for the patient and the programme.
- Delayed switching to second-line ART is likely to allow greater resistance to first-line NRTIs and has the potential to undermine the potency and durability of second-line options.

11.3 Background

Poor adherence, inadequate drug levels or prior existing drug resistance can all contribute to ARV treatment failure. Genetic differences in drug metabolism may also be important [115, 116]. To identify treatment failure, it is advised that programmes use clinical criteria, supported by immunological or virological confirmation wherever possible. When treatment failure is confirmed, switching to a new second-line regimen becomes necessary.[i] Prior to switching therapy, it is essential to assess and address adherence issues.

(i) Switching a regimen for treatment failure should not be confused with substitution of a single drug for toxicity (see Chapter 9)

It should not be concluded, on the basis of clinical criteria alone, that an ARV regimen is failing until the child in question has had a reasonable trial on that regimen, i.e. the child should have received the regimen for at least 24 weeks. Adherence to therapy should have been assessed and considered to be optimal, any intercurrent infection or major clinical event should have been treated and resolved, and IRIS excluded. Additionally, before considering a change in treatment because of growth failure, it should be ensured that the child is receiving adequate nutrition.

11.4 Clinical definition of treatment failure

The detection of new or recurrent WHO clinical stage 3 or 4 events in a child on ART may reflect progression of disease, and treatment failure should be considered provided the child is adherent to therapy [117-119].

Table 14 Using WHO clinical staging of events to guide decision-making on switching to second-line therapy for treatment failure

New or recurrent clinical event develops after at least 24 weeks on ART[a, b]	Management options[c, d]
No new events or stage 1 events	Do not switch to new regimen Maintain regular follow-up
Stage 2 events	Treat and manage event Do not switch to a new regimen Assess adherence and offer support Assess nutritional status and offer support Schedule earlier visit for clinical review and CD4 measurement
Stage 3 events	Treat and manage event and monitor response[e] Check if on treatment 24 weeks or more Assess adherence and offer support Assess nutritional status and offer support Check CD4[f] where available Institute early follow-up
Stage 4 events	Treat and manage event Check if on treatment 24 weeks or more Assess adherence and offer support Assess nutritional status and offer support Check CD4[f] where available Consider switching regimen

[a] A clinical event refers to a new or recurrent condition as classified in the WHO clinical staging at the time of evaluating the infant or child on ART. Annexes C and D provides more details about clinical events.

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

[c] Differentiating OIs from IRIS is important.

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

[e] Pulmonary or lymph node TB, which are clinical stage 3 conditions, may not be an indication of treatment failure, and thus may not require consideration of second-line therapy. The response to TB therapy should be used to evaluate the need for switching therapy (see Chapter 13).

[f] CD4 measurement is best performed once the acute phase of the presenting illness has resolved.

Clinical disease progression should be differentiated from IRIS. The worsening of disease after initial clinical improvement or the development of a new or recurrent OI soon after initiating ART in a child does not necessarily indicate treatment failure and is not always an indication to stop or switch ART (see Section 8.6 for further detail about IRIS).

11.5 Immunological definition of treatment failure

Immunological treatment failure can be identified by assessing the immunological response to ART in relation to baseline CD4. Treatment failure is characterized by a drop in the CD4 to values at or below the age-dependent values given in the box below (Box 11), or a failure of the CD4 count to rise above these threshold values. Recognition of treatment failure on the basis of immunological values relies on comparison with previous CD4 values, and underscores the need for CD4 measurement at the start of ART. Switching a regimen should be considered if CD4 values fall to <200 cells/mm^3 (or <10%) for a child aged between 2 and 5 years or <100 cells/mm^3 for a child aged 5 years or more (Box 11 and Table 15).

For any given CD4 threshold, the likelihood of disease progression or death is greater the younger the child. For infants and young children less than 2 years of age, the CD4 thresholds presented in Box 11 reflect very severe immunosuppression and should not be used. Specialist advice is needed to manage such cases.

Box 11: CD4 criteria suggesting immunological failure[a]

Immunological failure is recognized as developing or returning to the following age-related immunological thresholds after at least 24 weeks on ART, in a treatment-adherent child:

≥2 years to <5 years of age	**CD4 count of <200 cells/mm^3 or %CD4+ <10**
≥5 years of age	**CD4 count of <100 cells/mm^3**

[a] Preferably, at least two CD4 measurements should be available.
Use of %CD4+ in children <5 years and absolute CD4 counts in those ≥5 years of age is preferred.
If serial CD4 values are available, the rate of decline should be taken into consideration.

11.6 Virological definition of treatment failure

Where regular access to viral load monitoring is available and affordable, it may be used to identify treatment failure. Viral load is the most sensitive way to detect viral replication. However, individual viral load values do not directly correlate with clinically relevant outcomes (death or disease progression).

Virological failure is recognized if the child is adherent to their (first-line) ART regimen, more than 24 weeks from initiation of ART, and has a persistent viral load over 5000 copies/ml. In resource-limited settings it may not be feasible to perform viral load testing. The availability of viral load is not a prerequisite for initiation of ART or for the determination of treatment failure.

11.7 Use of clinical and immunological findings for decision-making on switching ARV regimen

CD4 values supplement clinical findings when decisions are being made on switching therapy (Box 11 and Table 15). Switching a regimen should usually be considered only if two or more of the CD4 values

obtained are below the age-related threshold. If the CD4 value begins to approach the age-related threshold, increased clinical and CD4 follow-up is advisable. A regimen switch is not recommended in children with no new clinical staging events where CD4 values drop but remain above their age-related threshold (Box 11 and Table 15). New or recurrent WHO clinical stage 4 conditions may warrant a switch in treatment regimen, although if the CD4 value remains above the age-related thresholds, it may be acceptable to delay switching. In children in whom a regimen switch is delayed based on the CD4 value, close monitoring and increased frequency of clinical and CD4 follow-up is indicated.

11.8 Decision-making on switching ART in the absence of CD4 measurement

In situations where CD4 values are not available, a simplified approach is needed to guide decisions on the need to switch to a second-line regimen (Table 14 and Table 15). A new or recurrent WHO stage 4 event may be a sufficient criterion to consider switching. In children developing a new or recurrent WHO stage 3 event, switching the regimen may be considered, however, it is recommended that a child with pulmonary or lymph node TB or with severe recurrent bacterial pneumonia (all considered WHO clinical stage 3 events) receive a course of appropriate TB or antibacterial therapy, with re-evaluation of the child after completion of treatment, before deciding whether to switch. In children who are clinically well, a regimen should not be switched if CD4 measurements are not available.

Table 15: Decision-making on switching to second-line ART for treatment failure based on availability of CD4 measurement

New or recurrent clinical event on ART	Availability of CD4 measurement	Management options
Stage 1 or stage 2 event	No CD4	Do not switch regimen
	CD4	Consider switching regimen only if two or more values are below the age-related threshold Increase clinical and CD4 follow-up if CD4 value approaches the age-related threshold Measure VL if available
Stage 3 event	No CD4	Manage event and assess response
	CD4	Switching regimen is recommended if CD4 value is below the age-related threshold and particularly if the child initially had a good immune response to ART Measure VL if available Increase clinical and CD4 follow-up if CD4 value approaches age-related threshold
Stage 4 event	No CD4	Consider switching regimen
	CD4	Switching regimen is recommended if CD4 value is below the age-related threshold and particularly if the child initially had a good immune response to ART Switching may not be necessary where CD4 value is above age-related threshold VL testing may resolve discordant CD4 results

11.9 Decision-making on switching ART using viral load measurement

Children with clinical failure and/or immunological failure may not all have virological failure, and may not need to switch to second-line therapy. However, a delay in switching therapy in a child with high levels of viral replication may lead to greater development of resistance and compromise the virological activity of standard second-line regimens. It is unclear whether this translates to compromised clinical outcomes. Therefore, in the context of accurately identifying treatment failure, measurement of viral load is useful. Currently, there are insufficient data to inform programmes on the best strategic approach to introducing viral load monitoring within ART programmes. viral load is recommended where available to confirm clinical and/or immunological failure. WHO encourages further research and evaluation of approaches to the use of viral load monitoring [39, 120].

11.10 Use of other laboratory parameters for decision-making regarding switching ART

Total lymphocyte count should not be used for the evaluation of response to ART, because a change in TLC is a poor predictor of treatment success [121]. Up24 Ag testing is also not currently recommended to monitor the virologic treatment response. At present, testing for HIV drug resistance (HIV-DR) is not recommended as a routine part of HIV care in resource-limited settings and so is not considered further in these recommendations (see Chapter 18).

12. CHOICE OF SECOND-LINE REGIMENS IN THE EVENT OF TREATMENT FAILURE

12.1 Recommendations

1. After failure on a first-line NNRTI-based regimen, a boosted PI plus 2 NRTIs are recommended for second-line ART.
   (Strong recommendation, moderate quality of evidence)
2. LPV/r is the preferred boosted PI for a second-line ART regimen after failure on a first-line NNRTI-based regimen.
   (Strong recommendation, high quality of evidence)
3. After failure on a first-line regimen of AZT or d4T + 3TC, ABC + 3TC is the preferred NRTI backbone option for second-line ART; ABC + ddI is an alternative.
   (Strong recommendation, low quality of evidence)
4. After failure on a first-line regimen of ABC + 3TC, AZT + 3TC is the preferred NRTI backbone option for second-line ART; AZT + ddI is an alternative.
   (Strong recommendation, low quality of evidence)

12.2 Principles

- Heat-stable FDCs or co-packaged formulations are recommended wherever possible for first- and second-line ART.
- Wherever possible, at least one new class of drugs should be used in a second-line regimen.
- NRTIs may need to be recycled based on empirical assessment of likely residual activity.
- If a PI was used as a substitute for a first-line NNRTI drug because of severe toxicity, should the PI fail, it is not considered safe to reintroduce the NNRTI class of drugs.
- Infants or children failing a LPV/r-based first-line regimen started because of known prior exposure to NVP will probably need referral to specialized paediatric HIV care center, as there is currently limited access to any new class of drugs or or indeed new PIs that are likely to be active. Second-line regimens would have to be based on the limited formulary available, including NNRTIs and NRTIs.

12.3 Background

Recommending potent and effective second-line regimens for infants and children is particularly difficult because of the current lack of experience with the use of second-line regimens in children in resource-limited settings and the limited formulary available. This highlights the importance of choosing potent and effective first-line regimens, and maximizing their durability and effectiveness by optimizing adherence.

12.4 Choice of second-line regimen following a preferred first-line regimen of two NRTIs plus one NNRTI

WHO recommends a regimen based on a PI, boosted with RTV, and combined with two NRTIs as the second-line treatment for children who fail a regimen of two NRTIs with an NNRTI (Table 17). New drugs that may be expected to have cross-resistance to drugs used in the first-line regimen should be avoided.

12.5 Choice of NRTIs

NRTI cross-resistance, especially in the wake of long-standing virological failure on a first-line regimen may compromise the potency of the NRTI component within second-line. Limited data currently make it necessary to make empirical choices for second-line NRTIs, with the aim of providing as much antiviral activity as possible. In children failing the most commonly used first-line regimen – d4T, 3TC and NVP [122-123] – it is likely that the virus is completely resistant to 3TC and to NVP, whereas it is less likely that the virus is also resistant to d4T [124, 125].

Given the cross-resistance that exists between d4T and AZT, for a child receiving a first-line d4T- or AZT-containing regimen, the recommended second-line regimen that might offer more activity includes ABC. However, AZT/d4T resistance that has resulted in the accumulation of multiple thymidine analog mutations (TAMs) can confer diminished susceptibility to ABC. In these guidelines, ABC + 3TC have been introduced as a nucleoside combination as part of the first-line regimen; in this case, AZT would be the NRTI choice in a second-line regimen. The added value of ddI in second-line regimens is unclear. Didanosine has weak acid stability and is easily damaged by stomach acid. In addition, although ddI is absorbed rapidly, bioavailability is fairly low (40%). Chewable ddI tablets include an antacid buffering compound to neutralize stomach acid. The chewable tablets are large, fragile, and unpleasant tasting, and the buffering compound tends to cause diarrhoea. The enteric-coated ddI formulation is better tolerated and is therefore the preferred formulation. Administration constraints for ddI in adults (i.e. administration one hour before or two hours after meals because of reduced bioavailability of ddI with food) may not apply in paediatric patients as the systemic exposure to ddI in children is similar in the presence or absence of food [46, 126-128]. In these guidelines, continuing 3TC despite the likely presence of 3TC resistance is offered as the preferred option over using ddI in second-line. Virus harboring 3TC-resistance with M184V mutation may have reduced viral replicative capacity and may also induce some degree of resensitization to AZT or TDF, although this is based on data derived in adults [129, 130].

12.6 Choice of PIs

The advantages of PI-based regimens include proven clinical efficacy and well-described toxicities. A PI boosted by low-dose RTV (e.g. LPV/r) is more active than a single (unboosted) PI (e.g. FPV, DRV or ATV) in second-line regimens [46, 131]. LPV/r is the only PI available to date in a co-formulation. It has been used extensively in children, and is the preferred PI for a second-line regimen for children. It should be noted that recently approved, once-daily dosing with LPV/r is not recommended for infants or children; nor is it recommended for pregnant women.

Fosamprenavir and tipranavir (TPV) are both available in liquid oral preparations as well as adult-size tablets (FPV) or capsules (TPV); both may be considered for use in children more than 2 years of age but require co-adminstration with low-dose RTV to achieve adequate drug levels. Of note, liquid RTV requires cold storage, is unpalatable, has significant gastrointestinal intolerance, and is poorly tolerated by infants and children. The heat-stable tablet formulation is better tolerated, but is only available in a 100 mg strength and cannot be cut or crushed.

Darunavir is available in 75, 150, 300 and 600 mg tablets, and may be considered for children more than six years of age with low-dose RTV boosting.

Atazanavir alone can be considered as an alternative PI, but only if a RTV-boosted PI is not available, if single-drug RTV is not feasible, or if there is a clinical contraindication to the use of another PI.

Indinavir (IDV) and saquinavir (SQV) are not available in easy-to-use paediatric formulations and lack appropriate dosing information for children. NFV and SQV are no longer included in the WHO Essential Medicines List (EML).

Other limitations related to the use of RTV-boosted PIs include the requirement of a cold chain. A tablet formulation of LPV/r for adult and paediatric dosing that does not require a cold chain recently became available. However, the tablet cannot be split for use in infants and young children. The only PI currently available and recommended for infant use is LPV/r in a syrup, but this is unpleasant tasting and requires a cold chain supply. New heat-stable paediatric sprinkle formulations are eagerly awaited. Simplified dosing recommendations are provide in Annex E.

Because of the high likelihood of adverse reactions associated with PIs, regimens containing 2 boosted PIs are generally not recommended. WHO urges manufacturers to ensure timely evaluation of new PIs for use in children and early access to these drugs if they are proven to be effective.

12.7 Choice of a second-line regimen following an alternative first-line regimen with triple nucleosides

Treatment failure on an alternative triple NRTI regimen can be managed with a wider choice of drug options because two important drug classes (i.e. NNRTIs and PIs) will have been spared. The PI component remains essential in constructing a second-line regimen (Table 17).

NRTI/NNRTI/PI combination regimens have been studied in treatment-experienced children and have been well tolerated. In a study of 175 ARV-experienced HIV-infected children with advanced HIV disease, four-drug regimens including two NRTIs, an NNRTI (NVP) and a PI (RTV or NFV) were well tolerated, and resulted in significant increases in CD4 cell counts, even in children who had only a partial virological response to therapy [132]. A multi-class regimen can be considered if these drugs are available. Because EFV and NVP are potent inducers of enzymes required to metabolize some PIs, dose adjustments may be needed and the use of a RTV-boosted PI is recommended to ensure adequate PI drug levels.

12.8 Choice of a second-line regimen following a PI-based initial regimen

PI regimens may have been used as initial therapy for infants who have been exposed directly or via maternal treatment for PMTCT to a NNRTI. In the event of failure, NNRTIs remain the only new drug class that can be introduced, but the durability of such a regimen may be compromised by the presence of archived NNRTI resistant virus and the potentially rapid development of clinical failure.

PIs may also have been used in a first-line regimen where the NNRTI has been substituted with a PI because of severe toxicity, or because a triple NRTI regimen is not feasible. If the PI was used as a

first-line substitution for an NNRTI drug because of severe toxicity, should the PI fail, it is not considered safe to reintroduce the NNRTI class.

In these circumstances, the child should be referred to a setting where specialized HIV care is provided, though this option may not be available in all settings.

Table 16: Preferred first- and second-line regimens

Situation	Preferred first-line regimen	Preferred second-line regimen
INFANTS AND CHILDREN <24 MONTHS		
Not exposed to ARV	NVP + 2 NRTIs	LPV/r + 2 NRTIs
Exposed to NNRTI	LPV/r + 2 NRTIs	NNRTI + 2 NRTIs
Unknown ARV exposure	NVP + 2 NRTIs	LPV/r + 2 NRTIs
CHILDREN		
Children 24 months or more	NNRTI + 2 NRTIs	Boosted PI + 2 NRTIs
CONCOMITANT CONDITIONS		
Child or adolescent with severe anaemia	NVP + 2 NRTIs no AZT	Boosted PI + 2 NRTIs
Child or adolescent with TB	EFV + 2 NRTIs or 3 NRTIs	Boosted PI + 2 NRTIs
Adolescent with hepatitis B	TDF + 3TC + NNRTI	Boosted PI + 2 NRTIs

Table 17: Recommended second-line regimens in infants and children in the event of treatment failure of first-line regimens

Recommended second-line regimen: boosted PI component + two NRTI components					
	Preferred second-line regimen				
First-line regimen at failure	RTI components (NRTI/NNRTI) [a]		PI component	Strength of recommendation	Quality of evidence
2 NRTIs + 1 NNRTI: AZT- or d4T-containing	ABC + 3TC or ABC + ddI	plus	LPV/r[d]	Strong	Moderate
or ABC-containing	AZT + 3TC or AZT + ddI		LPV/r[d]	Strong	High
Triple NRTI	ddI[d] + EFVc or NVP				

[a] Continuation of 3TC in second-line regimens may be considered.

[b] ddI may not need to be taken on an empty stomach in children.

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

[d] LPV/r is available as solid and liquid co-formulations.

13. CONSIDERATIONS FOR INFANTS AND CHILDREN WITH TUBERCULOSIS AND HIV

13.1 Recommendations

13.1.1 Isoniazid preventive therapy

1. All HIV-infected infants and children exposed to TB through household contacts, but with no evidence of active disease, should begin isoniazid preventive therapy (IPT).
   (Strong recommendation, very low quality of evidence)
2. Children living with HIV (>12 months of age and including those previously treated for TB), who are not likely to have active TB and are not known to be exposed to TB, should receive 6 months of IPT as part of a comprehensive package of HIV care.
   (Strong recommendation, moderate quality of evidence)
3. Infants living with HIV, who are unlikely to have active TB and are not known to be exposed, should not receive IPT as part of a comprehensive package of HIV care.
   (Conditional recommendation, very low quality of evidence)
4. The recommended dose of isoniazid (INH) for preventive therapy in HIV coinfection is 10 mg/kg daily for 6 months (maximum 300 mg/day). (For simplified dosing see Table 18)

13.1.2 Infants and children diagnosed with TB and HIV

5. Any child with active TB disease should begin TB treatment immediately, and start ART as soon as tolerated in the first 8 weeks of TB therapy, irrespective of the CD4 count and clinical stage.
   (Strong recommendation, very low quality of evidence)
6. The preferred first-line ARV regimen for infants and children less than 3 years of age who are taking a rifampicin-containing regimen for TB is 2 NRTIs + NVP or a triple NRTI regimen.
   (Conditional recommendation, very low quality of evidence)
7. The preferred first-line ARV regimen for children more than 3 years of age who are taking a rifampicin-containing regimen for TB is 2 NRTIs + EFV.
   (Conditional recommendation, very low quality of evidence)
8. The preferred first-line ARV regimen for infants and children less than 2 years of age who have been exposed to NVP and are taking a rifampicin-containing regimen for TB is a triple NRTI regimen.
   (Conditional recommendation, very low quality of evidence)

13.1.3 HIV-infected infants and children who develop TB on ART

9. For all HIV-infected children, anti-TB therapy should be started immediately upon the diagnosis of TB; ART should continue.
   (Conditional recommendation, very low quality of evidence)
10. Make adjustments to ART regimens as needed to decrease the potential for toxicities and drug interactions:
    - If on a regimen of 2 NRTIs + NVP, substitute EFV for NVP if the child is 3 years or more in age
    - If on a regimen of 2 NRTIs + NVP and substitution with EFV is not possible, ensure NVP is dosed at the maximum dose of 200 mg/m^2 per dose twice daily
    - If on a regimen of LPV/r, consider adding RTV in a 1:1 ratio of LPV: RTV to achieve a full therapeutic dose of LPV.

13.2 Background

Tuberculosis represents a significant threat to child health. HIV infection increases the susceptibility to infection with *M. tuberculosis*, the risk of rapid progression to TB disease, and reactivation of disease in older children with latent TB. Increasing levels of coinfection with TB and HIV in children have been reported from resource-limited countries [133], with the prevalence of HIV in TB-infected children ranging from 10% to 60% [134-139].

13.3 TB screening and prevention for HIV-infected infants and children

All HIV-infected infants and children should be evaluated for contact with a TB source case at every visit to a health-care facility. Those presenting with poor weight gain[i], current cough or fever should be evaluated for TB, and those with active TB disease should be treated [140].

Provide HIV-infected infants and children who present with no evidence of active TB, but who are a household contact of a TB patient, with IPT at a dose of of 10 mg/kg/day for 6 months (not to exceed a maximum daily dose of 300 mg) (see Table 18). The child should be seen monthly and provided one month's supply of INH at each visit. Overall, there is a paucity of evidence concerning the use of IPT in infants. Some experts believe that IPT should be provided for all HIV-infected infants (as is recommended for TB-exposed infants) in order reduce their risk of acquiring TB, which has high rates of morbidity and mortality [141-144]. However, research to date does not support this [145].

HIV-exposed infants who are identified as HIV-infected within 3 – 4 months of age should be monitored monthly, including an assessment for TB and for possible contact with an active TB case, but should not be prescribed IPT. However, if contact with an active TB case has occurred, TB infection should be strongly considered and once active TB disease has been excluded, IPT for 6 months must be given. In many settings, infants presenting late for HIV diagnosis have a high likelihood of TB coinfection.

Isoniazid preventive therapy is recommended for all HIV-infected children older han one year of age who are unlikely to have active TB, even in the absence of documented exposure to an active TB source case [146]. A randomized study showed that the provision of IPT to HIV-infected children reduces the incidence of TB by 72% and all-cause mortality by 64% [143], confirming the beneficial effect of IPT observed in the adult population [147]. However, findings from a randomized controlled trial performed in South Africa [145] showed that there is no benefit from IPT when HIV-infected infants with no known exposure to an active TB case are identified in the first 3 to 4 months of life, and started immediately on ART and carefully monitored for new TB exposure or disease on a monthly basis.

(*See* the graphic description for TB screening and initiation of IPT in Annex J, Figure 11.)

(i) "Poor weight gain" is defined as: 1. reported weight loss, or 2. very low weight (weight-for-age less than -3 z-score), or 3. underweight (weight-for-age less than -2 z-score), or 4. confirmed weight loss (>5%) since the last visit, or 5. growth curve flattening.

Table 18 Simplified, weight-based dosing for isoniazid 10 mg/kg/day

Weight range (kg)	Number of 100 mg tablets of INH to be administered per dose	Dose given (mg)*
<5	½ tablet	50
5.1 – 9.9	1 tablet	100
10 – 13.9	1 ½ tablet	150
14 – 19.9	2 tablets	200
20 – 24.9	2 ½ tablets	250
>25	3 tablets or one adult tablet	300

* For treatment or preventive therapy

Additionally, all HIV-exposed infants and children should benefit from co-trimoxazole preventive therapy (*see* http://www.who.int/hiv/pub/paediatric/co-trimoxazole/en/index.html). Co-trimoxazole preventive therapy is particularly important for children coinfected with TB and HIV [148, 149]. Studies in adults and children indicate better survival rates in patients coinfected with HIV and TB who received co-trimoxazole preventive therapy compared with those who didn't [150]. All eff ort must be made to identify HIV/TB coinfected infants and children in order to prevent TB disease [143].

13.4 Diagnosis of TB

Primary TB disease in children presents with a broad range of non-pulmonary and pulmonary manifestations.

In paediatric TB, bacteriological confirmation should be sought whenever possible, even if it is difficult and the results frequently negative. Appropriate clinical samples may include sputum (by expectoration, gastric aspiration or sputum induction), fine-needle aspiration of enlarged lymph nodes, pleural fluid or ear swab from chronically discharging ears. Gastric aspiration is advisable only when culture is available, as smear positivity on microscopy is low and the procedure is stressful for the child. Alternatively, induced sputum can be used for young children as this does not require hospital admission and the yield is greater than that for gastric aspirate. The disadvantage is the need for infection control to protect health-care personnel.

In many cases, particularly in young children, diagnosis is presumptive and based on a number of factors. These include; a constellation of clinical signs and symptoms, known contact with a household member with TB disease, a positive tuberculin skin test (TST)[ii] and radiological findings on chest x-ray. Different scoring systems have been proposed to assist the clinician; unfortunately, they are difficult to validate and perform poorly in HIV-infected children [151, 152]. A "trial of TB treatment" should not be used as a diagnostic test for TB in children.

(ii) In an HIV-infected child, induration of >5 mm diameter is read as a positive TST; however, coinfected children may also present with a negative TST.

Encouraging data show that interferon-gamma release assays (IGRAs) are more sensitive than TST in detecting TB in HIV-infected children, including those with a low CD4 count and/or malnutrition [153-155]. In addition, excellent specificity for *M. tuberculosis* infection has been reported and unlike TST, IGRAs are unaffected by prior BCG vaccination or exposure to environmental mycobacteria. However, more evidence is needed and range of implementation issues that are relevant in most TB/HIV endemic settings (e.g. cost, specific laboratory equipment and the need for a venous blood sample) must be solved. Therefore, the use of IGRAs is currently not recommended outside research settings with laboratory-validated procedures.

13.5 Treatment of TB in HIV-infected infants and children

The underlying principles for the treatment of TB in HIV-infected children are the same as for children who are not HIV-infected. However, the co-management of TB and HIV, and the treatment of HIV infection, is complicated by drug interactions, particularly between rifampicin and the NNRTI and PI classes of ARVs. These drugs have similar routes of metabolism and co-administration may result in sub-therapeutic drug levels. ART should not be interrupted but dose adjustments of ART may be needed when taken with the rifamycins, especially rifampicin. The potential use of rifabutin, considered in adults to overcome drug – drug interactions, is not recommended due to insufficient data and lack of an available formulation in children. In addition, the choice of ART regimen in TB/HIV coinfected children is complicated by the relatively limited number of available paediatric ARV formulations and the lack of dosing information for some ARVs (particularly for children less than 3 years of age).

13.6 Choice of first-line ARV regimens in children receiving rifampicin-containing TB treatment

Pharmacokinetic data are limited regarding the concomitant use of rifampicin and ARVs in children, though some studies are under way as these guidelines are being developed. Updated evidence-based guidance will be made available on the WHO website (www.who.int) as data become available. The current treatment recommendations for children with TB/HIV coinfection are as follows:

Box 12: Preferred ARV regimens for TB/HIV coinfected infants and children <3 years of age

2 NRTIs + NVP*
(except for infants and children <2 years if previously exposed to NVP)
OR
3 NRTIs: (d4T or AZT) + 3TC + ABC

* Since rifampicin is known to reduce levels of NVP, do not use lead-in dosing of NVP when initiating NVP-containing ART with TB treatment.

Box 13: Preferred ART regimens for TB/HIV coinfected children ≥3 years of age

2 NRTIs + EFV
OR
3 NRTIs: (d4T or AZT) + 3TC + ABC

In adults, both standard (600 mg) and increased (800 mg) EFV doses have been used with rifampicin. However, adequate virological and immunological response with standard 600 mg dosing has been documented [156], and higher doses are associated with a higher incidence of toxicity and are not recommended. NVP levels are reduced with concurrent administration of rifampicin, with reductions in the area under the curve (AUC) of 31–37% [157, 158]. The use of higher doses of NVP with rifampicin has not been evaluated. Additionally, NVP, like rifampicin and INH, has potential hepatotoxicity. As with EFV, some clinical reports indicate adequate virological and immunological responses and acceptable toxicity with standard doses of NVP administered concomitantly with rifampicin [159]. Additionally, in early 2009, new evidence emerged based on small studies in children, suggesting that co-administration of rifampicin may not result in lowered NNRTI concentrations in paediatric populations. Therefore, prescribing the maximum dose of 200mg/m^2 is currently recommended as a safer approach to avoid sub-therapeutic drug levels, but more data are urgently needed to address the exact dose requirements. A regimen of two NRTIs plus NVP should be considered only when careful clinical and laboratory monitoring for potential liver toxicity can be assured.

Alternatively, a triple NRTI regimen can be used, especially in infants previously exposed to NVP. A previous study of HIV-infected adults demonstrated that a regimen of AZT/3TC/ABC has lower virological potency than an EFV-based regimen (79% versus 89% efficacy at 32 weeks) [59]. However, recent findings (NORA substudy of the DART trial) provide reassurance on the triple NRTI regimen and show that patients on triple NRTIs do not appear to have any clinical disadvantage [162, 163].

13.7 When to start ART following initiation of rifampicin-containing TB treatment

ART is a priority for children with WHO clinical stages 3 and 4. Because the degree of immunodeficiency in TB/HIV coinfected children is highly correlated with mortality [133], earlier initiation of ART is critical in coinfected children with low CD4 values.

In HIV-infected children with TB disease, initiation of TB treatment is the priority. However, the optimal timing for the initiation of ART during TB treatment is not known. The decision on when to start ART after starting TB treatment involves a balance between the child's age, pill burden, potential drug interactions, overlapping toxicities and the possible development of IRIS versus the risk of further progression of immune suppression with the associated increase in mortality and morbidity.

Early initiation of ART is advocated for any patient with TB disease regardless of clinical stage and degree of immunosuppression. A randomized controlled trial (SAPIT) provides moderate evidence for early initiation of ART in terms of reduced all-cause mortality and improved TB outcomes in adults [164]. Trial participants were grouped into "integrated" (immediate and end of initiation phases com-

bined) and "sequential" treatment arms. Mortality was 55% lower in the integrated treatment arm compared with the sequential treatment arm. Similar data are not available in the paediatric population and additional research is urgently needed to address this issue. However, the expected benefits in terms of reduction in mortality and TB transmission outweigh the potential concerns related to onset of IRIS due to TB treatment and drug – drug interactions. Moreover, harmonization with adult recommendations will likely facilitate programme uptake.

Therefore, the current recommendation is that any child with active TB disease should begin TB treatment immediately and begin ART as soon as tolerated (2 to 8 weeks into TB therapy), irrespective of clinical stage and degree of immunosuppression.

The potential for IRIS (*see below*) should be considered in all children starting ART, particularly in those with low CD4 values.

13.8 Considerations for children diagnosed with drug-resistant TB

There are few data on the care of HIV-infected children who are exposed to multidrug-resistant TB (MDR-TB) or extensively drug-resistant TB (XDR-TB). These children will require referral to local TB experts familiar with the regional drug resistance profile. Treatment of the drug-resistant source case must be a priority. Initiation of ART at the earliest possible opportunity should also be ensured.

More detailed guidance is being developed by the WHO department of TB to address infection control for TB in infants, as well as guidance on managing XDR- and MDR-TB in HIV-infected children. The most up-to-date information on TB/HIV co-infection can be found at http://www.who.int/tb.

13.9 Considerations for children diagnosed with TB while on first-line ARV regimens

ART should continue in children already on a first-line ARV regimen who are subsequently diagnosed with TB. However, the ARV regimen should be reviewed and may need adjustment in order to ensure optimal treatment of both TB and HIV and to decrease the potential for toxicities and drug – drug interactions. In children on a standard NNRTI-based first-line regimen who develop TB due to either primary infection or unmasking of existing TB (see Section 13.11), consider substituting NNRTI-based therapy with a triple NRTI regimen. Alternatively, the children could remain on their standard regimen of two NRTIs + one NNRTI, which is preferred in children receiving EFV-based regimens. In children and adolescents for whom EFV is not recommended and who are taking NVP, an increased dose (up to a maximum of 200 mg/m^2) should be administered. Because of possible overlapping toxicities and drug – drug interactions, children who are given rifampicin and NVP concomitantly should be followed up more frequently and laboratory parameters, if available, should be checked.

Where TB is being considered as a sign of treatment failure of the first-line regimen, switching to a second-line regimen should be considered if the child has taken ART for an adequate time (i.e. more than 24 weeks), has initially responded to it, and has not responded to anti-TB treatment. Consultation with a paediatric TB expert is suggested for the construction of a second-line regimen.

13.10 Considerations for children diagnosed with TB while on RTV-boosted PI ARV regimens

For children who are receiving a second-line regimen with RTV-boosted PIs and who are diagnosed with TB, the choice of ART regimen is more difficult because of likely resistance to first-line NRTI and NNRTI drugs and varying interactions between rifampicin and the PIs. Unboosted PIs are not recommended to be administered with rifampicin because of the decrease in PI drug levels.

Although there are few published data relating to children, for those coinfected with TB/HIV whose anti-TB treatment includes rifampicin, the dosage of RTV in the LPV/r regimen can be increased to a ratio of 1:1 in order to achieve adequate LPV exposure. Where available, monitoring of therapeutic drug levels should be considered when these medications are co-administered. Further research on the toxicity and efficacy of super boosted LPV/r is, however, still needed [165]. The presence of a cold chain should be ensured if heat-stable formulations are not available. One study of this regimen used by healthy adults demonstrated a high incidence of adverse reactions; in another study, the only one published to date of TB/HIV coinfected children, this regimen was generally well tolerated [165].

The use of SQV with higher-dose (i.e. full-dose) RTV boosting has been suggested but, because of significant hepatocellular toxicity in adults receiving this combination with rifampicin, concomitant administration of rifampicin with RTV-boosted SQV as part of ART is not recommended.

NFV should not be administered with rifampicin and the use of other boosted PI combinations is discouraged until further data become available [166, 167]. Reassessment and referral for the construction of a salvage regimen, as appropriate, are indicated.

Table 19, Table 20 and Annex J, Figure 11 summarize the WHO recommendations for ART in HIV-infected children diagnosed with TB. Research is urgently needed to evaluate the pharmacokinetics and clinical outcomes of administration of NNRTIs and PIs with rifampicin in children so that evidence-based recommendations can be made.

13.11 IRIS in the context of co-therapy for TB/HIV

IRIS has been observed in children receiving anti-TB therapy who have initiated ART. This syndrome is primarily reported in adults, but is also seen in children (see Section 8.6 for more on IRIS).

A clinical case definition of paradoxical TB-associated IRIS has recently been proposed (Table 21). Where available, an increase in CD4 count and a decrease in viral load since start of ART would further support the diagnosis of IRIS.

Some cases of IRIS in HIV-infected children may in fact be TB. Other cases may be localized or disseminated BCG disease in children who have received a BCG vaccination. HIV-infected children suspected of having disseminated BCG disease should be referred to an appropriate expert for management, as the diagnosis of BCG disease is difficult and the treatment is specialized [141, 168].

Table 19: Recommendations for the timing of ART following the initiation of TB treatment with a rifampicin-containing regimen in HIV-infected infants and children

Clinical stage of child with TB (as an event indicating need for ART)	Timing of ART following initiation of TB treatment (rifampicin-containing regimen) [a]	Recommended ART regimen [b]
Any CD4 count and any WHO clinical stage of HIV for infants and children	Start ART soon after TB treatment between 2 and 8 weeks following start of TB treatment.	**In children <3 years** Preferred first-line regimen Two NRTIs + NVP[b] (Except if <2 years of age and previously exposed to NVP) or Triple NRTI first-line regimen (d4T or AZT) + 3TC + ABC **In children ≥3 years:** Preferred first-line regimen Two NRTIs + EFV[c] or Triple NRTI first-line regimen (d4T or AZT + 3TC + ABC) In chidren who have been started on a triple NRTI regimen for the purposes of TB/HIV co-treatment, it is preferable to switch to a standard first line regimen on completion of TB treatment

[a] Administration of co-trimoxazole prophylaxis is important in children with TB/HIV coinfection.

[b] Lead-in dosing should not be used when initiating NVP-containing ART with TB treatment. In addition, the NVP dose should be close to the maximum target dose of 200 mg/m^2. Careful clinical monitoring with laboratory support, if available, is recommended where NVP is administered concurrently with rifampicin.

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

Table 20: Recommendations for co-management of TB and HIV in infants and children diagnosed with TB while on ART

Time of TB diagnosis in relation to ART	Underlying cause of TB	Considerations for ART following initiation of TB treatment (rifampicin-containing regimen) [a]	ART regimen
Child on **first-line** regimen with 2 NRTIs + NNRTI diagnosed with TB	TB attributable to primary infection (consider at any time during ART, depending on exposure to TB)	Continue ART but assess for need to change ART regimen – response to TB therapy should be used to evaluate need for change	Continue on standard two NRTIs + NNRTI first-line; if on NVP [b], substitute with EFV [c] if the child is ≥3 years; if <3 years increase NVP to maximum dose or Substitute NNRTI to triple NRTI first-line regimen
	TB as part of IRIS (consider in first 6 months of ART)		
	TB as a sign of treatment failure of first-line regimen (consider only after at least 24 weeks of ART)		Consider consultation with experts for construction of second-line regimen [d]
Child on standard PI regimen (2 NRTIs + boosted PI) diagnosed with TB	TB attributable to primary infection (consider at any time during ART, depending on exposure to TB)	Assess for need to change regimen – response to TB therapy should be used to evaluate need for changing or stopping	Continue same regimen, consider adding RTV to achieve full therapeutic dose (increase RTV until same dose as LPV in mg, in a ratio of 1:1) Consider consultation with experts for construction of salvage regimen [d]
	TB as a sign of treatment failure of second-line regimen		Consider consultation with experts for construction of salvage regimen [d]

[a] Administration of co-trimoxazole prophylaxis is important in children with TB/HIV coinfection.

[b] Careful clinical and laboratory monitoring should be ensured where NVP is administered concurrently with rifampicin.

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

[d] Few data are available to guide ART recommendations; research is urgently needed.

Table 21: Proposed clinical case definition of paradoxical TB-associated IRIS

Antecedent requirements	Both of the following requirements must be met: 1. Diagnosis of TB in line with WHO recommendations is made before starting ART 2. A good initial response to TB therapy is observed before the patient started on ART
Clinical criteria	The onset of TB-associated IRIS should be within 3 months of starting ART with at least one major criterion and two minor criteria: Major criteria: • New/enlarging lymph nodes or other focal tissue enlargement • New/worsening radiological features • New/worsening CNS tuberculosis • New/worsening serositis Minor criteria: • New/worsening constitutional symptoms such as fever • New/worsening respiratory symptoms such as cough • New/worsening abdominal pain
Alternative explanations for clinical deterioration excluded	• Poor adherence to TB therapy • Failure of TB therapy due to TB drug resistance • Another OI or neoplasm • Drug toxicity or drug reaction

Source: [169]

14. NUTRITION FOR HIV-INFECTED INFANTS AND CHILDREN

14.1 Recommendations

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

14.2 Background

The evidence base of the interaction between HIV and nutrition, which is specifically derived from observations or studies in HIV-infected children, is limited. However, some general points can be extrapolated from research findings related to the nutritional status of HIV-infected adults and additional points can be drawn from children who are malnourished but not HIV-infected.

A summary of key nutritional points and interventions relevant to the care of HIV-infected children before or during ART is presented below. For further information, reference should be made to existing manuals and guidelines on the clinical or nutritional management of HIV-infected children and infants [140, 170-175].

(i) For details, see *Guidelines for an integrated approach to nutritional care of HIV-infected children (6 months – 14 years)* http://www.who.int/nutrition/publications/hivaids/9789241597524/en/index.html

14.2.1 The link between HIV and nutrition

Adverse nutritional outcomes, such as abnormalities in growth and metabolism, are common in children infected with HIV and can be major contributors to both morbidity and mortality. The association between HIV infection and low weight-for-age or growth faltering in HIV-infected children has been reported in both resource-rich and resource-poor settings. In adults, the nutritional consequences of HIV were also among the first to be recognized and reported.

These interactions have particular relevance for children living with HIV because of the significant geographical overlap between regions with a high HIV prevalence and areas where food insecurity and moderate and severe malnutrition are common. In HIV-uninfected children, the relationship between protein-energy malnutrition, micronutrient deficiency and adverse effects on the immune system has been recognized for many years [176]. The ability of HIV to cause profound anorexia and wasting further complicates the situation, especially where resources are not available to thoroughly investigate children to determine whether the primary cause of wasting is HIV infection or food insufficiency or other infections.

14.2.2 The relationship between poor growth and survival of children living with HIV

Poor growth in HIV-infected children may have many causes. Poor growth can be attributed to reduced food intake due to socioeconomic circumstances or altered care-giving practices such as when the mother herself is unwell. OIs and their effect on food intake, absorption and metabolism can cause weight loss, which is sometimes very rapid. However, even when children are otherwise asymptomatic, HIV infection and the metabolic disturbances that it can induce may result in poor linear growth and weight gain [177].

The poor nutritional status of children living with HIV, including those children who have already started ART, is closely associated with their likelihood of dying. HIV-infected children who are significantly underweight are much more likely to die than HIV-infected children who are not malnourished. [178] Similar findings have been described in adults living with HIV, including adults receiving ART.

Given the important relationship between HIV, nutrition, growth and survival of children living with HIV, WHO recommends that nutritional assessment and support be an integral part of the care plan of an HIV-infected infant or child, irrespective of whether the child is on ART (WHO 2009). For further information on poor growth and detailed definitions of growth parameters and appropriate nutritional interventions, reference should be made to the *WHO Guidelines for an integrated approach to nutritional care of HIV-infected children* (6 months – 14 years) [140].

Table 22: Definitions of nutritional terms

Undernutrition	Food intake of insufficient quantity or quality to meet nutritional needs for growth and development
Poor growth or growth faltering	Ideally these should be determined using more than one-time measurements to indicate changes over time and whether a child is following an appropriate growth curve/trajectory. In the absence of several measurements, it is possible to consider proxy measurements such as: • Weight-for-age less than -2 z-score (underweight) • Height-for-age less than -2 z-score (stunting) • Weight-for-height less than -2 z-score (wasting) • Mid-upper arm circumference (MUAC) less than -2 z-score (*see* WHO growth reference charts)
Very low weight for age	Weight-for-age less than -3 z-score
Weight loss	Weight loss of >5% since last visit

14.2.3 The energy and protein needs of children living with HIV

HIV and associated OIs increase nutritional needs. This is compounded by the decreased appetite and food intake that frequently occurs during any febrile illness or infection. Loss of weight and especially loss of lean body mass are associated with HIV disease progression and decreased survival. The following points are recognized:

- **During symptomatic HIV or episodes of OI, energy requirement increases by 20 – 30%** [140, 173-175]. Identification and prompt treatment of OIs causing growth failure, in addition to nutrition counselling and support, may prevent further decline in nutritional status. In particular, diarrhoeal illnesses and TB can result in significant weight loss. Nutrition support for HIV-infected children with prolonged diarrhoea has been shown to result in significant and sustained weight gain. [179]
- **During and following periods of severe malnutrition, energy requirements may increase by 50 – 100% in order to recover weight** [140, 173-175]. Evidence from children who are severely malnourished and who are not HIV infected indicates that energy intake needs to increase by 50 – 100% in order for children to recover lean body mass and achieve normal weight-for-age. There are no data specific for severely malnourished HIV-infected children but it is likely that they will have the same energy and protein needs as severely malnourished HIV-uninfected children. Studies from Malawi suggest that the WHO-recommended management of children with severe malnutrition can be effective in HIV-infected children. Ready-to-use therapeutic feeds (RUTF) appear to be equally effective in severely malnourished HIV-infected children as in severely malnourished HIV-uninfected children. However, there are few data available to specifically address this question. In particular, there is little knowledge about the energy requirements of HIV-infected children who have been started on ART and who are recovering from severe malnutrition.

- **During asymptomatic HIV infection, energy requirements in adults increase by 10% to maintain body weight. There is currently inconclusive evidence to support this in children**. Resting energy expenditure (REE) has been found to be 10% higher in asymptomatic HIV-infected adults [180]. This has been a consistent finding in energy balance studies conducted among adults in North America and Europe. The increase in REE has been correlated with HIV viral load and is potentially reversed with effective viral suppression during ART [181]. Few comparable studies have been conducted in HIV-infected children and results from these studies are not conclusive [177, 182, 183].

However, in a meta-analysis of macronutrient interventions in HIV-infected, asymptomatic, well-nourished adults, balanced nutritional supplementation providing 600 – 960 kcal/day improved energy and protein intake, but was found to have no effect on body weight, fat mass, fat-free mass or CD4 count [184]. In non-malnourished HIV-infected children, current evidence does not support increased energy intake, either through increased food intake or macronutrient supplements. Data are insufficient to support an increase in protein intake above normal requirements for health (i.e. 12 – 15% of total energy intake) [173-175]. Further research is needed in children and situations where malnutrition is common.

14.2.4 The micronutrient needs of children living with HIV

Micronutrient deficiencies are common in HIV-infected adults and children, particularly in developing countries where diets are often inadequate. HIV is known to impact on nutrient intake, absorption, metabolism and storage. Micronutrient deficiency and HIV both impact on immune function and for this reason there has been much interest in micronutrient supplementation and its possible role in improving immune function and HIV disease progression. Micronutrient supplementation has been shown to correct deficiency in malnourished HIV-infected individuals but it is unclear how much this contributes to restoration of immune function. Some studies have investigated the use of very high doses of different micronutrients, more than required to simply replenish nutrient stores. However, micronutrient supplementation above 1 RDA may have harmful effects and so caution is required. The following points are recognized:

- **Micronutrient supplementation does not appear to have any effect on HIV progression, mortality or morbidity**. In a meta-analysis examining the effect of vitamin A or multiple micronutrient supplementation trials in HIV-infected adults and children, there was no conclusive evidence that these reduced morbidity, mortality or AIDS-defining infections, or improved CD4 counts [185]. Trials of very high-dose (up to 22 x RDA) micronutrient supplementation in adults and pregnant women have shown some effect on markers of HIV progression, but the efficacy and safety of such approaches in children has not been evaluated [185, 186].
- **High-dose vitamin A supplementation in children, as given to their uninfected peers, has been shown to reduce all-cause mortality and diarrhoeal morbidity**. In several studies conducted in Africa, vitamin A supplements were found to improve health outcomes in HIV-infected children including growth reduced diarrhoeal morbidity and all-cause mortality [187-190]. Vitamin A supplements should be given in accordance with the WHO IMCI recommendations, as well as the prevention schedule for children at high risk for vitamin A deficiency [170, 191]. Current evidence indicates that zinc is a useful adjunct to oral rehydration therapy for all children with diar-

rhoea. Zinc has been found to be safe when given to HIV-infected children in similar doses as for HIV-uninfected children [192]. In one study, it was found to reduce diarrhoeal prevalence and severity while in another it was not found to have any effect on recovery from diarrhoea in HIV-infected children [193, 194]. The WHO recommends zinc supplementation for acute diarrhoea in children and HIV-infected children should be managed in the same way as their uninfected peers [140]. There are insufficient data on the effect of other micronutrients in HIV-infected children to draw any conclusion and so HIV-infected children should be managed in the same way as other children with clinical evidence of micronutrient deficiency.

14.3 Integration of nutrition into the care of HIV-infected children

14.3.1 Nutritional assessment

Nutritional assessment, i.e. the systematic evaluation of nutritional status, diet (including caregiving practices and family food security) and nutrition-related symptoms, is essential for the early identification of malnutrition and growth faltering. Growth monitoring can also contribute to monitoring HIV disease progression and treatment efficacy of children on ART.

For these reasons, HIV-infected infants and children should initially undergo a complete nutritional assessment and thereafter be weighed and have height measured and recorded at each scheduled visit and more often if weight gain is inadequate. Weight and height gain should be evaluated with reference to the WHO or national reference growth curves [195]. If growth faltering is identified, then further assessment should be made to determine the cause, and plan appropriate clinical responses with appropriate nutritional counselling and referral as needed. The *Guidelines for an integrated approach to the nutritional care of HIV-infected children (6 months – 14 years)* provide details of appropriate nutritional interventions [140]. Growth monitoring should be integrated into the assessment of ART response.

In children who are responding well to ART, nutritional assessment and counselling should include information on healthy eating and avoidance of obesity. Further research is needed to assess the rates and determinants of lipodystrophy in children on ART. There is currently insufficient evidence on the effect of nutrition on the development and potential for amelioration of lipodystrophy and its long-term cardiovascular effects.

14.3.2 Meeting the energy needs of children living with HIV

At clinic visits, the nutritional needs of children living with HIV should be assessed and a nutritional care plan agreed upon with the mother or caregiver. The assessment should consider the child's growth pattern, appetite, presence of OIs and any clinical signs of malnutrition.

If children are growing normally, then no additional food is necessary. However, mothers or caregivers should be encouraged to provide a balanced diet and counselled on the nutritional value of different foods and general food hygiene [140].

If a child is found to be growing poorly, then a full dietary assessment is needed in addition to an assessment of drug adherence if the child is on ART [140]. Mothers or caregivers should be asked

about food availability and food types offered to the child, as well as who feeds the child, how much and how often. Children should be examined to detect signs of OIs or wasting. Appropriate clinical interventions should be provided. Additional energy can be provided through a combination of increasing the energy density of family foods, increasing the quantity of food consumed each day and providing energy supplements. Mothers or caregivers should be referred to food support programmes, if available. Caregivers should also be counselled on how to manage anorexia, alleviate the symptoms of conditions that interfere with normal ingestion or digestion, such as mouth sores, oral thrush and diarrhoea, and ensure adequate energy intake [140].

In children experiencing growth failure (failure to gain weight, weight loss), feeding difficulties (due to oral thrush, loss of appetite) or malabsorption due to persistent diarrhoea, more targeted support may be necessary. Following acute illnesses when weight loss might have occurred, it is important to prioritize nutritional support and interventions to enable the child to recover nutritionally as well as from the clinical illness. Common illnesses should be managed according to the IMCI guidelines [191]. The *Guidelines for an integrated approach to the nutritional care of HIV-infected children (6 months – 14 years)* provides details of appropriate nutritional interventions [140].

14.3.3 Meeting the micronutrient needs of children living with HIV

Adequate micronutrient intake is best achieved through a balanced diet [175]. Caregivers should be counselled on optimum local food choices and preparation methods to ensure maximal micronutrient intake through healthy eating, equivalent to 1 RDA [140]. Food support programmes may be beneficial.

In situations where appropriate micronutrient intake cannot be achieved, supplementation may be necessary. Special consideration should be given to the micronutrient intake and status of HIV-infected children experiencing growth failure, OIs or prolonged diarrhoea. HIV-infected children should receive regular vitamin A supplementation and zinc during diarrhoeal illness according to WHO recommendations. Currently, there are inadequate data to inform the optimal formulation of micronutrient supplements for HIV-infected children [175]. The efficacy and safety of very high-dose supplements in immunocompromised and malnourished children needs urgent consideration.

All children suspected of specific micronutrient deficiency should be assessed further. Micronutrient deficiency is difficult to diagnose in patients with chronic or acute infections, due to the interaction between acute-phase response proteins and micronutrient metabolism, storage and sequestration, making serum levels of certain micronutrients misleading [196, 197]. Special care should be taken when evaluating the micronutrient status of HIV-infected children, particularly during episodes of OIs.

14.3.4 Managing the HIV-infected child who has severe malnutrition

Severe wasting is a common clinical presentation of HIV infection in children [172]. All children with severe malnutrition are at risk for a number of life-threatening problems and require urgent and appropriate nutritional rehabilitation. HIV-infected children with severe malnutrition have a higher risk of mortality than uninfected children due to the frequency and severity of OIs including TB. Those who survive the initial rehabilitation period usually recover in a manner similar to uninfected children [198, 199], though they need urgent initiation of ART.

The treatment of severe malnutrition in HIV-infected children is the same as for uninfected children [200]. In uninfected children, the initial period of stabilization of acute complications and cautious re-feeding may take 5 – 7 days. In HIV-infected children, this may take longer due to direct effects of HIV on the gut, appetite suppression or presence of OIs that may be hard to diagnose, such as TB. The optimal time at which to start ART in severely malnourished children is not presently known [201]. There are inadequate data on the effectiveness, pharmacokinetics and safety of ARVs in severely malnourished children to accurately inform this decision and further research on these matters is urgently needed. Expert opinion suggests that HIV-infected children with severe malnutrition, according to international or national guidelines, should be stabilized from the acute phase of malnutrition while simultaneously preparing for initiation of ART; ART should be initiated as soon as clinically possible following stabilization [171, 172, 200].

It needs to be emphasized that where malnutrition is endemic, HIV-infected children may become severely malnourished due to a lack of an adequate, balanced diet. In these settings, it is very difficult to differentiate severe malnutrition that is primarily due to HIV infection from other non-HIV causes, including food insecurity and starvation. Children with an unknown HIV status, who present with severe malnutrition in settings where HIV and food insecurity are common, should be tested for HIV and considered for ART.

Immediate initiation of ART is indicated in HIV-infected infants and children with unexplained severe malnutrition that is not caused by an untreated OI, and who do not respond to standard nutritional therapy (i.e. WHO stage 4 disease).

14.3.5 Nutritional considerations for the child who is receiving ART

Successful viral suppression and immune restitution with ART can reverse losses in weight and linear growth. Children who gain weight rapidly with ART and adequate nutrition should be reassessed frequently and ARV dosages revised as needed (see Annex E). The recurrence of growth failure and severe malnutrition that is not due to food insufficiency in children receiving ART may indicate treatment failure, non-adherence to ARVs, or an OI.

Currently available data are insufficient to determine whether ART ameliorates micronutrient deficiencies and further research is required in this field.

Caregivers should be counselled as to potential food interactions with prescribed ART and how to alleviate any drug-related gastrointestinal side-effects. Nutrition counselling and support should aim to enable caregivers to provide a balanced diet that meets energy, protein and micronutrient needs. This should include referral to food programmes and micronutrient supplementation to rectify deficiencies.

15. CONSIDERATIONS FOR ART IN ADOLESCENTS

15.1 Principles

- The physical and psychological changes associated with adolescence have implications for the provision of appropriate HIV treatment and care.
- WHO recommends that the choice of ART regimen and dosages for adolescents be based on sexual maturity rating.
- The use of EFV and NVP in adolescent girls requires special clinical considerations.
- Adherence to long-term therapy is particularly difficult among adolescents, and education and provision of support systems may be most effective if specifically tailored to the considerations relevant to this age group.

15.2 Background

WHO considers adolescence as the period between 10 and 19 years of age, during which healthy adolescents pass through well-described stages of physical, psychological and sexual maturation. These have implications for the provision of appropriate treatment and care for HIV-infected adolescents.

There are distinct groups of HIV-infected adolescents who may require ART: adolescents with long-standing HIV infection who were infected around birth and survived, and those who become infected during adolescence. Adolescents with long-standing HIV infection who began ART during early childhood have typically had many years of contact with the health system and are likely to have experienced various ART regimens. In addition, their parents are often aware of their HIV status. In this group of adolescents, the challenges relate mainly to the following:

- disclosure of HIV status to them if this has not been done by their parents
- developmental delay
- the transition from paediatric to adult care, including the choice of appropriate ART regimens
- adherence [7].

HIV-infected adolescents with long standing HIV infection often face considerable physical challenges. They may experience delayed growth and development, often resulting in late puberty and, in girls, delayed or irregular menstrual cycles [202]. Stunting and/or wasting caused by progressing HIV illness, frequently exacerbated by malnutrition, may further complicate decision-making on whether to follow ART guidelines for adults or children.

15.3 Regimens and dosing

WHO recommends basing the choice of ART regimen and dosages for adolescents on sexual maturity rating (i.e. Tanner staging, Annex H): adolescents in Tanner stage I, II or III should be started on the paediatric schedule and monitored with particular care because they are undergoing hormonal changes associated with the growth spurt. Adolescents in Tanner stage IV or V are considered to be adults and the same recommendations and special considerations apply as for adults [203].

However, in choosing an appropriate ART regimen and dosages, it is necessary to go beyond the consideration of maturity. Simplification of treatment regimens and anticipated long-term adherence are also important criteria. Other considerations relate to the use of EFV and NVP in adolescent girls. EFV should not be used in adolescent girls who are at risk of becoming pregnant (i.e. are sexually active and not using adequate contraception) or those in the first trimester of pregnancy. Symptomatic NVP-associated hepatotoxicity or serious rash, while uncommon, is more frequent in females than in males, and is more likely to be seen in ARV-naive females with higher absolute CD4 cell counts (>250 cells/mm^3). NVP should therefore be used with caution in adolescent girls with absolute CD4 counts between 250 and 350 cells/mm^3. If used in such adolescent girls, careful monitoring, preferably including liver enzymes, is needed during the first 12 weeks of therapy. In situations where both EFV and NVP are contraindicated in first-line regimens for adolescent girls, the use of a triple NRTI regimen may be indicated.

15.4 Adherence for adolescents

Adherence to long-term therapy is particularly difficult among adolescents. In addition to providing routine adherence assessment and support (see Chapter 16), health-care providers should consider issues which are particularly relevant to adolescents and which may impair optimal adherence to ART. These include the possible perception of adolescents of being immortal, their desire for independence, lack of disclosure of HIV status and stigma. The parents of adolescents who have become infected as infants or young children may find it hard to share the diagnosis of HIV with their children because of fear of stigma or blame from their own children. However, without this knowledge, it is impossible for adolescents to progress completely through the transition process into adult care. Sharing this diagnosis with peers is difficult for adolescents who are aware of their HIV status [204].

15.5 Summary

For these reasons, it is especially important that young people [205]:

- are informed about their HIV status
- are well educated about their condition, its treatment and the importance of adhering to care and ART
- are confident of their ability to talk about HIV with those whom they want to share knowledge of their condition with
- have a support system so that they know where to obtain help and advice when necessary.

16. ADHERENCE TO ART

16.1 Recommendations

1. Pill boxes/calendars/diaries or other practical tools should be used to support adherence.

The panel was not able to make strong recommendations for specific interventions due to lack of evidence. However, the principles should always be applied.

16.2 Principles

- Adherence preparation should begin as soon as possible and before initiation of ART, but should not put the child at risk of disease progression or death through delaying the initiation of ART.
- Adherence should be assessed at each visit, and parental, caregiver and child issues addressed to support adherence.
- Intervene early if problems with adherence are identified, and before switching therapy.
- Local programmes should select the most efficacious regimens and preparations, which are easiest for caregivers to administer to young children and adolescents. Child-friendly formulations are needed to facilitate adherence.

16.3 Background knowledge and evidence

Adherence is directly related to the clinical and virological outcomes of ART in infants and children [206-208]. Studies of drug adherence in adult patients in western countries have suggested that higher levels of drug adherence are associated with improved virological and clinical responses, and that rates exceeding 95% are desirable in order to maximize the benefits of ART. In low- and middle-income countries, research suggests that adherence to ART can be associated with family structure, socioeconomic status, disclosure and medication regimen [208]. It is critical to ensure optimal adherence in order to maximize the durability of first-line ART and minimize the emergence of drug resistance. Experience has demonstrated that it can be particularly difficult to adhere to daily medication regimens, especially over long periods [209]. A range of approaches to support and improve adherence have been investigated and have begun to be explored. As ART becomes increasingly available to children in low-resource settings, attention to adherence will be just as important. Furthermore, various programmatic issues cause barriers to optimal adherence to treatment, and may have to be addressed.

16.4 Challenges

Adherence in children is a special challenge because of factors relating to children, caregivers, medications, and the interrelationships of these factors. The limited number of paediatric formulations, poor palatability, high pill burden or liquid volume, frequent dosing requirements, dietary restrictions and side-effects may hamper the regular intake of required medications. Furthermore, the successful treatment of a child requires the commitment and involvement of a responsible caregiver. This may be particularly complicated if the family unit is disrupted as a consequence of adverse health or economic conditions. Mothers of HIV-infected children are very often HIV-infected themselves. As a result, the care of the child may be less than optimal because of the mother's compromised health. It is preferable that a secondary (back-up) informed caregiver be involved in the care of an HIV-infected child. In addi-

tion, caregivers are often concerned with the disclosure of HIV status to family members, friends or school teachers, thus restricting the child's options for seeking support. Finally, an understanding of how the developmental stage of the child influences the extent to which he or she will cooperate with the regular administration of medicine helps to guide planning and support for the process.

16.4.1 Maximizing adherence

Efforts to support and maximize adherence should begin before the initiation of treatment [210]. The development of an adherence plan and education of the child and their caregivers are important first steps. Initial patient education should cover basic information about HIV and its natural history, the benefits and side-effects of ARV medications, how the medications should be taken and the importance of not missing any doses. If medication is mixed with food or dispersed in water, all the food or water must be taken in order to ensure administration of the full dose. Especially for young children, additional elements may be necessary, including practising the measurement and administration of liquids with caregivers and training children in how to swallow pills. When choosing regimens, policymakers, programmers and providers should consider ways to minimize the number of pills, the volumes of liquids and the number of doses. Regimens that avoid food restrictions and that can be dosed using FDCs, blister packs or other child-friendly formulations should be used whenever possible. Fitting the ARVs into the child's (and/or caregiver's) lifestyle or, where possible and appropriate, matching drug regimens for children to regimens of adults in the same family, as well as preparedness for common, non-severe adverse effects, may facilitate successful adherence.

Adherence during the first days and weeks of treatment can be critical to the long-term success of a regimen, particularly for some ART combinations with a higher risk of development of resistance. Where children stop ARV drugs within first-line regimens (either intentionally or unintentionally), it should be recognized that NNRTI components have half-lives that are several days to weeks longer than the half-lives of NRTI components. Therefore, sudden interruption of first-line therapy may result in the persistence of subtherapeutic NNRTI drug levels which can lead to the premature development of NNRTI drug-resistant virus. Emphasizing the need to consistently take all the ARV drugs is therefore particularly important with an NNRTI/NRTI-based first-line regimen. An uninterrupted ARV supply at both facility and household level is clearly essential.

Continuous assessment of and support for adherence are vital components of a proactive approach to ART. The assessment of adherence should be a concern of every health-care provider participating in the care of infants and children. Adherence assessment should be performed whenever there is a visit to a health centre in order to identify children and caregivers in need of the greatest adherence support.

16.4.2 Measuring and evaluation

The measurement of adherence may be particularly difficult in children. Quantitative methods are generally employed (asking children or caregivers how many doses of medication have been missed during the past 3, 7 or 30 days) but the responses may not reflect true adherence as children and caregivers learn the social desirability of reporting complete adherence. Reviews of pharmacy records as well as pill counts can provide valuable information about adherence. Measurement of VL

can be used to assess adherence to medication but this is unlikely to be widely available in resource-limited settings at present.

Qualitative evaluations of adherence can more effectively identify barriers to optimal medication-taking but can be more difficult and time-consuming for health-care providers as well as children and/or their caregivers. These evaluations focus on obtaining descriptions of impediments to adherence or problems encountered. Furthermore, the assessment of adherence can be complicated by diverging reports between children and caregivers, as well as by the limited availability of information when the caregivers bringing children to clinics are not the ones responsible for supervising ART administration [211].

16.4.3 Ongoing support

In addition to the assessment of adherence, ongoing support for adherence is a vital component of successful treatment [207]. Practical aids can be helpful, including the use of calendars, pillboxes, blister packs and labelled syringes. Directly observed therapy (DOT) and the use of treatment buddies or partners have been successful in some settings, but such strategies have not been widely studied in the paediatric population. Community and psychological support can be critical for caregivers as well as children and peer support groups may be particularly beneficial for mothers with young children on ART. Adherence may vary with time: families may have periods when adherence is excellent and other periods when it fails, often because of changing life circumstances. Adherence may also suffer as the child responds to therapy, health improves and the impetus to take daily medication decreases.

16.5 Programmatic issues

Programmatic issues can affect paediatric adherence and must be considered as programmes expand to scale up paediatric ART. Problems with adherence in children, their caregivers and adolescents (in particular, those who are in transition of care) should be anticipated; they are encountered at every level of the health-care system involved in providing ART. Continuous access to a supply of free ARV drugs as well as the development of well-functioning systems for forecasting, procurement and supply management are essential components of paediatric treatment programmes. The limited formulations currently available for children present significant barriers to optimal adherence. The development of formulations appropriate for use in infants and young children is strongly encouraged.

17. STRATEGIES IN THE EVENT OF FAILURE OF SECOND-LINE REGIMENS

17.1 Principles

- Strategies that balance benefits and risks for children need to be explored in the event of second-line treatment failure.
- For older children who have more therapeutic options available to them, it may be possible to construct third-line ARV regimens using novel drugs used in the treatment of adults such as darunavir and raltegravir.
- Children on a failing second-line regimen with no new ARV options should continue with a tolerated regimen.
- When stopping ART may have to be considered, the prevention of OIs, relief of symptoms and management of pain needs to continue.

17.2 Background

Multidrug resistance in children who have received multiple ARV regimens is an increasing problem. Limited data are available on which to base recommendations about treatment options. The objective of treatment should be to maintain CD4 values,[i] reduce adverse reactions and enhance the prevention of OIs. If children have end-stage HIV disease and no further suitable ARVs are available, stopping ART and keeping them comfortable with symptom-based care may have to be considered.

17.3 Considerations for the use of ARV salvage regimens

A number of treatment approaches have been considered in clinical trial settings, mainly in adults and where VL monitoring and resistance testing is possible. These approaches include the addition or substitution of new drugs (such as enfuvirtide/T20), mega-HAART (combination of five or more drugs, including two or more PIs), strategic recycling of drugs, structured treatment interruptions (STIs) and continuation of current therapy until additional drugs become available. An analysis of 13 HIV cohorts involving adult patients who had three-class virological failure indicates that achieving and maintaining an absolute CD4 count above 200 cells/mm^3 becomes the primary aim. Treatment regimens that achieve suppression of viral load below 10 000 copies per ml may be associated with better maintenance of CD4 levels [212]. Immunological and clinical benefits have been reported even among patients who have partial virological response or virological rebound, presumably as a result of decreased viral fitness attributable to the presence of multiple resistance mutations. Studies in adults suggest therapeutic benefit from NRTI treatment in the presence of drug-resistant HIV [130, 132, 213-217]. Decisions about therapy in such situations are complex and require, at a minimum, consultation with an HIV specialist.

17.4 Considerations for palliative care and stopping ART

The prevention of OIs, relief of symptoms and management of pain need to continue, even when the option to stop ART may have to be considered. Symptoms and pain are a major cause of discomfort

(i) Where virological monitoring is available, maintenance of low VL may be included in the strategies.

and poor quality of life during the course of HIV infection in infants and children. Many of these symptoms can be prevented, treated or controlled with basic medications and therapies. Non-pharmacological methods are an important adjuvant to symptom management. Efforts to identify the cause of symptoms and pain should be pursued as much as possible, without adversely affecting the quality of the child's life and within the limits of available resources. Symptoms and related pain should be anticipated and prevented to the extent possible.

The care of the terminally ill child is a particular challenge in resource-limited settings because there are few replicable models of planned terminal care, both institutional and community-based [218]. At the end of life, there are typically more symptoms that must be addressed, and the child may need to take multiple drugs to control and treat a variety of symptoms and conditions. Terminal care preparation for children and their families is a long-term process and requires continuity of care providers and services.

Critical factors in effective long-term planning include early and active communication with and involvement of parents/guardians/caregivers and their ongoing support, community-level support structures, a functional health infrastructure, knowledgeable human resources, and access to essential drugs and supplies. Terminally ill children are often placed in acute care facilities that may not be appropriate for their needs. Few resource-limited settings have inpatient facilities for terminal care, and home-based care is usually preferred. Families must be involved in decisions about the best place for care and the preferred place of death if children have end-stage HIV disease.

Box 14: Examples of palliative care support and programmes

World Health Organization

A community health approach to palliative care for HIV/AIDS and cancer patients in sub-Saharan Africa. Dept. of HIV/AIDS, WHO, 2004

Programmes in Botswana, Ethiopia, Tanzania, Uganda, Zimbabwe
http://www.who.int/hiv/pub/prev_care/palliativecare/en

WHO Pain and Palliative Care Communication Programme
https://whocancerpain. bcg. wisc. edu/?q = node/75

Clinical resources for palliative care in HIV/AIDS in countries with limited resources

International Children's Palliative Care Network (ICPCN)
http://www.icpcn.org.uk

Foundation for Hospices in sub-Saharan Africa
http://www.fhssa.org

A clinical guide to supportive and palliative care for HIV/AIDS in sub-Saharan Africa. 2006.
http://www.fhssa.org/i4a/pages/index.cfm?pageid=3359

African Palliative Care Association
http://www.apca.co.ug

Hospice Palliative Care Association of South Africa
http://www.hospicepalliativecaresa.co.za

The Diana, Princess of Wales Memorial Fund
http://www.theworkcontinues.org

OSI Palliative Care Initiative
http://www.soros.org/initiatives/health/focus/ipci

18. DRUG RESISTANCE

18.1 Principles

- Children with HIV may develop HIV drug resistance as a result of being on ART or through exposure to the maternal or infant ARVs and ART used to prevent MTCT.
- WHO does not recommend routine HIV drug resistance testing for individual patient management in settings where other basic laboratory measurements such as CD4 and HIV VL are not yet available.
- Countries are encouraged to implement strategies for minimizing the development and spread of HIVDR, by selecting appropriate drug combinations, ensuring reliable ARV drug quality and supply, and providing culturally appropriate support for adherence.
- Surveillance and monitoring for HIVDR in paediatric populations at country level is recommended. The use of ART site-based HIVDR early warning indicators (EWIs) of factors that may be associated with the preventable emergence of HIVDR is recommended.

18.2 HIV drug resistance in infants and children

HIV drug resistance (HIVDR) in infants and children with HIV infection may result either from a drug-resistant strain being transmitted from the mother [219-222] or a drug-resistant strain developing due to administration of paediatric ART or maternal or infant ARVs used for PMTCT or maternal ART. The risk of HIV-1 transmission to the infant is reduced from about 35% to about 2 – 20% if the mother receives ARVs or ART during pregnancy and delivery, and the infant is given ARVs in the postpartum period. The success of PMTCT depends on the ARV regimen used, the duration of prophyalxis and the degree of adherence. Extended maternal or infant prophylaxis with ARVs, or continued maternal ART is also required to minimize transmission through breastfeeding where breastfeeding is the selected infant-feeding strategy [20, 102, 223, 224].

Development of HIVDR in children on ART is usually related to poor adherence, use of suboptimal regimens, or to problems with drug absorption of pharmacokinetics [225-227]. All of these factors give rise to subtherapeutic drug levels and the rebound of viraemia with resistant virus.

WHO does not recommend routine HIV drug resistance testing for individual infant, child or adult patient management in settings where other basic laboratory measurements, such as CD4 and HIV VL, are not yet available.

18.3 Minimizing the emergence of HIV drug resistance

The emergence of HIVDR is of increasing concern in countries where ART and ARV prophylaxis is widely used and represents a potential impediment to the achievement of long-term success in treatment outcomes for children, adolescents and adults. Minimizing the emergence and transmission of HIVDR is therefore essential in order to ensure the efficacy of the limited number of ARV drugs available in many countries. As in adults, optimization of adherence is vital for minimizing HIVDR, alongside adherence to standardized protocols for ARV use for prophylaxis and treatment. Specific problems that should be considered in treating children include the need to change dose and formulations as children cross thresholds of weight or age, and limited availability of suitable paediatric ARV for-

mulations. To avoid emergence of HIVDR in the event of discontinuation of ARVs due to toxicity, it may be necessary to not discontinue all ARVs at the same time.

Countries are encouraged to develop and implement strategies to minimize the development and spread of HIVDR by selecting appropriate drug combinations, ensuring reliable ARV drug quality and supply, and providing appropriate support for adherence. Furthermore, surveillance and monitoring for HIVDR in paediatric populations is recommended as part of the overall monitoring of the effectiveness of ART programmes. These surveys are an important public health tool to assist national, regional and global ART scale-up efforts, and guide programmes about trends in drug resistance patterns with a view to enabling timely policy review so as to minimize the impact of such resistance.

The Global HIV Drug Resistance Network (HIVResNet), a group of international experts on HIVDR that advises WHO, has developed an essential package for a national and global HIVDR prevention and assessment strategy, which complements plans for the implementation of ART scale-up [228].[i] WHO is supplementing this strategy with approaches that specifically target the paediatric population. The main elements of the strategy include the following:

- regular assessment of HIVDR EWIs in paediatric ART sites (See Table 23);
- monitoring surveys to assess the emergence of HIVDR and associated factors in cohort(s) of treated children 12 months after ART initiation in sentinel paediatric ART sites; and
- surveillance for drug-resistant HIV-1 among infants newly diagnosed with HIV prior to treatment initiation.

18.4 Monitoring HIVDR early warning indicators

ART site-based HIVDR EWIs are identifiable factors that may be associated with the emergence of HIVDR and which, if addressed at either the ART site or programme level (*see* http://www.who.int/hiv/drugresistance for current documentation and tools), may prevent the development of HIVDR. Implementing an HIVDR EWI monitoring system allows ART programmes to assess the extent to which they are optimally preventing HIVDR.

WHO recommends that countries monitor those EWIs for which current information is readily available from data routinely recorded at the site level. Six EWIs (and two optional indicators) are recommended by WHO.

(i) The WHO/HIVResNet strategy for HIVDR in the paediatric population is being developed under the coordination of WHO in collaboration with HIVResNet.

Table 23: WHO HIV drug resistance early warning indicators

EWI 1 **ART prescribing practices**	Percentage of paediatric patients *initiating ART at the site* who are initially prescribed, or whose caregiver initially picks up from the pharmacy, an *appropriate first-line ART regimen* Target 100%
EWI 2 **Lost to follow-up**	Percentage of children initiating ART who are lost to follow-up during the 12 months after starting ART Target ≤20%
EWI 3 **Patient retention on first-line ART**	Percentage of paediatric patients initiating ART at the site who are taking an appropriate first-line ART regimen 12 months later Target ≥70%
EWI 4 **On-time drug pick-up**	Percentage of children whose caregiver picks up prescribed ARV drugs on time Target ≥90%
EWI 5 **On-time ART clinic appointment-keeping**	Percentage of children who attended scheduled or expected clinical consultations on time Target ≥80%
EWI 6 **ARV drug supply continuity**	Percentage of months in a designated year in which there were no paediatric ARV drug stock-outs Target 100%

The EWIs should be monitored in all ART sites in a country when feasible, or from a representative sample of ART sites. Achieving the best possible performance as measured by these indicators will help minimize the preventable emergence of drug-resistant HIV. Sites which do not achieve one or more of the EWI targets may require increased resources, staff training, or additional review to clarify the kind of support needed. Likewise, lessons may be learned from sites achieving and surpassing targets and applied to sites observed to be functioning less well.

18.5 Monitoring emergence of HIVDR transmission in infants and children on ART

The use of ART in high-income countries has been associated with the development of HIVDR [229]. HIV is a retrovirus characterized by very rapid replication, a high mutation rate in the presence of drug-selective pressure, viral recombination, and the need for lifelong treatment [230]. Because of these characteristics, some degree of HIVDR is anticipated to occur among persons on treatment even if appropriate ARV regimens are provided and optimal adherence to therapy is supported [229]. A population-based approach to ART scale-up requires a population-based strategy to assess and prevent the emergence of HIVDR, using an epidemiological approach to evaluate ART programmes. WHO has developed a generic monitoring protocol to monitor the emergence of HIVDR and associated programmatic factors in cohorts of infected children starting first-line ART. The survey is designed for implementation following a rolling three-year cycle in sentinel ART sites treating children. The survey identifies programmatic factors associated with the emergence of HIVDR, which can be

adjusted to optimize patient care and minimize the emergence of preventable drug-resistant HIV. The paediatric monitoring survey protocol is based on the adult HIVDR monitoring protocol [231] and is currently being piloted in Mozambique. The final paediatric protocol will be updated based on evidence derived from the pilot.

18.6 Surveillance for HIVDR in newly infected treatment-naive infants

An unwanted outcome related to the use of ARVs for PMTCT is the development of drug-resistance in the small number of infants who do become infected. Administration of one or more ARVs, especially if one NNRTI is administered alone, can lead to the development of drug-resistance in the infant in the event that HIV is transmitted.

Combination regimens for PMTCT have been recommended since 2006; however, many countries continue to provide single-dose nevirapine (sd-NVP), which is associated with development of NNRTI resistance among both HIV-infected mothers and infants who become infected. In relatively small studies (9 – 80 infants), the few infected infants exposed to NVP alone antepartum/intrapartum and postpartum have been shown to have NNRTI resistance at rates between 38% and 92% [221, 232-236]. Maternal prophylaxis regimens with two or more ARVs are not only more effective in preventing transmission but are also less likely to result in maternal HIVDR and infant HIVDR if transmission occurs. Small research studies have evaluated the prevalence of drug-resistant among infants associated with various PMTCT regimens administered to mothers and infants. The very few infected infants exposed to combinations of NVP and one or more NRTIs have been seen to have resistance at rates between 13% and 57% [232, 237 [not in list of refs], 238-241] with lower rates (between 13% and 14%) seen in two other small studies (of 7 and 8 infants, respectively) among infants receiving two NRTIs: AZT/3TC [239].

However, nationwide surveillance systems have not yet been developed to evaluate the association between PMTCT and HIVDR among infants, largely because of the expense and difficulty of collecting specimens and performing resistance assays. With expanding access to infant diagnosis using DBS, many laboratories have stored DBS for quality assurance purposes. These may be useful for drug-resistance testing. Stored DBS present an important opportunity to evaluate resistance systematically among infants newly diagnosed with HIV, and may provide critical information to guide optimal selection of an ART regimen. HIV has been successfully amplified and genotyped for drug-resistance testing from DBS in a large number of studies.

WHO is planning to evaluate the use of stored DBS to determine initial HIVDR among infants diagnosed with HIV as part of national HIVDR surveillance efforts.

The objective of surveillance for HIVDR in newly infected treatment-naive infants is to assess the extent of HIVDR in specific geographical areas where ART and ARVs for maternal and infant PMTCT have been widely available to eligible maternal and paediatric populations for at least three years. The survey results will help to guide policy-makers on the likely future efficacy of currently available or future paediatric ART regimens.

Further details can be provided by the WHO HIVDR programme at http://www.who.int/hiv/drugresistance/.

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On behalf of the WHO HIV Department Siobhan Crowley initiated and coordinated the bulk of this work, and Sally Girvin and Shaffiq Essajee helped to finalize and edit the guidelines prior to publication.

ANNEX B: GRADING OF RECOMMENDATIONS AND LEVELS OF EVIDENCE

Recommendations developed using the GRADE system are made based on consideration of costs, values, preference, feasibility and the balance of desirable and undesirable effects (risk – benefit assessment), along with assessment of the quality of available scientific evidence. The criteria used to assess the quality of this evidence, and the terminology used to rank the quality of the evidence, is described in Table 1.

Table 1: GRADE approach to ranking the quality of a body of evidence

Quality of evidence (summary score)	Study design	Lower if*	Higher if*
High (4)	Randomized trials or valid accuracy studies for diagnostic tests	**Study design:** -1 Serious limitations -2 Very serious limitations -1 Important inconsistency **Directness:** -1 Some uncertainty -2 Major uncertainty -1 Sparse or imprecise data -1 High probability of reporting bias	Strong association: +1 Strong, no plausible confounders, consistent and direct evidence +2 Very strong, no major threats to validity and direct evidence +1 Evidence of a dose – response gradient
Moderate (3)			
Low (2)	Observational studies or indirect accuracy studies for diagnostic tests		
Very low (1)			

* Presence can move quality of evidence up or down one grade (for example, from high to moderate), or it can can move quality of evidence up or down two grades (for example, from high to low).

High = Further research is very unlikely to change our confidence in the estimate of effect.

Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low = Any estimate of effect is very uncertain.

Limitations = Include problems in study design, such as for RCTs lack of blinding or allocation concealment, incomplete reporting, selective outcome reporting, or use of unvalidated outcome measures.

Inconsistency = Differences exist in the direction and size of the effect across the studies.

Uncertainty = Indirect comparisons or indirect populations have been considered across the studies, and there may be compelling reasons to expect important differences in the size of the effect.

Validity = Patients participating in RCTs are assessed to have same risk and/or mortality as non-enrolled patients in whom the intervention is expected to be required.

Where minimal evidence is available, recommendations are based on the reference group's opinions as to what constitutes best practice. The recommendations made in this document are graded as "strong" or "conditional", terminology which is defined in Table 2. Where it has not been possible to make recommendations, the reference group has indicated an urgent need for research. In the cur-

rent guideline revision, one of the noticeable effects of using the GRADE system is that the text now includes the terminology of the various grading processes that have been used since 2004. In the coming few years, each of the recommendations included in this text will be updated and presented in a consistent manner in accordance with the GRADE system.

Table 2: 2006 system for grading of recommendations and levels of evidence

Strength of recommendation	Level of evidence to guide recommendation
Recommended – should be followed	At least one RCT with clinical, laboratory or programmatic end-points. At least one high-quality study or several adequate studies with clinical, laboratory or programmatic end-points.
Consider – applicable in most situations	Observational cohort data, one or more case – control or analytical studies adequately conducted.
Optional	Expert opinion based on evaluation of other evidence.

The strength of a recommendation reflects the degree of confidence to which the desirable effects of adherence to a recommendation outweigh the undesirable effects. Desirable effects can include beneficial health outcomes, reduced burden and savings. Undesirable effects can include harm, more burden and costs. Burdens are the demands of adhering to a recommendation that patients or caregivers (e.g. family) may dislike, such as having to undergo more frequent tests or opting for a treatment that may require a longer time for recovery.

Although the degree of confidence is a continuum, the GRADE system defines two categories: strong and conditional.

- A strong recommendation is one for which the panel is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects. This can be both in favour of an intervention and against it.
- A conditional recommendation is one for which the panel concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but the panel is not confident about these trade-offs. Reasons for not being confident can include:
  - absence of high-quality evidence
  - presence of imprecise estimates of benefits or harms
  - uncertainty or variation in how different individuals value the outcomes
    - small benefits
    - the benefits may not be worth the costs (including the costs of implementing the recommendation).

Despite the lack of a precise threshold for going from a strong to a conditional recommendation, the presence of important concerns about one or more of the above factors make a conditional recommendation more likely (see Table 3 below). Panels should consider all of these factors and make the reasons for their judgements explicit.

Table 3: Understanding WHO recommendations

Strong	Weak/Conditional	Research
Panel is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects.	Panel concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects. *However:* • It is only applicable to a specific group, population or setting; or • New evidence may result in changing the balance of risk to benefit; or • The benefits may not warrant the cost or resource requirements in all settings.	Further research is required before any recommendations can be made.

Implications of a strong recommendation:

- For patients:
  - Most people in your situation would want the recommended course of action and only a small proportion would not.
- For clinicians:
  - Most patients should receive the recommended course of action.
  - Adherence to this recommendation is a reasonable measure of good-quality care.
- For policy-makers:
  - The recommendation can be adapted as a policy in most situations. Quality initiatives could use this recommendation to measure variations in quality.

Implications of a conditional recommendation:

- For patients:
  - The majority of people in your situation would want the recommended course of action, but many would not.
- For clinicians:
  - Be prepared to help patients to make a decision that is consistent with their own values.
- For policy-makers:
  - There is a need for substantial debate and involvement of stakeholders.

ANNEX C: WHO CLINICAL STAGING OF HIV FOR INFANTS AND CHILDREN WITH ESTABLISHED HIV INFECTION

All clinical events or conditions referred to are described in Annex D

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 infections
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 ºC, intermittent or constant, for longer than one month)
Persistent oral Candidiasis (after first 6 weeks of life)
Oral hairy leukoplakia
Acute necrotizing ulcerative gingivitis/periodontitis
Lymph node TB
Pulmonary TB
Severe recurrent bacterial pneumonia
Symptomatic lymphoid interstitial pneumonitis
Chronic HIV-associated lung disease including bronchiectasis
Unexplained anaemia (<8.0 g/dl), neutropenia (<0.5x109/L^3) or chronic thrombocytopenia (<50 x $10^9/L^3$)

Clinical stage 4 [a]
Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy
Pneumocystis pneumonia
Recurrent severe bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)
Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration, or visceral at any site)
Extrapulmonary TB
Kaposi sarcoma
Oesophageal candidiasis (or candiadisis of trachea, bronchi or lungs)
Central nervous system toxoplasmosis (after the neonatal period)
HIV encephalopathy
Cytomegalovirus (CMV) infection; retinitis or CMV infection affecting another organ, with onset at age more than 1 month
Extrapulmonary cryptococcosis including meningitis
Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidioidomycosis, penicilliosis)
Chronic cryptosporidiosis (with diarrhoea)
Chronic isosporiasis
Disseminated non-tuberculous mycobacterial infection
Cerebral or B cell non-Hodgkin lymphoma
Progressive multifocal leukoencephalopathy
HIV-associated cardiomyopathy or nephropathy

[a] Some additional specific conditions can be included in regional classifications (e.g. penicilliosis in Asia, HIV-associated rectovaginal fistula in Southern Africa, reactivation of typanosomiasis in Latin America).
Ref: http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf

ANNEX D: PRESUMPTIVE AND DEFINITIVE CRITERIA FOR RECOGNIZING HIV-RELATED CLINICAL EVENTS IN INFANTS AND CHILDREN WITH ESTABLISHED HIV INFECTION

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

Clinical event	Clinical diagnosis	Definitive diagnosis
Stage 2		
Unexplained parotid enlargement	Asymptomatic bilateral swelling that may spontaneously resolve and recur, in absence of other known cause; usually painless	Clinical diagnosis
Herpes zoster	Painful rash with fluid-filled blisters, dermatomal distribution, may be haemorrhagic on erythematous background, and may become large and confluent. Does not cross the midline.	Clinical diagnosis
Recurrent upper respiratory tract infection (URTI)	Current event with at least one episode in past six months. Symptom complex: fever with unilateral face pain and nasal discharge (sinusitis) or painful swollen eardrum (otitis media), sore throat with productive cough (bronchitis), sore throat (pharyngitis) and barking croup-like cough (laryngotracheal bronchitis [LTB]), persistent or recurrent ear discharge	Clinical diagnosis
Stage 3		
Unexplained moderate malnutrition	Weight loss: low weight-for-age, up to -2 standard deviations (SDs), not explained by poor or inadequate feeding and/or other infections, and not adequately responding to standard management	Documented loss of body weight of -2 SD, failure to gain weight on standard management and no other cause identified during investigation
Unexplained persistent diarrhoea	Unexplained persistent (14 days or more) diarrhoea (loose or watery stool, three or more times daily) not responding to standard treatment	Stools observed and documented as unformed. Culture and microscopy reveal no pathogens.
Unexplained persistent fever (intermittent or constant for longer than one month)	Reports of fever or night sweats for longer than one month, either intermittent or constant, with reported lack of response to antibiotics or antimalarials. No other obvious foci of disease reported or found on examination. Malaria must be excluded in malarious areas.	Documented fever of >37.5 ºC with negative blood culture, negative malaria slide and normal or unchanged CXR, and no other obvious foci of disease

Clinical event	Clinical diagnosis	Definitive diagnosis
Stage 3		
Oral candidiasis (after first 6 weeks of life)	Persistent or recurring creamy white, soft, small plaques which can be scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender (erythematous form)	Microscopy or culture
Oral hairy leukoplakia	Fine small, linear patches on lateral borders of tongue, generally bilateral, which do not scrape off	Clinical diagnosis
Lymph node TB	Non-acute, painless "cold" enlargement of lymph nodes, usually matted, localized in one region. May have draining sinuses. Response to standard anti-TB treatment in one month.	Histology or isolation of M. tuberculosis from fine needle aspirate
Pulmonary TB	Non-specific symptoms, e.g. chronic cough, fever, night sweats, anorexia and weight loss. In older children, productive cough and haemoptysis as well. Abnormal CXR.	Isolation of M. tuberculosis on sputum culture
Severe recurrent bacterial pneumonia	Cough with fast breathing, chest indrawing, nasal flaring, wheezing and grunting. Crackles or consolidation on auscultation. Responds to course of antibiotics. Current episode plus one or more in previous six months.	Isolation of bacteria from appropriate clinical specimens (induced sputum, bronchoalveolar lavage [BAL], lung aspirate)
Acute necrotizing ulcerative gingivitis or stomatitis, or acute necrotizing ulcerative periodontitis	Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odour, and rapid loss of bone and/or soft tissue	Clinical diagnosis
Symptomatic lymphoid interstitial pneumonitis (LIP)	No presumptive clinical diagnosis	CXR: bilateral reticulonodular interstitial pulmonary infiltrates present for more than two months with no response to antibiotic treatment and no other pathogen found. Oxygen saturation persistently <90%. May present with cor pulmonale and may have increased exercise-induced fatigue. Characteristic histology.

Clinical event	Clinical diagnosis	Definitive diagnosis
Stage 3		
Chronic HIV-associated lung disease (including bronchiectasis)	History of cough productive with copious amounts of purulent sputum (bronchiectasis only), with or without clubbing, halitosis, and crepitations and/or wheeze on auscultation	CXR: may show honeycomb appearance (small cysts) and/or persistent areas of opacification and/or widespread lung destruction, with fibrosis and loss of volume.
Unexplained anaemia (<8 g/dl), or neutropenia (<0.5 x 10^9/L) or chronic thrombocytopenia (<50 X 10^9/L/	No presumptive clinical diagnosis	Laboratory testing, not explained by other non-HIV conditions, or not responding to standard therapy with haematinics, antimalarials or anthelminthics as outlined in the IMCI.
Stage 4		
Unexplained severe wasting, stunting or severe malnutrition not adequately responding to standard therapy	Persistent weight loss not explained by poor or inadequate feeding or other infections and not adequately responding in two weeks to standard therapy. Characterized by: visible severe wasting of muscles, with or without oedema of both feet, and/or weight-for-height of -3 SDs, as defined by the WHO IMCI guidelines	Confirmed by documented weight loss of >-3 SD +/- oedema
Pneumocystis pneumonia (PCP)	Dry cough, progressive difficulty in breathing, cyanosis, tachypnoea and fever; chest indrawing or stridor. (Severe or very severe pneumonia as in IMCI.) Usually of rapid onset especially in infants <6 months of age. Response to high-dose co-trimoxazole +/- prednisolone	Confirmed by: CXR, typical bilateral perihilar diffuse infiltrates; microscopy of induced sputum or BAL or nasopharyngeal aspirate (NPA)
Recurrent severe bacterial infection, e.g. empyema, pyomyositis, bone or joint infection, meningitis but excluding pneumonia	Fever accompanied by specific symptoms or signs that localize infection. Responds to antibiotics. Current episode plus one or more in previous six months.	Confirmed by culture of appropriate clinical specimen
Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration or visceral at any site)	Severe and progressive painful orolabial, genital, or anorectal lesions caused by HSV infection present for more than one month	Confirmed by culture and/or histology

Clinical event	Clinical diagnosis	Definitive diagnosis
Stage 4		
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)	Chest pain and dysphagia (difficulty in swallowing), odynophagia (pain on swallowing food and fluids) or retrosternal pain worse on swallowing (food and fluids); responds to specific treatment. In young children, suspect particularly if oral Candida observed and food refusal occurs and/or difficulties/crying when feeding.	Confirmed by macroscopic appearance at endoscopy, microscopy of specimen from tissue or macroscopic appearance at bronchoscopy or histology
Extrapulmonary/ disseminated TB	Systemic illness usually with prolonged fever, night sweats, weight loss. Clinical features of organs involved, e.g. sterile pyuria, pericarditis, ascites, pleural effusion, meningitis, arthritis, orchitis	Positive microscopy showing AFB or culture of Mycobacterium tuberculosis from blood or other relevant specimen except sputum or BAL. Biopsy and histology
Kaposi sarcoma	Typical appearance in skin or oropharynx of persistent, initially flat, patches with a pink or blood-bruise colour, skin lesions that usually develop into nodules	Macroscopic appearance or by histology: • typical red-purple lesions seen on bronchoscopy or endoscopy; • dense masses in lymph nodes, viscera or lungs by palpation or radiology; • histology
CMV retinitis or CMV infection affecting another organ, with onset at age >1 month	Retinitis only CMV retinitis may be diagnosed by experienced clinicians: progressive floaters in field of vision, light flashes and scotoma; typical eye lesions on serial fundoscopic examination; discrete patches of retinal whitening with distinct borders, spreading centrifugally, often following blood vessels, associated with retinal vasculitis, haemorrhage and necrosis	Definitive diagnosis required for other sites. Histology or CMV demonstrated in CSF by culture or DNA-PCR
CNS toxoplasmosis with onset at age >1 month	Fever, headache, focal neurological signs, convulsions. Usually responds within 10 days to specific therapy.	Postive serum Toxoplasma antibody and if available, neuroimaging showing single/multiple intracranial mass lesions
Extrapulmonary cryptococcosis including meningitis	Meningitis: usually subacute, fever with increasing severe headache, meningism, confusion, behavioural changes that respond to cryptococcal therapy	Isolation of Crytococcus neoformans from extrapulmonary site or positive cryptococall antigen test (CRAG) in CSF or blood.

Ref: http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf

ANNEX E: PRESCRIBING INFORMATION AND WEIGHT-BASED DOSING OF AVAILABLE ARV FORMULATIONS FOR INFANTS AND CHILDREN

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Introduction

The availability of low-cost, high-quality, child-friendly ARV formulations, particularly FDC products, has had a significant impact on the scale-up of ART for children.

WHO strongly endorses the use of these products, and encourages the continued development of improved formulations appropriate for paediatric use.

This Annex contains information on antiretroviral (ARV) drugs for which there are paediatric indications, formulations or sufficient information and evidence to provide guidance on prescribing and dosing. Situations that are frequently encountered in resource-limited settings are taken into consideration, including the possible lack of refrigeration and the lack of liquid or formulations of ARVs for small children. For simplification, doses are provided in ranges based on children's weights. Although weight and height can both be measured, it may be impractical to expect providers in many settings to accurately calculate body surface area (BSA). When determining weight-band-based dosing for drugs that are usually dosed by BSA, careful consideration was given to the usual surface area for children of that weight in cohorts from developing countries.

WHO began the work of developing simplified guidance on ARVs for use in children as a result of recommendations made at a technical consultation in November 2004. Since then, the guidance has been regularly updated by the Paediatric ARV Working Group. Members of this working group are listed in Annex A.

The Paediatric ARV Working Group reviews current scientific data and uses pharmacokinetic modelling data to develop guidance to manufacturers on which ARV medicines are likely to be required.

The primary sources of information for the guidance are the package inserts from the innovator for each drug at the time of writing. This information is supplemented with data from other authoritative publications and expert consultation. Providers are advised to consider the most recent guidelines and product labelling as this information may have been updated.

Generic (multisource) ARV drugs are manufactured by several companies. These products include a number of important paediatric fixed-dose combination (FDC) tablets that contain doses of drugs appropriate for small children. Paediatric FDCs are preferable for implementation in resource-limited settings, and while most of them are of acceptable quality, providers should consult the WHO document *Access to HIV/AIDS drugs and diagnostics of acceptable quality* for guidance (http://www.who.int/hiv/amds/selection/en/index.html).

WHO operates a voluntary prequalification system that was set up in 2001. This service facilitates access to medicines that meet unified standards of quality, safety and efficacy for HIV/AIDS, malaria and tuberculosis (TB). Manufacturers (including manufacturers of generic products) who wish their medicines to be included in the prequalified products list are invited to apply. Each manufacturer must present extensive information on the product (or products) submitted to allow qualified assessment teams to evaluate quality, safety and efficacy. The manufacturer must open its manufacturing sites to an inspection team that assesses working procedures for compliance with WHO Good

Manufacturing Practices. Alternatively, the inspections carried out by stringent regulatory bodies are recognized and their work is not duplicated by WHO. A list of WHO-prequalified products is continuously updated and is available at http://mednet3.who.int/prequal/.

This Annex will be updated regularly as new data become available and readers are recommended to check the WHO website on paediatric HIV care (http://www.who.int/hiv/topics/paediatric/en/index.html).

General principles

Details on individual drugs are available from the various manufacturers or the US treatment guidelines (http://www.aidsinfo.nih.gov) or the PENTA 2009 guidelines for the use of antiretroviral therapy (ART) in paediatric HIV-1 infection, which are published in the journal *HIV Medicine* (*HIV Med. 2009* Nov; 10 (10): 591 – 613). Common and important toxicities of ARV drugs are provided in the main text of this document.

The WHO dosing guidance provided here includes weight-based tables. The target dose for each ARV drug is shown in the introduction of the individual drug tables. However, in some cases, the dosing in a particular weight-band may be somewhat above or below that recommended by the manufacturer. Decisions about dosing were based upon the manufacturer's information, ARV drug formulation choices, available data from clinical studies, and expert paediatric pharmacology consultation, and were directed towards what could be considered the "optimal" dose for a particular weight-band, given the limitations imposed by currently available drug formulations and the public health advantages of simplified dosing.

It is recommended that national treatment advisory panels and/or expert groups review and consider these principles and the prescribing information given in this Annex within the context of their current national policies, practice and drug regulatory requirements.

The principles that were followed in developing the WHO simplified tables include the following.

- Liquid formulations are difficult to use for a variety of reasons, including cost, difficulty of storage, need for accurate measurement, palatability and the nature of the excipient.
- Solid formulations and FDCs generally are preferred to liquid formulations.
- It is preferable to use one type of formulation when constructing a treatment regimen.
- Where solid formulations are not available or suitable, and liquid formulations are the only option:
  - Oral syringes or other standardized devices of various sizes should be made available to support accurate dosing.
  - Large volumes of liquid formulations should be avoided where possible.
  - In general, children should be switched to available solid formulations as soon as possible or as soon as they are tolerated.
- Many tablets, but not all, may be divided in half but generally not further for drug safety reasons. Scored tablets are more easily split, and most paediatric tablets and FDCs are manufactured with a score line. Where tablets are not scored, WHO recommends that tablet splitting is conducted in the dispensing pharmacy using appropriate tablet cutters.

- If paediatric solid formulations are not available, use solid formulations currently available for adults. However, some adult FDCs may contain ratios of ARVs that are not best suited for children and this can result in underdosing of individual components when tablets are halved. Underdosing should be avoided, particularly for those drugs that may lead to rapid emergence of resistance (e.g. non-nucleoside reverse transcriptase inhibitors [NNRTIs]).
- In order to deliver once-daily dosing of nevirapine (NVP) during the first two weeks of induction of a NVP-containing regimen, triple-drug FDCs should be combined with dual FDCs (that do not contain NVP). Alternatively, if dual FDCs are not available, the individual components of the regimen should be prescribed.
- Different morning and evening doses should be avoided where possible. Where tablets can be divided, the use of even quantities of tablets is recommended (e.g. where 3 tablets daily is recommended, the morning dose would be 1.5 tablets and the evening dose 1.5 tablets). When tablets cannot be divided and morning and evening doses have to be unequal, it is recommended that the larger of the two doses be taken in the morning (e.g. where 3 tablets daily is recommended, dose 2 tablets in the morning and 1 tablet in the evening).
- The doses in the tables are presented in weight-bands, accepting that some deviation from target dosing will occur.
- Children have to be weighed at each clinic visit so that appropriate dose changes can be made as children grow and gain weight.
- When capsules are opened or tablets dissolved or crushed and added to food or liquid, it is important that the dose be consumed immediately and that the entire volume/amount of food or liquid is consumed to ensure administration of the full dose.

Where manufacturers'dosing was provided in BSA, weight-based doses were determined by using BSA values estimated from median heights-for-weight from international growth charts. BSA estimates for each weight were derived from the mid-upper arm circumference/weight-for-height study database (MUAC/WFH), which includes data from over 560 nutritional anthropometry surveys. These weight-for-BSA estimates were structured into a dosing tool developed by WHO (http://www.who.int/hiv/paediatric/generictool/en/index.html). The Paediatric Working Group used this tool to assess various dosing schedules in terms of the intended dose delivered relative to the target dose at each weight for a variety of single drugs and FDCs. The tool demonstrates potential over- or underdosing for any given weight. Available evidence was reviewed, including published and unpublished data, to better understand the potential impact of off-target dosing (http://www.who.int/hiv/pub/paediatric/ARV_WG_meeting_report_may2008.pdf).

In general, the Working Group attempted to avoid dosing any drug or component of an FDC below 90% or above 125% of the target dose (or target range for products with an established dosing range). Exceptions to this rule may be justified based on available pharmacokinetic data, toxicity considerations, and thresholds for the development of HIV drug resistance. In particular, the Working Group accepted higher dosing for children less than 3 years of age for drugs with a known increase in metabolism or clearance in this population, such as NVP, lamivudine (3TC), stavudine (d4T), abacavir (ABC) and lopinavir/ritonavir (LPV/r). A primary objective of the Working Group was to create a single, simplified and harmonized dosing schedule wherein, for all drugs or combinations, changes

in the numbers of tablets/capsules and switches from one formulation to another occurred within the same weight-bands.

The first harmonized schedule was published in 2008 and, since then, has been expanded significantly to include a number of additional drugs and formulations.

WHO will continue to work to simplify prescribing, dispensing and dosing guidance, and to work with the pharmaceutical industry (originator and generic manufacturers) and other partners to develop more practical recommendations on the range of formulations required to safely accelerate scaling up of paediatric ART. WHO will make available additional guidance on required formulations, dosing information and pharmacovigilance activities.

The need for new formulations and new research

Although a number of child-friendly formulations, particularly paediatric FDC tablets and paediatric single drugs in solid forms, are available, it is clear that additional formulations will be needed to facilitate the scale-up of treatment for infants and children, and to keep pace with new recommendations and guidance.

Additional research is necessary to better understand the best dosing formulations for children. Dispersible tablets are easier to dose in children, but require access to clean water, and have not been studied in breast milk, which is important for administration to infants. Breast milk dispersibility is especially important for formulations that will be used for infant prophylaxis to prevent mother-to-child transmission (MTCT) of HIV infection. One option for prevention of mother-to-child transmission (PMTCT) in the new WHO recommendations calls for long-term infant prophylaxis with NVP. In the first few weeks of life, this is best accomplished by using NVP liquid, but beyond 6 weeks, infant dosing would be made easier if there was a dispersible scored 20 mg NVP tablet.

Darunavir (DRV) will be an important drug for paediatric treatment in the future, especially as increasing numbers of children require third-line therapy. DRV is usually boosted with low-dose ritonavir (RTV). At present, although there are several capsule strengths of DRV available, including strengths that are suitable for paediatric dosing, no DRV/RTV co-formulation is available.

Once-daily FDCs containing tenofovir (TDF), efavirenz (EFV) and emtricitabine (FTC) or 3TC have become the mainstays of adult treatment. Currently, TDF is not approved for use in children less than 12 years, but a number of paediatric studies are in progress and a paediatric approval is expected. An FDC containing TDF 75 mg and 3TC 75 mg together with a scored adult tablet containing TDF 300 mg and 3TC 300 mg would align well with the harmonized schedule.

For countries that choose to use ABC as a first-line drug in children, it is critical to have access to a triple-drug FDC containing ABC, 3TC and NVP. This would complement the dual FDC of ABC/3TC.

A number of additional high-priority formulations have been identified by the Paediatric ARV Working Group and these are listed below.

Urgently needed dosing strengths of drugs not yet available in child-friendly formulations

Drug	Formulation (mg)	Comments
DRUGS NEEDED FOR PMTCT		
NVP	20 mg scored tablet	Used for infant prophylaxis from 6 weeks onwards
DRUGS NEEDED FOR PAEDIATRIC ART		
LPV/RTV	40/10 mg sprinkle	Heat-stable formulation that will be equivalent to 0.5 ml of liquid and used to treat infants and children who are unable to take the paediatric tablet
ABC/3TC	Scored adult 300/150 mg tablet	Used in children >25 kg
ABC/3TC/NVP	60/30/50 mg	Triple FDC to align with the dual FDC
RTV	50 mg heat-stable sprinkle or tablet	Useful for co-administration with unboosted PIs and for super boosting when PIs need to be dosed with rifampicin
TDF/3TC	75/75 mg tab	
	Scored 300/300 mg tab	
DRV/RTV	Unclear	Current labelling calls for different ratios of DRV to RTV for different age brackets. It is unclear what the correct ratio should be to produce a co-formulated FDC, but this is a priority formulation
Raltegravir	Unclear	Raltegravir is not yet approved for paediatric use but this is high-priority formulation

See updated guidance on required paediatric formulations at http://www.who.int/hiv/topics/paediatric/technical/en/index.

Simplified table giving number of tablets of child-friendly solid formulations for morning and evening dosing

Drug	Strength of paediatric tab (mg)	Children 6 weeks of age and above										Strength of adult tab (mg)	Number of tablets by weight-band	
		Number of tablets by weight-band morning and evening												
		3 – 5.9 kg		6 – 9.9 kg		10 – 13.9 kg		14 – 19.9 kg		20 – 24.9 kg			25 – 34.9 kg	
		am	pm	am	pm	am	pm	am	pm	am	pm		am	pm
SINGLE DRUGS														
AZT	60	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300	1	1
ABC	60	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300	1	1
NVP	50	1	1	1.5	1.5	2	2	2.5	2.5	3	3	200	1	1
ddI	25	2[a]	2[a]	3	2	3	3	4	3	4	4	25	5	5
COMBINATIONS														
AZT/3TC	60/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300/150	1	1
AZT/3TC/NVP	60/30/50	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300/150/200	1	1
ABC/AZT/3TC	60/60/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300/300/150	1	1
ABC/3TC	60/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	[b]		
d4T/3TC	6/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	30/150	1	1
d4T/3TC/NVP	6/30/50	1	1	1.5	1.5	2	2	2.5	2.5	3	3	30/150/200	1	1
LPV/r [c]	100/25	NR	NR	NR	NR	2	1	2	2	2	2	100/25	3	3

[a] This dose of ddI is only appropriate for children 3 months of age or older and weighing between 5 kg and 5.9 kg.

[b] See ABC/3TC FDC dosing table.

[c] Higher doses of LPV/r may be required when co-administered with enzyme-inducing drugs such as NVP, EFV, fos-amprenavir (FPV), rifampicin.

Simplified table giving ml of liquid formulation and number of tablets or capsules of adult solid formulation for morning and evening dosing

Drug	Strength of paediatric liquid (mg/ml) and adult tab/cap (mg)	Children 6 weeks of age and above									
		Number of tablets/capsules or ml by weight-band morning and evening									
		3 – 5.9 kg		6 – 9.9 kg		10 – 13.9 kg		14 – 19.9 kg		20 – 24.9 kg	
		am	pm	am	pm	am	pm	am	pm	am	pm
AZT	10 mg/ml; 300 mg	6 ml	6 ml	9 ml	9 ml	12 ml	12 ml	0.5	0.5	1	0.5
ABC	20 mg/ml; 300 mg	3 ml	3 ml	4 ml	4 ml	6 ml	6 ml	0.5	0.5	1	0.5
3TC	10 mg/ml; 150 mg	3 ml	3 ml	4 ml	4 ml	6 ml	6 ml	0.5	0.5	1	0.5
d4T	1 mg/ml; 15 mg or 20 mg	6 ml	6 ml	9 ml	9 ml	1 (15 mg)	1 (15 mg)	1 (20 mg)	1 (20 mg)	1 (20 mg)	1 (20 mg)
NVP	10 mg/ml; 200 mg	5 ml	5 ml	8 ml	8 ml	10 ml	10 ml	1	0.5	1	0.5
ddI	10 mg/ml; 25 mg	3 ml [a]	3 ml [a]	5 ml	5 ml	6 ml	6 ml	4	3	4	4
LPV/r	80/20 mg/ml	1 or 1.5 ml[b]	1 or 1.5 ml[b]	1.5 ml	1.5 ml	2 ml	2 ml	2.5 ml	2.5 ml	3 ml	3 ml

[a] This dose of ddI is only appropriate for children 3 months of age or older and weighing between 5 kg and 5.9 kg.

[b] LPV/r liquid: for 3 – 3.9 kg, use 1 ml a.m. and 1 ml p.m.; for 4 – 5.9 kg use 1.5 ml a.m. and 1.5 ml p.m. In addition, higher doses of LPV/r may be required when co-administered with enzyme-inducing drugs such as NVP, EFV, FPV or rifampicin.

Simplified table giving number of tablets of child-friendly solid formulations for once-daily dosing

Drug	Strength of tab/cap (mg)	Number of tablets or capsules by weight-band once daily					Strength of tab/cap (mg)	Number of tablets or capsules by weight-band once daily
		3 – 5.9 kg	6 – 9.9 kg	10 – 13.9 kg	14 – 19.9 kg	20 – 24.9 kg		25 – 34.9 kg
		Once daily	Once daily	Once daily	Once daily	Once daily		Once daily
SINGLE DRUGS								
EFV [a]	200 mg	NR	NR	1	1.5	1.5	200	2
ddI [b]	125 mg or 200 mg EC	NR	NR	1 (125 mg)	1 (200 mg)	2 (125 mg)	125 mg EC	2

[a] EFV is not recommended for children below 3 years and weighing less than 10 kg.

[b] ddI EC is not recommended for children weighing less than 10 kg; this dose is recommended only for those 10 kg and above.

NR = not recommended EC = enteric coated

Drug formulations and dosages

1. Nucleoside reverse transcriptase inhibitors (NRTIs)

1.1. LAMIVUDINE (3TC)

FORMULATIONS

Tablets	Capsules	Liquid	FDC
150 mg	None	10 mg/ml	**Baby 30 mg 3TC** **Adult 150 mg 3TC** • 3TC + d4T + NVP • 3TC + d4T • 3TC + AZT + NVP • 3TC + AZT + ABC • 3TC + AZT • 3TC + ABC **Junior 60 mg 3TC** • 3TC + d4T + NVP • 3TC + d4T

DOSE AND FREQUENCY OF DOSING

Target doses

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

Note: Once-daily dosing is not yet approved for children but encouraging pharmacokinetic data are available for children switching to once-daily dosing once viral suppression occurs on ART.

Administration – adult tablets

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

Storage

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

OTHER COMMENTS

General

- Well tolerated
- No food restrictions
- Also active against hepatitis B

Pharmacokinetic data

- Available for all ages

Major drug interactions

- None

Ref: http://us.gsk.com/products/assets/us_epivir. pdf
http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html

LAMIVUDINE					
Recommended dosing based on weight-bands for children >6 weeks of age using liquid and adult tablets					
Weight range (kg)		Target dose 4 mg/kg twice daily to a maximum of 150 mg twice daily		Dose (ml or tablets)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	10	mg/ml liquid	3 ml	3 ml
4	4.9	10	mg/ml liquid	3 ml	3 ml
5	5.9	10	mg/ml liquid	3 ml	3 ml
6	6.9	10	mg/ml liquid	4 ml	4 ml
7	7.9	10	mg/ml liquid	4 ml	4 ml
8	8.9	10	mg/ml liquid	4 ml	4 ml
9	9.9	10	mg/ml liquid	4 ml	4 ml
10	10.9	10	mg/ml liquid	6 ml	6 ml
11	11.9	10	mg/ml liquid	6 ml	6 ml
12	13.9	10	mg/ml liquid	6 ml	6 ml
14	16.9	150	mg tablet	½	½
17	19.9	150	mg tablet	½	½
20	24.9	150	mg tablet	1	½
25	29.9	150	mg tablet	1	1
30	34.9	150	mg tablet	1	1

1.2 STAVUDINE (d4T)

FORMULATIONS

Tablets	Capsules	Liquid	FDC
None	15 mg 20 mg 30 mg	1 mg/ml	**Baby 6 mg d4T** **Junior 12 mg d4T** **Adult 30 mg d4T** • d4T + 3TC + NVP • d4T + 3TC

DOSE AND FREQUENCY OF DOSING

Target doses

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

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

- Adults — 30 mg/dose twice daily

Administration – capsules

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

Administration – liquid

- Liquid must be well shaken prior to each use.

Storage

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

OTHER COMMENTS

General

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

Pharmacokinetic data

- Available for all ages

Major drug interactions

- Do not use d4T with AZT due to an antagonistic effect.

Ref: http://packageinserts.bms.com/pi/pi_zerit. pdf
http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html

STAVUDINE					
Recommended dosing based on weight-bands for children >6 weeks using liquid and capsules					
Weight range (kg)		Target dose 1 mg/kg twice daily up to 30 mg twice daily		Dose (ml or tablets)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	1	mg/ml liquid	6 ml	6 ml
4	4.9	1	mg/ml liquid	6 ml	6 ml
5	5.9	1	mg/ml liquid	6 ml	6 ml
6	6.9	1	mg/ml liquid	9 ml	9 ml
7	7.9	1	mg/ml liquid	9 ml	9 ml
8	8.9	1	mg/ml liquid	9 ml	9 ml
9	9.9	1	mg/ml liquid	9 ml	9 ml
10	10.9	15	mg capsule	1	1
11	11.9	15	mg capsule	1	1
12	13.9	15	mg capsule	1	1
14	16.9	20	mg capsule	1	1
17	19.9	20	mg capsule	1	1
20	24.9	20	mg capsule	1	1
25	29.9	30	mg capsule	1	1
30	34.9	30	mg capsule	1	1

1.3 ZIDOVUDINE (AZT OR ZDV)

FORMULATIONS

Tablets	Capsules	Liquid	FDC
60 mg 300 mg	100 mg 250 mg	10 mg/ml	**Baby 60 mg AZT** **Adult 300 mg AZT** • AZT + 3TC + NVP • AZT + 3TC • AZT + 3TC + ABC

DOSE AND FREQUENCY OF DOSING

• Maximum dose 300 mg twice daily

Target dose
• Liquid (oral dosing) 180 – 240 mg/m^2 per dose given twice daily (total daily dose 360 – 480 mg/m^2)
• For children with suspected nervous system involvement, it may be beneficial to use a dose at the higher end of the range.

Maximum dose
• 300 mg twice daily

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

Administration – capsules
• Can be opened and dispersed in water or onto a small amount of food and immediately ingested

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

Storage
• Store capsules at room temperature (25°C; range 15 – 30°C) in a tightly closed container (to protect from moisture).
• Store tablets at room temperature (25°C; range 15 – 30°C).
• Liquid is stable at room temperature but needs storage in a glass jar and is light sensitive.

OTHER COMMENTS

General
• No food restrictions
• Use with caution in children with anaemia due to potential for bone marrow

Pharmacokinetic data
• Available for all ages

Major drug interactions
• Do not use with d4T or ribavirin.

Ref: http://us.gsk.com/products/assets/us_retrovir. pdf
http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html

ZIDOVUDINE					
Recommended dosing based on weight-bands for children >6 weeks using liquid and adult tablets					
Weight range (kg)		Target dose 180 – 240 mg/m^2 twice daily		Dose (ml or tablets)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	10	mg/ml liquid	6 ml	6 ml
4	4.9	10	mg/ml liquid	6 ml	6 ml
5	5.9	10	mg/ml liquid	6 ml	6 ml
6	6.9	10	mg/ml liquid	9 ml	9 ml
7	7.9	10	mg/ml liquid	9 ml	9 ml
8	8.9	10	mg/ml liquid	9 ml	9 ml
9	9.9	10	mg/ml liquid	9 ml	9 ml
10	10.9	10	mg/ml liquid	12 ml	12 ml
11	11.9	10	mg/ml liquid	12 ml	12 ml
12	13.9	10	mg/ml liquid	12 ml	12 ml
14	16.9	300	mg tablet	½	½
17	19.9	300	mg tablet	½	½
20	24.9	300	mg tablet	1	½
25	29.9	300	mg tablet	1	1
30	34.9	300	mg tablet	1	1

ZIDOVUDINE					
Recommended dosing based on weight-bands for children >6 weeks using liquid and capsules					
Weight range (kg)		Target dose 180 – 240 mg/m^2 twice daily		Dose (ml or capsules)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	10	mg/ml liquid	6 ml	6 ml
4	4.9	10	mg/ml liquid	6 ml	6 ml
5	5.9	10	mg/ml liquid	6 ml	6 ml
6	6.9	10	mg/ml liquid	9 ml	9 ml
7	7.9	10	mg/ml liquid	9 ml	9 ml
8	8.9	100	mg capsule	1	1
9	9.9	100	mg capsule	1	1
10	10.9	100	mg capsule	1	1
11	11.9	100	mg capsule	1	1
12	13.9	100	mg capsule	1	1
14	16.9	100	mg capsule	2	1
17	19.9	100	mg capsule	2	1
20	24.9	100	mg capsule	2	2
25	29.9	100	mg capsule	2	2
30	34.9	100	mg capsule	3	3

ZIDOVUDINE					
Recommended dosing based on weight-bands for children >6 weeks using paediatric tablets					
Weight range (kg)		Target dose 180 – 240 mg/m^2 twice daily		Dose (tablets)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	60	mg tablet	1	1
4	4.9	60	mg tablet	1	1
5	5.9	60	mg tablet	1	1
6	6.9	60	mg tablet	1.5	1.5
7	7.9	60	mg tablet	1.5	1.5
8	8.9	60	mg tablet	1.5	1.5
9	9.9	60	mg tablet	1.5	1.5
10	10.9	60	mg tablet	2	2
11	11.9	60	mg tablet	2	2
12	13.9	60	mg tablet	2	2
14	16.9	60	mg tablet	2.5	2.5
17	19.9	60	mg tablet	2.5	2.5
20	24.9	60	mg tablet	3	3
25	29.9	300	mg tablet	1	1
30	34.9	300	mg tablet	1	1

1.4 ABACAVIR (ABC)

FORMULATIONS

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

DOSE AND FREQUENCY OF DOSING

Target dose

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

Maximum dose

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

Administration – tablets

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

Storage

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

OTHER COMMENTS

General

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

Pharmacokinetic data

- Available for children above the age of 3 months

Major drug interactions

- None reported.

Ref: http://us.gsk.com/products/assets/us_ziagen. pdf
http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html

ABACAVIR					
Recommended dosing based on weight-bands for children >6 weeks using liquid and adult tablets					
Weight range (kg)		Target dose <16 years or <37.5 kg: 8 mg/kg/dose given twice daily Maximum dose >16 years or ≥37.5 kg: 300 mg/dose given twice daily		Dose (ml or tablets)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	20	mg/ml liquid	3 ml	3 ml
4	4.9	20	mg/ml liquid	3 ml	3 ml
5	5.9	20	mg/ml liquid	3 ml	3 ml
6	6.9	20	mg/ml liquid	4 ml	4 ml
7	7.9	20	mg/ml liquid	4 ml	4 ml
8	8.9	20	mg/ml liquid	4 ml	4 ml
9	9.9	20	mg/ml liquid	4 ml	4 ml
10	10.9	20	mg/ml liquid	6 ml	6 ml
11	11.9	20	mg/ml liquid	6 ml	6 ml
12	13.9	20	mg/ml liquid	6 ml	6 ml
14	16.9	300	mg tablet	½	½
17	19.9	300	mg tablet	½	½
20	24.9	300	mg tablet	1	½
25	29.9	300	mg tablet	1	1
30	34.9	300	mg tablet	1	1

Recommended dosing based on weight-bands for children >6 weeks using paediatric tablets					
Weight range (kg)		Target dose <16 years or <37.5 kg: 8 mg/kg/dose given twice daily Maximum dose >16 years or ≥37.5 kg: 300 mg/dose given twice daily		Dose (tablet)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	60	mg tablet	1	1
4	4.9	60	mg tablet	1	1
5	5.9	60	mg tablet	1	1
6	6.9	60	mg tablet	1.5	1.5
7	7.9	60	mg tablet	1.5	1.5
8	8.9	60	mg tablet	1.5	1.5
9	9.9	60	mg tablet	1.5	1.5
10	10.9	60	mg tablet	2	2
11	11.9	60	mg tablet	2	2
12	13.9	60	mg tablet	2	2
14	16.9	60	mg tablet	2.5	2.5
17	19.9	60	mg tablet	2.5	2.5
20	24.9	60	mg tablet	3	3
25	29.9	300	mg tablet	1	1
30	34.9	300	mg tablet	1	1

1.5 DIDANOSINE (ddI)

FORMULATIONS

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

DOSE AND DOSE FREQUENCY

Target dose

- Age less than 3 months: 50 mg/m^2/dose twice daily
- Age 3 months to 13 years: 90 – 120 mg/m^2/dose twice daily

Maximum dose

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

Administration – chewable (buffered) tablets

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

Administration – enteric-coated beadlets in capsules (EC)

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

Administration – liquid

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

Storage

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

OTHER COMMENTS

General

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

Pharmacokinetic data

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

Major drug interactions

- TDF and ribavirin are not recommended to be taken with ddI.

Ref: http://packageinserts.bms.com/pi/pi_videx_ec. pdf
http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html

DIDANOSINE					
Recommended dosing based on weight-bands for children >3 months using liquid and chewable tablets					
Weight range (kg)		Target dose 3 months to <13 years: 90–120 mg/m^2/dose twice daily		Dose (ml or tablets)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	10	mg/ml liquid	NR	NR
4	4.9	10	mg/ml liquid	NR	NR
5	5.9	10	mg/ml liquid	3 ml	3 ml
6	6.9	10	mg/ml liquid	5 ml	5 ml
7	7.9	10	mg/ml liquid	5 ml	5 ml
8	8.9	10	mg/ml liquid	5 ml	5 ml
9	9.9	10	mg/ml liquid	5 ml	5 ml
10	10.9	10	mg/ml liquid	6 ml	6 ml
11	11.9	10	mg/ml liquid	6 ml	6 ml
12	13.9	10	mg/ml liquid	6 ml	6 ml
14	16.9	25	mg tablet	4	3
17	19.9	25	mg tablet	4	3
20	24.9	25	mg tablet	4	4
25	29.9	25	mg tablet	5	5
30	34.9	25	mg tablet	5	5

Recommended dosing based on weight-bands for children >3 months using chewable tablets					
Weight range (kg)		Target dose 3 months to <13 years: 90–120 mg/m^2/dose twice daily		Dose (tablet)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	25	mg tablet	NR	NR
4	4.9	25	mg tablet	NR	NR
5	5.9	25	mg tablet	2	2
6	6.9	25	mg tablet	3	2
7	7.9	25	mg tablet	3	2
8	8.9	25	mg tablet	3	2
9	9.9	25	mg tablet	3	2
10	10.9	25	mg tablet	3	3
11	11.9	25	mg tablet	3	3
12	13.9	25	mg tablet	3	3
14	16.9	25	mg tablet	4	3
17	19.9	25	mg tablet	4	3
20	24.9	25	mg tablet	4	4
25	29.9	25	mg tablet	5	5
30	34.9	25	mg tablet	5	5

Note: 25 mg chewable tablets can be substituted with other strengths to the same mg amount but each a.m. and p.m. dose must always be made up of at least two tablets.

NR not recommended

DIDANOSINE				
Recommended once-daily dosing based on weight-bands using enteric-coated capsules				
Weight range (kg)		Target dose 240–300 mg/m^2/day		Dose (ml or tablets)
Bottom	Top	Formulation		a.m. or p.m.
3	3.9	NR		NR
4	4.9	NR		NR
5	5.9	NR		NR
6	6.9	NR		NR
7	7.9	NR		NR
8	8.9	NR		NR
9	9.9	NR		NR
10	10.9	125	mg EC capsule	1
11	11.9	125	mg EC capsule	1
12	13.9	125	mg EC capsule	1
14	16.9	200	mg EC capsule	1
17	19.9	200	mg EC capsule	1
20	24.9	125	mg EC capsule	2
25	29.9	125	mg EC capsule	2
30	34.9	125	mg EC capsule	2

NR not recommended

1.6 EMTRICITABINE (FTC)

FORMULATIONS

Tablets	Capsules	Liquid	FDC
None	200 mg	10 mg/ml	None

DOSE AND FREQUENCY OF DOSING

Target dose

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

Storage

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

OTHER COMMENTS

Pharmacokinetic data

- Available for children aged 3 months to 18 years

Major drug interactions

- None reported

Ref: http://www.gilead.com/pdf/emtriva_pi. pdf
http://www.pediatrics.org/cgi/content/full/121/4/e827

1.7 TENOFOVIR (TDF)

FORMULATIONS

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

DOSE AND FREQUENCY OF DOSING

Target dose

• 300 mg/day for children 12 years of age and more

Storage

• Store tablets at 25°C (range 15 – 30°C).

OTHER COMMENTS

General

• TDF is the preferred ARV in children with hepatitis B aged more than 12 years.

Pharmacokinetic data

• Available for children 12 years of age and above

Major drug interactions

• None reported

Ref: http://www.gilead.com/pdf/viread_pi. pdf

2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

2.1 EFAVIRENZ (EFV)

FORMULATIONS

Tablets	Capsules	Liquid	FDC
200 mg 600 mg	50 mg 100 mg 200 mg	30 mg/ml	**Adult 600 mg EFV** • EFV + TDF + FTC • EFV + TDF + 3TC

DOSE AND FREQUENCY OF DOSING

Target dose

- Liquid — 19.5 mg/kg/day or
- Capsule/tablet — 15 mg/kg/day once daily
- Weight more than 40 kg — 600 mg once daily

Administration – tablets

- 200 mg tablet is double-scored and can be split.

Administration – capsules

- Capsules may be opened and added to a small amount of food or liquid; they have a very peppery taste but can be mixed with sweet foods to disguise the taste.

Storage

- Storage at 25°C (range 15 – 30°C)

OTHER COMMENTS

General

- EFV can be given with food but if taken with food, especially high-fat meals, absorption is increased by an average of 50%.

Pharmacokinetic data

- Available for children more than 3 years of age
- Insufficient data on dosing for children less than 3 years of age or weighing less than 10 kg

Major drug interactions

- It is not recommended to take amodiaquine with EFV.

Ref: http://packageinserts.bms.com/pi/pi_sustiva. pdf
http://www.medicines.org.uk/emc/medicine/10381
http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html

EFAVIRENZ				
Recommended maintenance dosing based on weight-bands				
Weight range (kg)		Target dose 15 mg/kg/day (capsule/tablet) Weight >40 kg: 600 mg once daily		Dose (tablets)
Bottom	Top	Formulation		Once daily
3	3.9	NR		NR
4	4.9	NR		NR
5	5.9	NR		NR
6	6.9	NR		NR
7	7.9	NR		NR
8	8.9	NR		NR
9	9.9	NR		NR
10	10.9	200	mg tablet	1
11	11.9	200	mg tablet	1
12	13.9	200	mg tablet	1
14	16.9	200	mg tablet	1.5
17	19.9	200	mg tablet	1.5
20	24.9	200	mg tablet	1.5
25	29.9	200	mg tablet	2
30	34.9	200	mg tablet	2

NR not recommended

2.2 NEVIRAPINE (NVP)

FORMULATIONS

Tablets	Capsules	Liquid	FDC
50 mg 200 mg	None	10 mg/ml	**Baby 50 mg NVP** **Adult 200 mg NVP** • NVP + d4T + 3TC • NVP + AZT + 3TC **Junior 100 mg NVP** • NVP + d4T + 3TC

DOSE AND DOSE FREQUENCY

Target dose – maintenance therapy

- 160 – 200 mg/m^2 to maximum dose of 200 mg twice daily

Target dose – prophylaxis

Aim for exposure of 100 ng/ml

- Birth to 6 weeks of age:
  - weight less than 2.5 kg — 10 mg per day
  - weight more than 2.5 kg — 15 mg per day
- Age 6 weeks to 6 months — 20 mg per day
- Age 6 months to 9 months — 30 mg per day
- Age 9 months to end of breastfeeding — 40 mg per day

Special considerations for PMTCT in infants

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

Special considerations on maintenance therapy

- Induction dose: during the first 14 days omit the evening dose of NVP. If the morning and evening doses are unequal, give the higher dose in the morning and omit the lower evening dose.
- Maintenance dose: target dose is 160–200 mg/m^2 given twice daily and adjusted for more aggressive dosing in the younger age group.
- If a mild rash occurs during the first 14 days of induction dosing, continue once-daily dosing and only escalate dose once the rash has subsided and the dose is well tolerated. If a severe rash occurs (especially if accompanied by fever, blistering or mucosal ulcerations), discontinue the drug.

Administration – tablets

- Some manufacturers make 200 mg tablets that are scored and can be divided into two equal parts. Other preparations may not be scored and where possible should be divided with a pill cutter. Broken tablets can be crushed and combined with a small amount of water or food and taken immediately.
- 50 mg tablets are scored and can be split.

Administration – liquid

- Use an oral dosing syringe or dosing cup.
- Shake well before use.

Storage

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

NEVIRAPINE (NVP)

OTHER COMMENTS

General

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

Pharmacokinetic data

- Available from birth

Major drug interactions

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

Ref: http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt & folderPath =/Prescribing + Information/PIs/Viramune/Viramune. pdf
http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html

NEVIRAPINE					
Recommended maintenance dose based on weight-bands for children >6 weeks using liquid and adult tablets					
Weight range (kg)		Target dose 160 – 200 mg/m^2 to max 200 mg twice daily		Dose (ml or tablets)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	10	mg/ml liquid	5 ml	5 ml
4	4.9	10	mg/ml liquid	5 ml	5 ml
5	5.9	10	mg/ml liquid	5 ml	5 ml
6	6.9	10	mg/ml liquid	8 ml	8 ml
7	7.9	10	mg/ml liquid	8 ml	8 ml
8	8.9	10	mg/ml liquid	8 ml	8 ml
9	9.9	10	mg/ml liquid	8 ml	8 ml
10	10.9	10	mg/ml liquid	10 ml	10 ml
11	11.9	10	mg/ml liquid	10 ml	10 ml
12	13.9	10	mg/ml liquid	10 ml	10 ml
14	16.9	200	mg tablet	1	½
17	19.9	200	mg tablet	1	½
20	24.9	200	mg tablet	1	½
25	29.9	200	mg tablet	1	1
30	34.9	200	mg tablet	1	1

NEVIRAPINE					
Recommended maintenance dose based on weight-bands for children >6 weeks using paediatric and adult tablets					
Weight range (kg)		Target dose 160 – 200 mg/m^2 to max 200 mg twice daily		Dose (tablets)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	50	mg tablet	1	1
4	4.9	50	mg tablet	1	1
5	5.9	50	mg tablet	1	1
6	6.9	50	mg tablet	1.5	1.5
7	7.9	50	mg tablet	1.5	1.5
8	8.9	50	mg tablet	1.5	1.5
9	9.9	50	mg tablet	1.5	1.5
10	10.9	50	mg tablet	2	2
11	11.9	50	mg tablet	2	2
12	13.9	50	mg tablet	2	2
14	16.9	50	mg tablet	2.5	2.5
17	19.9	50	mg tablet	2.5	2.5
20	24.9	50	mg tablet	3	3
25	29.9	200	mg tablet	1	1
30	34.9	200	mg tablet	1	1

2.3 ETRAVIRINE (ETV)

FORMULATIONS

Tablets	Capsules	Liquid	FDC
25 mg 100 mg	None	None	None

DOSE AND FREQUENCY OF DOSING

Target dose
- 5.2 mg/kg twice daily from 6 years of age to a maximum adult dose of 200 mg twice daily

Administration – tablets
- Tablets are scored.
- Tablets are dispersible in water.

Storage
- Store tablets at 25°C (range 15 – 30°C) in a tightly closed container (to protect from moisture).

OTHER COMMENTS

General
- Well-tolerated and no flavour
- Safety and effectiveness not yet well established in younger children

Major drug interactions
- Rifampicin and rifabutin

Ref: http://www.intelence-info.com/intelence/assets/pdf/INTELENCE_PI. pdf (100 mg tablets)
Konigs et al., *Pharmacokinetics and dose selection of etravirine in HIV-infected children between 6 and 17 years, inclusive.* Conference on retroviruses and Opportunistic Infections, Montreal, Canada February 2009

3. Protease inhibitors (PIs)

3.1 SAQUINAVIR (SQV) HGC

FORMULATIONS

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

DOSE AND FREQUENCY OF DOSING

Target dose – hard gel capsules (HGCs)
- Studies have reported using 33 mg/kg three times a day.

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

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

OTHER COMMENTS

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

Major drug interactions
- None reported

Ref: http://www.gene.com/gene/products/information/invirase/pdf/pi.pdf
http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html

3.2 LOPINAVIR/RITONAVIR (LPV/r) (CO-FORMULATION)

FORMULATIONS

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

DOSE AND FREQUENCY OF DOSING

LPV target dose
- 230 – 350 mg/m^2 twice daily

Maximum dose
- LPV 400 mg + RTV 100 mg twice daily

Administration – tablets
- Must be administered intact and cannot be split or crushed

Administration – liquid
- Must be well shaken

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

OTHER COMMENTS

General
- Higher doses of LPV/r may be required when co-administered with enzyme-inducing drugs such as NVP, EFV, FPV, rifampicin.
- No food restrictions although bioavailability is reportedly increased when administered with food
- Should be taken with food
- In non-fasting state, absolute bioavailability of LPV/r liquid is decreased by 22% compared with LPV/r tablet.
- Low volume but bitter taste
- Once-daily dosing is not approved for infants or children.
- LPV/r liquid has a high alcohol content.

Pharmacokinetic data
- Available for 14 days and older

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

Ref: http://www.rxabbott.com/pdf/kaletratabpi.pdf
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ ApprovalHistory
http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html

LOPINAVIR/RITONAVIR					
Recommended dosing based on weight-bands for children >6 weeks using liquid					
Weight range (kg)		Target dose 230 – 350 mg/m^2 twice daily		Dose (ml)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	80 mg LPV/20 mg RTV	ml liquid	1 ml	1 ml
4	4.9	80 mg LPV/20 mg RTV	ml liquid	1.5 ml	1.5 ml
5	5.9	80 mg LPV/20 mg RTV	ml liquid	1.5 ml	1.5 ml
6	6.9	80 mg LPV/20 mg RTV	ml liquid	1.5 ml	1.5 ml
7	7.9	80 mg LPV/20 mg RTV	ml liquid	1.5 ml	1.5 ml
8	8.9	80 mg LPV/20 mg RTV	ml liquid	1.5 ml	1.5 ml
9	9.9	80 mg LPV/20 mg RTV	ml liquid	1.5 ml	1.5 ml
10	10.9	80 mg LPV/20 mg RTV	ml liquid	2 ml	2 ml
11	11.9	80 mg LPV/20 mg RTV	ml liquid	2 ml	2 ml
12	13.9	80 mg LPV/20 mg RTV	ml liquid	2 ml	2 ml
14	16.9	80 mg LPV/20 mg RTV	ml liquid	2.5 ml	2.5 ml
17	19.9	80 mg LPV/20 mg RTV	ml liquid	2.5 ml	2.5 ml
20	24.9	80 mg LPV/20 mg RTV	ml liquid	3 ml	3 ml
25	29.9	80 mg LPV/20 mg RTV	ml liquid	3.5 ml	3.5 ml
30	34.9	80 mg LPV/20 mg RTV	ml liquid	4 ml	4 ml

LOPINAVIR/RITONAVIR					
Recommended dosing based on weight-bands for children >6 weeks using paediatric tablets					
Weight range (kg)		Target dose 230 – 350 mg/m^2 twice daily		Dose (tablets)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	100 mg LPV/25 mg RTV	tablet	NR	NR
4	4.9	100 mg LPV/25 mg RTV	tablet	NR	NR
5	5.9	100 mg LPV/25 mg RTV	tablet	NR	NR
6	6.9	100 mg LPV/25 mg RTV	tablet	NR	NR
7	7.9	100 mg LPV/25 mg RTV	tablet	NR	NR
8	8.9	100 mg LPV/25 mg RTV	tablet	NR	NR
9	9.9	100 mg LPV/25 mg RTV	tablet	NR	NR
10	10.9	100 mg LPV/25 mg RTV	tablet	2	1
11	11.9	100 mg LPV/25 mg RTV	tablet	2	1
12	13.9	100 mg LPV/25 mg RTV	tablet	2	1
14	16.9	100 mg LPV/25 mg RTV	tablet	2	2
17	19.9	100 mg LPV/25 mg RTV	tablet	2	2
20	24.9	100 mg LPV/25 mg RTV	tablet	2	2
25	29.9	100 mg LPV/25 mg RTV	tablet	3	3
30	34.9	100 mg LPV/25 mg RTV	tablet	3	3

Note: Children 14 – 24.9 kg can be dosed with adult tabs (200 mg LPV/50 mg RTV), 1 tab am and 1 tab pm.
Children 25 – 34.9 kg can be dosed with adult tabs (200 mg LPV/50 mg RTV), 2 tabs am and 1 tab pm.

3.3 RITONAVIR (RTV)

FORMULATIONS

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

DOSE AND FREQUENCY OF DOSING

Target dose
- RTV is used to boost other protease inhibitors.

Administration – tablets
- Must be administered intact and cannot be split or crushed

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

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

OTHER COMMENTS

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

Pharmacokinetic data
- Available for infants and children

Major drug interactions
- None reported

Ref: http://www.rxabbott.com/pdf/kaletratabpi.pdf
http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html

3.4 DARUNAVIR (DRV)

FORMULATIONS

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

DOSE AND FREQUENCY OF DOSING

Target dose
- 10 – 20 mg/kg twice daily

Maximum dose
- 600 mg DRV with 100 mg RTV twice daily

Administration – tablets
- Once-daily dosing should not be used in paediatric patients.
- Should be taken with food

Storage
- Store at temperature of 25°C (range 15 – 30°C).

OTHER COMMENTS

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

Pharmacokinetic data
- Available for children aged 6 years or more

Major drug interactions
- None reported

Ref: http://www.prezista.com/prezista/documents/us_package_insert. pdf

3.5 ATAZANAVIR (ATV)

FORMULATIONS

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

DOSE AND FREQUENCY OF DOSING

Target dose ATV/RTV

Treatment-naive

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

Treatment-experienced

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

Maximum dose

- ATV 300 mg/RTV 100 mg once daily

Administration

- Should be taken with food

Storage

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

OTHER COMMENTS

General

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

Pharmacokinetic data

- Available for children aged 3 months to 21 years

Major drug interactions

- None reported

Ref: http://packageinserts.bms.com/pi/pi_reyataz. pdf

4. Fixed-dose combinations (FDCs)

Antiretroviral therapy generally requires the use of three or more drugs. This often requires taking a large number of tablets/capsules each day. Fixed-dose combinations (FDCs) of ARV drugs allow for once- or twice-daily dosing, leading to improved adherence, which may result in greater efficacy and may assist in reducing the development of viral resistance. FDCs are cheaper than individual drugs and may help to alleviate programmatic concerns of logistics regarding drug supply and delivery. WHO encourages the use of FDCs when formulations of assured quality and proven bioequivalence are available and offer operational advantages. Not all available FDCs have been evaluated for prequalification by WHO. Further details and a list of current prequalified drugs are available at: http://mednet3.who.int/prequal/.

Countries that have not included FDCs in their national formularies are encouraged to do so.

4.1 ZIDOVUDINE (AZT) PLUS LAMIVUDINE (3TC)

FORMULATION

FDC tablets

AZT 60 mg + 3TC 30 mg
AZT 300 mg + 3TC 150 mg

DOSE AND FREQUENCY OF DOSING

Target dose

- AZT 180 – 240 mg/m^2 twice daily
- 3TC 4 mg/kg twice daily

Maximum dose

- 1 adult tablet/dose twice daily

Administration

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

Storage

- Store tablets between 2°C and 30°C

OTHER COMMENTS

General

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

Pharmacokinetic data

- Available for adolescents and adults

Ref: http://us.gsk.com/products/assets/us_combivir. pdf
http://www.cipladoc.com/therapeutic/pdf_cipla/duovir. pdf
http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html

AZT PLUS 3TC					
Recommended dosing based on weight-bands					
Weight range (kg)		Target dose as for individual components		Dose (tablets)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	60/30	tablet	1	1
4	4.9	60/30	tablet	1	1
5	5.9	60/30	tablet	1	1
6	6.9	60/30	tablet	1.5	1.5
7	7.9	60/30	tablet	1.5	1.5
8	8.9	60/30	tablet	1.5	1.5
9	9.9	60/30	tablet	1.5	1.5
10	10.9	60/30	tablet	2	2
11	11.9	60/30	tablet	2	2
12	13.9	60/30	tablet	2	2
14	16.9	60/30	tablet	2.5	2.5
17	19.9	60/30	tablet	2.5	2.5
20	24.9	60/30	tablet	3	3
25	29.9	300/150	tablet	1	1
30	34.9	300/150	tablet	1	1

4.2 ZIDOVUDINE (AZT) PLUS LAMIVUDINE (3TC) PLUS NEVIRAPINE (NVP)

FORMULATION

FDC tablets

AZT 60 mg + 3TC 30 mg + NVP 50 mg
AZT 300 mg + 3TC 150 mg + NVP 200 mg

DOSE AND FREQUENCY OF DOSING

Target dose

- AZT 180 – 240 mg/m^2 twice daily
- 3TC 4 mg/kg twice daily
- NVP 160 – 200 mg/m^2

Maximum dose

- 1 adult tablet/dose twice daily

Administration

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

Storage

- Store tablets between 2°C and 30°C.

OTHER COMMENTS

General

- See comments under individual drug components.
- No food restrictions

Pharmacokinetic data

- Available for adolescents and adults

Ref: http://www.cipladoc.com/therapeutic/pdf_cipla/duovir_n. pdf
http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html

AZT PLUS 3TC PLUS NVP					
Recommended dosing based on weight-bands					
Weight range (kg)		Target dose as for individual components		Dose (tablets)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	60/30/50	tablet	1	1
4	4.9	60/30/50	tablet	1	1
5	5.9	60/30/50	tablet	1	1
6	6.9	60/30/50	tablet	1.5	1.5
7	7.9	60/30/50	tablet	1.5	1.5
8	8.9	60/30/50	tablet	1.5	1.5
9	9.9	60/30/50	tablet	1.5	1.5
10	10.9	60/30/50	tablet	2	2
11	11.9	60/30/50	tablet	2	2
12	13.9	60/30/50	tablet	2	2
14	16.9	60/30/50	tablet	2.5	2.5
17	19.9	60/30/50	tablet	2.5	2.5
20	24.9	60/30/50	tablet	3	3
25	29.9	300/150/200	tablet	1	1
30	34.9	300/150/200	tablet	1	1

4.3 STAVUDINE (D4T) PLUS LAMIVUDINE (3TC)

FORMULATION

FDC tablets

d4T 6 mg + 3TC 30 mg
d4T 12 mg + 3TC 60 mg
d4T 30 mg + 3TC 150 mg

DOSE AND FREQUENCY OF DOSING

Target dose

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

Administration

- Paediatric tablet is dispersible and crushable, can be split.

Storage

- Store tablets between 2°C and 30°C.

OTHER COMMENTS

General

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

Pharmacokinetic data

- Available for adolescents and adults

Ref: http://www.cipladoc.com/therapeutic/pdf_cipla/lamivir_s_baby_junior. pdf
http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html

D4T PLUS 3TC					
Recommended dosing based on weight-bands					
Weight range (kg)		Target dose as for individual components		Dose (tablets)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	6/30	mg tablet	1	1
4	4.9	6/30	mg tablet	1	1
5	5.9	6/30	mg tablet	1	1
6	6.9	6/30	mg tablet	1.5	1.5
7	7.9	6/30	mg tablet	1.5	1.5
8	8.9	6/30	mg tablet	1.5	1.5
9	9.9	6/30	mg tablet	1.5	1.5
10	10.9	6/30	mg tablet	2	2
11	11.9	6/30	mg tablet	2	2
12	13.9	6/30	mg tablet	2	2
14	16.9	6/30	mg tablet	2.5	2.5
17	19.9	6/30	mg tablet	2.5	2.5
20	24.9	6/30	mg tablet	3	3
25	29.9	30/150	mg tablet	1	1
30	34.9	30/150	mg tablet	1	1

4.4 STAVUDINE (D4T) PLUS LAMIVUDINE (3TC) PLUS NEVIRAPINE (NVP)

FORMULATION

FDC tablets

d4T 6 mg + 3TC 30 mg + NVP 50 mg
d4T 12 mg + 3TC 60 mg + NVP 100 mg
d4T 30 mg + 3TC 150 mg + NVP 200 mg

DOSE AND FREQUENCY OF DOSING

Target dose

- d4T 1 mg/kg twice daily
- 3TC 4 mg/kg twice daily
- NVP 160 – 200 mg/m^2 to a maximum dose of 200 mg twice daily

Maximum dose

- One 30 mg d4T-based tablet twice daily

Administration

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

Storage

- Store tablets below 25°C.

OTHER COMMENTS

General

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

Pharmacokinetic data

- Available for adolescents and adults

Ref: http://www.cipladoc.com/therapeutic/pdf_cipla/triomune_baby_junior. pdf
http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html

D4T PLUS 3TC PLUS NVP					
Recommended dosing based on weight-bands					
Weight range (kg)		Target dose as for individual components		Dose (tablets)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	6/30/50	tablet	1	1
4	4.9	6/30/50	tablet	1	1
5	5.9	6/30/50	tablet	1	1
6	6.9	6/30/50	tablet	1.5	1.5
7	7.9	6/30/50	tablet	1.5	1.5
8	8.9	6/30/50	tablet	1.5	1.5
9	9.9	6/30/50	tablet	1.5	1.5
10	10.9	6/30/50	tablet	2	2
11	11.9	6/30/50	tablet	2	2
12	13.9	6/30/50	tablet	2	2
14	16.9	6/30/50	tablet	2.5	2.5
17	19.9	6/30/50	tablet	2.5	2.5
20	24.9	6/30/50	tablet	3	3
25	29.9	30/150/200	tablet	1	1
30	34.9	30/150/200	tablet	1	1

4.5 ABACVIR (ABC) PLUS ZIDOVUDINE (AZT) PLUS LAMIVUDINE (3TC)

FORMULATION

FDC tablets

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

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

DOSE AND FREQUENCY OF DOSING

Target dose
- ABC 8 mg/kg twice daily
- AZT 180 – 240 mg/m^2 twice daily
- 3TC 4 mg/kg twice daily

Maximum dose
- 1 adult tablet/dose twice daily

Administration
- Paediatric tablet is crushable and can be split.

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

OTHER COMMENTS

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

Pharmacokinetic data
- Available for adolescents and adults

Ref: http://us.gsk.com/products/assets/us_trizivir. pdf
http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html

ABC PLUS AZT PLUS 3TC					
Recommended dosing based on weight-bands					
Weight range (kg)		Target dose as for individual components		Dose (tablets)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	60/60/30	tablet	1	1
4	4.9	60/60/30	tablet	1	1
5	5.9	60/60/30	tablet	1	1
6	6.9	60/60/30	tablet	1.5	1.5
7	7.9	60/60/30	tablet	1.5	1.5
8	8.9	60/60/30	tablet	1.5	1.5
9	9.9	60/60/30	tablet	1.5	1.5
10	10.9	60/60/30	tablet	2	2
11	11.9	60/60/30	tablet	2	2
12	13.9	60/60/30	tablet	2	2
14	16.9	60/60/30	tablet	2.5	2.5
17	19.9	60/60/30	tablet	2.5	2.5
20	24.9	60/60/30	tablet	3	3
25	29.9	300/300/150	tablet	1	1
30	34.9	300/300/150	tablet	1	1

4.6 ABACVIR (ABC) PLUS LAMIVUDINE (3TC)

FORMULATION

FDC tablets

Paediatric
ABC 60 mg + 3TC 30 mg

Adult
ABC 600 mg + 3TC 300 mg

DOSE AND FREQUENCY OF DOSING

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

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

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

OTHER COMMENTS

General
- See comments under individual drug components.
- No food restrictions

Pharmacokinetic data
- Available for adolescents and adults

Ref: http://us.gsk.com/products/assets/us_ziagen. pdf
http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html

ABC PLUS 3TC					
Recommended dosing based on weight-bands					
Weight range (kg)		**Target dose as for individual components**		**Dose (tablets)**	
Bottom	**Top**	**Formulation**		**a.m.**	**p.m.**
3	3.9	60/30	tablet	1	1
4	4.9	60/30	tablet	1	1
5	5.9	60/30	tablet	1	1
6	6.9	60/30	tablet	1.5	1.5
7	7.9	60/30	tablet	1.5	1.5
8	8.9	60/30	tablet	1.5	1.5
9	9.9	60/30	tablet	1.5	1.5
10	10.9	60/30	tablet	2	2
11	11.9	60/30	tablet	2	2
12	13.9	60/30	tablet	2	2
14	16.9	60/30	tablet	2.5	2.5
17	19.9	60/30	tablet	2.5	2.5
20	24.9	60/30	tablet	3	3
25	29.9	600/300 [i]	tablet	½	½
30	34.9	600/300 [i]	tablet	½	½

(i) Currently, there is no experience in using the 600/300 tablet to provide 300/150 twice-daily dosing. Consider halving the 600/300 tablet and giving one half tablet twice daily, or give one tablet daily. Adult ABC/3TC FDC tablets are not scored; a tablet cutter would be required to divide these tablets.

ANNEX F: SERIOUS, ACUTE AND CHRONIC TOXICITIES CAUSED BY ARV DRUGS

Clinical presentation, laboratory abnormalities and implications for ART management.

These toxicities may require therapy modification. Alternative explanations for toxicity should be excluded before concluding that it is caused by the ARV drug.

This table describes management of the ART regimen but does not indicate detailed clinical toxicity management.

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

Possible clinical manifestations (most common ARV drug or drugs associated with the toxicity)	Possible laboratory abnormalities[a]	Implications for ARV drug treatment
Hypersensitivity reaction (ABC or NVP)		
• *ABC:* Combination of acute onset of both respiratory and gastrointestinal symptoms after starting ABC, including fever, fatigue, myalgia, nausea, vomiting, diarrhoea, abdominal pain, pharyngitis, cough, dyspnoea; rash (usually mild) may or may not occur; progressive worsening of symptoms soon after receiving ABC dose, usually occurs within 6–8 weeks • *NVP:* Systemic symptoms of fever, myalgia, arthralgia, hepatitis, with or without rash usually occurs within 6–8 weeks	• Elevated transaminases • Elevated eosinophil count	• Immediately discontinue all ARVs until symptoms resolve • NVP or ABC should NOT be readministered to the patient in future • Once symptoms resolve, restart ART with substitution of an alternative ARV for ABC or NVP[b]
Lactic acidosis (NRTI class, particularly d4T)		
• Generalized fatigue and weakness • Gastrointestinal features (nausea, vomiting, diarrhoea, abdominal pain, hepatomegaly, anorexia, poor weight gain and/or sudden unexplained weight loss) • May have hepatitis or pancreatitis (see above) • Respiratory features (tachypnoea and dyspnoea) • Neurological symptoms (including motor weakness) Can occure at any time on ART	• Increased anion gap • Lactic acidosis • Elevated aminotransferase • Elevated creatine phosphokinase (CPK) • Elevated lactate dehydrogenase (LDH)	• Discontinue all ARVs until symptoms resolve • Symptoms associated with lactic acidosis may continue or worsen despite discontinuation of ART • Once symptoms resolve, restart ART with substitution of an alternative NRTI with lower mitochondrial toxicity risk (e.g. ABC or AZT[b]

Possible clinical manifestations (most common ARV drug or drugs associated with the toxicity)	Possible laboratory abnormalities [a]	Implications for ARV drug treatment
Severe rash/Stevens – Johnson syndrome (NNRTI class, particularly NVP, less common EFV)		
• Rash usually occurs during first 6–8 weeks of treatment • *Mild-to-moderate rash:* erythematous, maculopapular, confluent, most often on the body and arms, with no systemic symptoms • *Severe rash:* extensive rash with moist desquamation, angioedema, or serum sickness-like reaction; or rash with constitutional findings such as fever, oral lesions, blistering, facial oedema, conjunctivitis • Life-threatening Stevens–Johnson syndrome or toxic epidermal necrolysis (TEN)	• Elevated transaminases	• If mild or moderate rash, ART can continue without interruption staying at induction dose until rash settles but with close observation, and only increase to maintenance dose once tolerated • For severe or life-threatening rash, discontinue all ARVs until symptoms resolve • NVP should NOT be readministered to the patient in the future • Once symptoms resolve, restart ART with substitution of an alternative ARV for NVP (note: most experts would not change to another NNRTI drug if patient had severe or life-threatening Stevens – Johnson syndrome with NVP) [b]
Severe life-threatening anaemia (AZT)		
• Severe pallor, tachycardia • Significant fatigue • Congestive heart failure	• Low haemoglobin	• refractory to symptomatic treatment (e.g. transfusion), discontinue AZT only and substitute an alternative NRTI [b]
Severe neutropenia (AZT)		
• Sepsis/infection	• Low neutrophil count	• If refractory to symptomatic treatment (e.g. transfusion), discontinue AZT only and substitute an alternative NRTI [b]

Possible clinical manifestations (most common ARV drug or drugs associated with the toxicity)	Possible laboratory abnormalities[a]	Implications for ARV drug treatment
Chronic late serious adverse reactions		
Lipodystrophy/metabolic syndrome (d4T; PIs)		
• Fat accumulation and/or fat loss in distinct regions of the body: – increased fat around the abdomen, buffalo hump, breast hypertrophy – fat loss from limbs, buttocks and face occurs to a variable extent • Insulin resistance, including diabetes mellitus • Potential risk for later coronary artery disease	• Hyper-triglyceridaemia • Hyper-cholesterolaemia; • Low high-density lipoprotein (HDL) levels • Hyperglycaemia	• Substitution of ABC or AZT for d4T may prevent progression of lipoatrophy • Substitution of an NNRTI for a PI may decrease serum lipid abnormalities
Severe peripheral neuropathy (d4T, ddI; more rarely 3TC)		
• Pain, tingling, numbness of hands or feet; inability to walk • Distal sensory loss • Mild muscle weakness and areflexia may occur	• None	• Stop suspected NRTI only and substitute a different NRTI that is not associated with neurotoxicityb • Symptoms may take several weeks to resolve

[a] All laboratory abnormalities may not be observed.

[b] See Table 7 (Section 9) for recommended ARV drug substitutions.

ANNEX G: 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 *½ x 10^9 – 0.749 x 10^9/L*	250 – 500/mm^3 *0.25 x 10^9 –½ 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				
Laboratory				
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
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				

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

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

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

PARAMETER	MILD (grade 1)	MODERATE (grade 2)	SEVERE (grade 3)	SEVERE AND POTENTIALLY LIFE-THREATENING (grade 4)
Diarrhoea ≥1 year of age <1 year of age	Transient or intermittent episodes of unformed stools OR increase of ≤3 stools over baseline per day Liquid stools (more unformed than usual) but usual number of stools	Persistent episodes of unformed to watery stools OR increase of 4 – 6 stools over baseline per day Liquid stools with increased number of stools OR mild dehydration	Grossly bloody diarrhoea OR increase of ≥7 stools per day OR intravenous fluid replacement indicated Liquid stools with moderate dehydration	Life-threatening consequences (e.g. hypotensive shock) Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR hypotensive shock
Nausea	Transient (<24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for >48 hours OR aggressive rehydration indicated (e.g. 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 indicated (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 angioedema	Generalized urticaria OR angioedema 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, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens – Johnson syndrome OR ulceration of mucous membrane involving two or more distinct mucosal sites OR toxic epidermal necrolysis (TEN)
NEUROLOGICAL				
Alteration in personality, behaviour or mood[b]	Alteration causing no or minimal interference with usual social and functional activitiesb	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

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

PARAMETER	MILD (grade 1)	MODERATE (grade 2)	SEVERE (grade 3)	SEVERE AND POTENTIALLY LIFE-THREATENING (grade 4)
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 *5.16 – 7.77 mmol/L*	>300 mg/dl *>7.77 mmol/L*	Not applicable
Glucose, serum, high: non-fasting	116 – <161 mg/dl *6.44 – <8.89 mmol/L*	161 – <251 mg/dl *8.89 – <13.89 mmol/L*	251 – 500 mg/dl *13.89 – 27.75 mmol/L*	>500 mg/dl *>27.75 mmol/L*
Glucose, serum, high: fasting	110 – <126 mg/dl *6.11 – <6.95 mmol/L*	126 – <251 mg/dl *6.95 – <13.89 mmol/L*	251 – 500 mg/dl *13.89 – 27.75 mmol/L*	>500 mg/dl *>27.75 mmol/L*
Lactate	<2.0 x ULN without acidosis	≥2.0 x ULN without acidosis	Increased lactate with pH <7.3 without life-threatening consequences or related condition present	Increased lactate with pH <7.3 with life-threatening consequences (e.g. neurological findings, coma) or related condition present
Triglycerides (fasting)	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.

interactions, play activities, learning tasks).

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

ANNEX H: SEXUAL MATURITY RATING (TANNER STAGING) IN ADOLESCENTS

Stage	Female				Male				
	Age range (years)	Breast growth	Pubic hair growth	Other changes	Age range (years)	Testes growth	Penis growth	Pubic hair growth	Other changes
I	0–15	Pre-adolescent	None	Pre-adolescent	0–15	Pre-adolescent testes (≤2.5 cm)	Pre-adolescent	None	Pre-adolescent
II	8–15	Breast budding (thelarche); areolar hyperplasia with small amount of breast tissue	Long downy pubic hair near the labia, often appearing with breast budding or several weeks or months later	Peak growth velocity often occurs soon after stage II	10–15	Enlargement of testes; pigmentation of scrotal sac	Minimal or no enlargement	Long downy hair, often appearing several months after testicular growth; variable pattern noted with pubarche	Not applicable
III	10–15	Further enlargement of breast tissue and areola, with no separation of their contours	Increase in amount and pigmentation of hair	Menarche occurs in 2% of girls late in stage III	11½–16.5	Further enlargement	Significant enlargement, especially in diameter	Increase in amount; curling	Not applicable

Stage	Female				Male				
	Age range (years)	Breast growth	Pubic hair growth	Other changes	Age range (years)	Testes growth	Penis growth	Pubic hair growth	Other changes
IV	10–17	Separation of contours; areola and nipple form secondary mound above breasts tissue	Adult in type but not in distribution	Menarche occurs in most girls in stage IV, 1–3 years after thelarche	Variable: 12–17	Further enlargement	Further enlargement, especially in diameter	Adult in type but not in distribution	Development of axillary hair and some facial hair
V	12.5–18	Large breast with single contour	Adult in distribution	Menarche occurs in 10% of girls in stage V.	13–18	Adult in size	Adult in size	Adult in distribution (medial aspects of thighs; linea alba)	Body hair continues to grow and muscles continue to increase in size for several months to years; 20% of boys reach peak growth velocity during this period

Source: Adapted from reference [218].

ANNEX I: SUMMARY OF WHO RECOMMENDATIONS ON LABORATORY INVESTIGATIONS FOR CLINICAL CARE BY LEVEL OF HEALTH CARE FACILITY

Laboratory tests recommended by level of health care facility for providing HIV-related clinical care. These tables are adapted from WHO, available at http://www.who.int/hiv/amds/WHOLabRecommendationBylevelFinal.pdf

Laboratory tests for diagnosis and monitoring[1]	Primary care level[2]		District level[3]		Regional or referral level[4]		National level[5]
	Send out[6]	Perform on-site	Send out[6]	Perform on-site	Send out[6]	Perform on-site	Perform on-site
HIV antibody testing							
Lab ELISA	✔			✔		✔	✔
Rapid point of care 1		✔		✔		✔	✔
Rapid point of care 2		✔		✔		✔	✔
Rapid point of care 3				✔			
HIV virological diagnostic testing							
RNA	✔		✔			✔	✔
DNA	✔		✔			✔	✔
Up24 Ag	✔		✔			✔	✔
HIV viral load measurement					✔	✔	✔
Haemoglobin							
Haemoglobinometer such as HemoCue		✔		✔		✔	✔
WHO colour scale		✔		✔		✔	✔
Full blood count and differential	✔			✔		✔	✔
CD4							
Absolute count	✔		✔	✔		✔	✔
%	✔		✔	✔		✔	✔
HIV resistance testing[7]							✔[8]
Pregnancy testing							
Urine rapid test?[9]		?[9]		✔		✔	✔
Liver function tests (transaminases and bilirubin)				✔		✔	✔
Glucose							
Blood dipstick				✔		✔	✔
Urine dipstick		✔		✔		✔	✔
Blood				✔		✔	✔

Laboratory tests for diagnosis and monitoring[1]	Primary care level[2]		District level[3]		Regional or referral level[4]		National level[5]
	Send out[6]	Perform on-site	Send out[6]	Perform on-site	Send out[6]	Perform on-site	Perform on-site
Serum electrolytes	?			✔		✔	✔
Renal function tests (creatinine/urea)				✔		✔	✔
Urine protein dipstick		✔		✔		✔	✔
Lipids						✔	✔
Amylase				✔		✔	✔
Lactate				✔		✔	✔
Oxygen saturation – pulse oximetry				✔		✔	✔
Blood gases Ph						✔	✔

1. These are the generic recommendations and it is recognized that exceptions apply (e.g., some health centers will send out some tests). Where appropriate these tests may used for public health surveillance and quality assurance activities.
2. Primary health care services are those providing first point of contact with the health care system.
3. District level is defined as hospital at the first referral level that is responsible for a district of a defined geographical area containing a defined population and governed by a politico-administrative organization such as a district health management team.
4. In some smaller countries there may not be regional laboratories.
5. Including the national reference laboratory or public health laboratory, which is usually responsible for quality assurance and surveillance activities.
6. "Send out" refers to not having the testing capability on site and samples or patients are sent to another site for the actual test to be performed.
7. HIV DR testing is only recommended as part of national efforts for surveillance and monitoring as outlined in WHO HIV DR strategy and is usually done by sending out to an accredited international lab.
8. May be done at national level or sent to accredited lab.
9. May need to reconsider recommendation at primary care level.
   WHO ART guidelines recommend in context of efavirenz initiation.
   Pregnancy test not recommended for routine pregnancy care at the primary level. Most women seek antenatal care when pregnancy is "obvious" and the pregnancy test does not add additional information.

Diagnostic tests for treatable co-infections and major HIV-related opportunistic diseases

Laboratory tests for diagnosis and monitoring[1]	Primary care level[2]		District level[3]		Regional or referral level[4]		National level[5]
	Send out[6]	Perform on-site	Send out[6]	Perform on-site	Send out[6]	Perform on-site	Perform on-site
Tuberculosis							
Microscopy							
Light	✔	✔		✔[7]		✔	✔
Fluorescence				✔		✔	✔
Culture							
Solid medium	✔		✔	?[7]		✔	✔
Liquid medium	✔		✔			✔	✔
Drug susceptibility tes[8]							
First-line			✔			✔	✔
Second-line			✔		✔		✔
Diagnosis of malaria							
Rapid test for malaria		✔		✔		✔	✔
Microscopy for malaria (thick/thin)		✔		✔		✔	✔
Cerebrospinal fluid (CSF)							
Basic CSF microscopy including India ink and Gram stain and Ziehl-Neelsen				✔		✔	✔
CSF culture			✔			✔	✔
CSF glucose			✔			✔	✔
Cryptococcal antigen (serum or CSF)				✔		✔	✔
STI diagnostic tests							
Microscopy (Gram & wet)				✔		✔	✔
Gonorrhea			✔			✔	✔
Chlamidya			✔			✔	✔
Syphilis rapid diagnostic test		✔		✔		✔	✔
Syphilis serological (RPR, FTA and TPHA)				✔		✔	✔

Laboratory tests for diagnosis and monitoring[1]	Primary care level[2]		District level[3]		Regional or referral level[4]		National level[5]
	Send out[6]	Perform on-site	Send out[6]	Perform on-site	Send out[6]	Perform on-site	Perform on-site
Hepatitis B			✔	✔		✔	✔
Hepatitis C[12]			✔	✔			✔[10]
PCP						✔	
Blood culture			✔			✔	✔
Radiography				✔		✔	✔

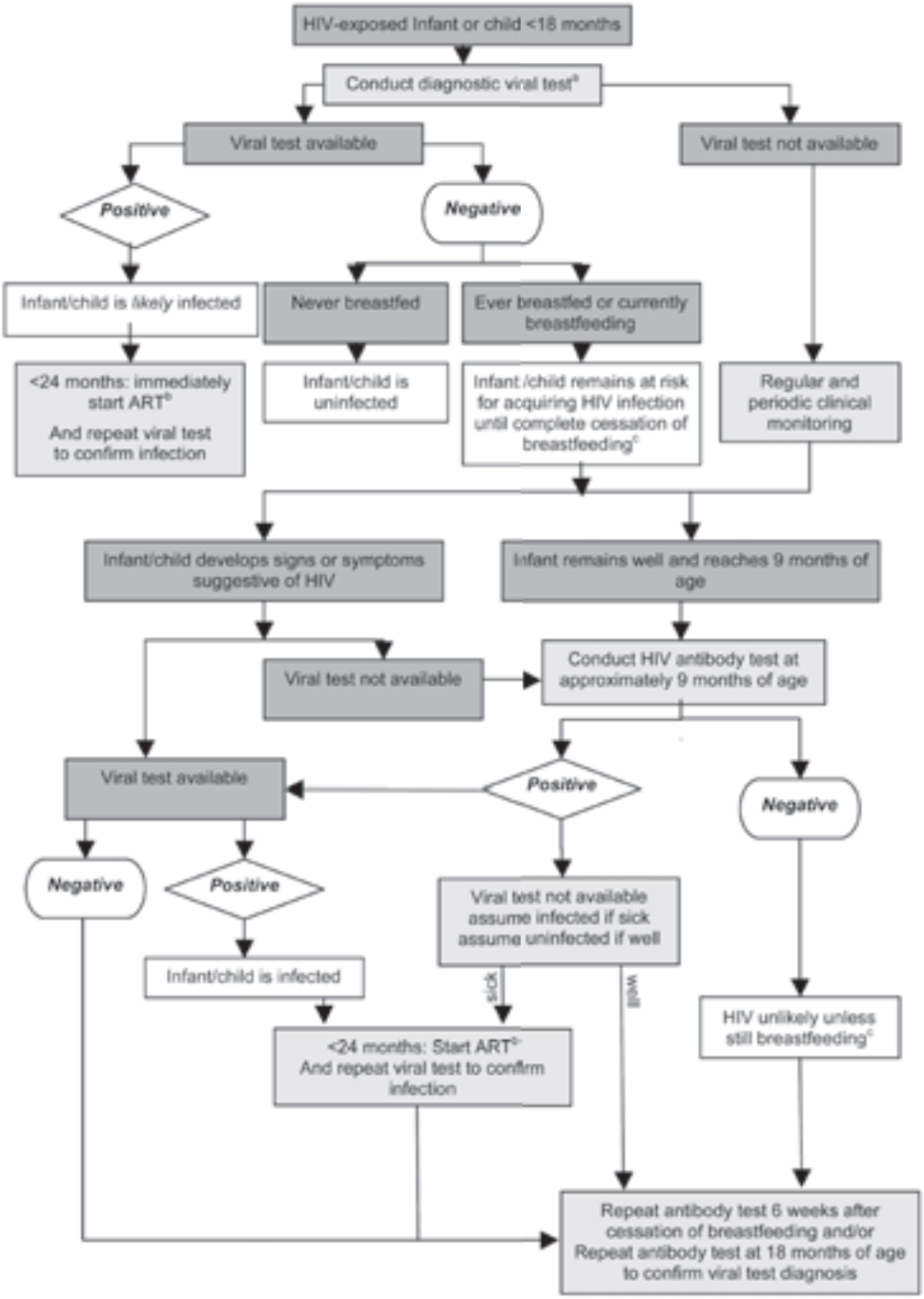
References for *Summary of WHO recommendations on laboratory investigations for clinical care by level of health care facility* are available at http://www.who.int/hiv/amds/WHOLabRecommendation-BylevelFinal.pdf

1. These are the generic recommendations and it is recognized that exceptions apply (e.g., some health centers will send out some tests). Where appropriate these tests may used for public health surveillance and quality assurance activities.
2. Primary health care services are those providing first point of contact with the health care system.
3. District level is defined as hospital at the first referral level that is responsible for a district of a defined geographical area containing a defined population and governed by a politico-administrative organization such as a district health management team.
4. In some smaller countries there may not be regional laboratories.
5. Including the national reference laboratory or public health laboratory, which is usually responsible for quality assurance and surveillance activities.
7. At some health centres depending on specimen load.
8. Given complexity of usng DSTs may need adaptation.
9. Provision guided by Hepatitis C prevalence.
10. High prevalence, Low IDU and for sureiillance.

ANNEX J: FIGURES

The figures in this Annex are referred to in the relevant chapters throughout these guidelines. Each figure represents a graphic format of the guidance provided on the topic specified in the chapter and noted in the title of the figure.

Figure 1. Establishing the presence of HIV infection in HIV-exposed infants and children less than 18 months of age in resource-limited settings



[a] For newborn, test first at or around birth or at the first postnatal visit (usually 4 – 6 weeks).

[b] Start ART, if indicated, without delay. At the same time, retest to confirm infection.

[c] The risk of HIV transmission remains as long as breastfeeding continues.

Figure 2. Establishing the presence of HIV infection in sick infants and children less than 18 months of age, in resource-limited settings where viral testing is available

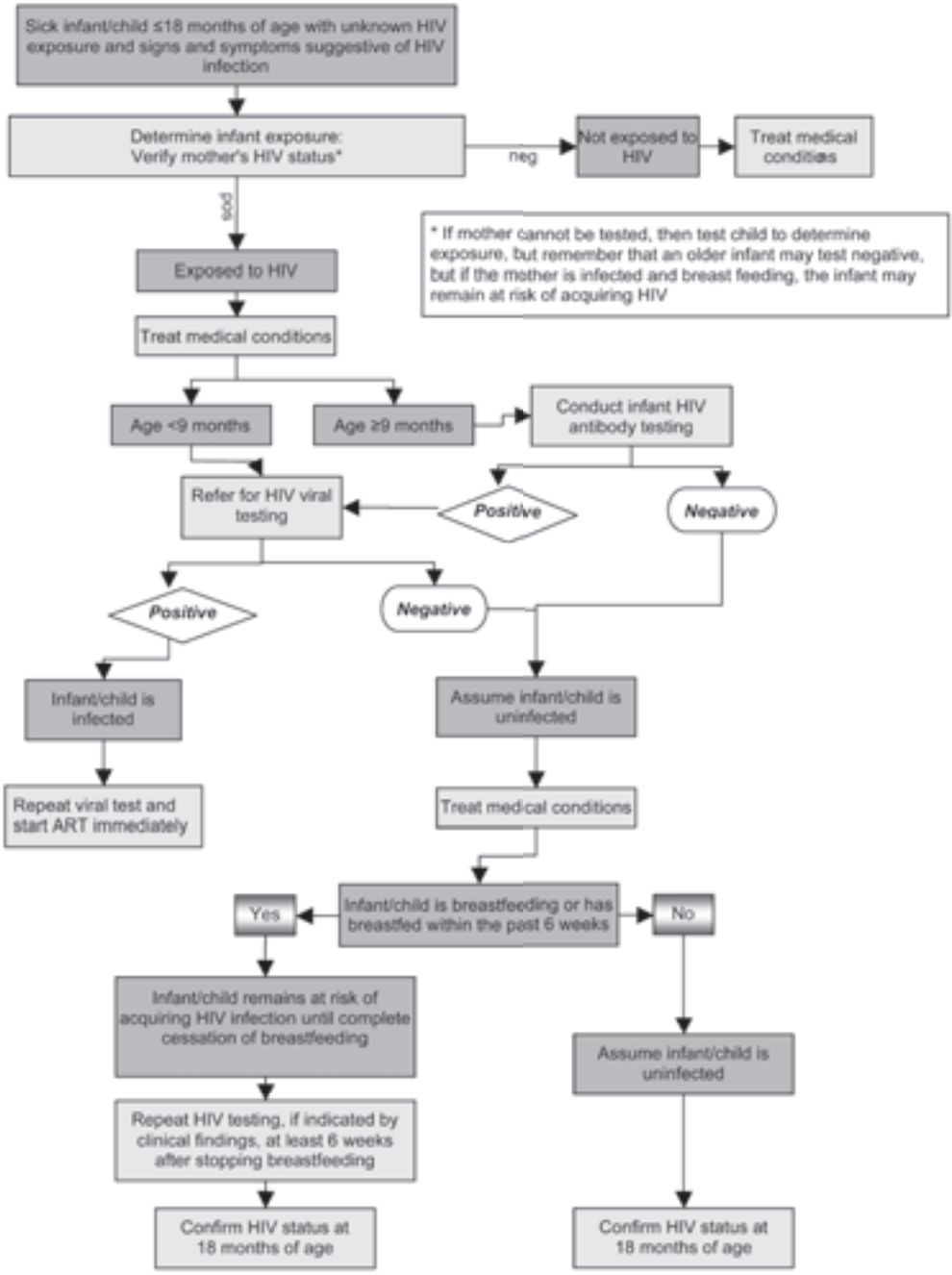


Figure 3. Establishing the presence of HIV infection in sick infants and children less than 18 months of age, in resource-limited settings where viral testing is not available

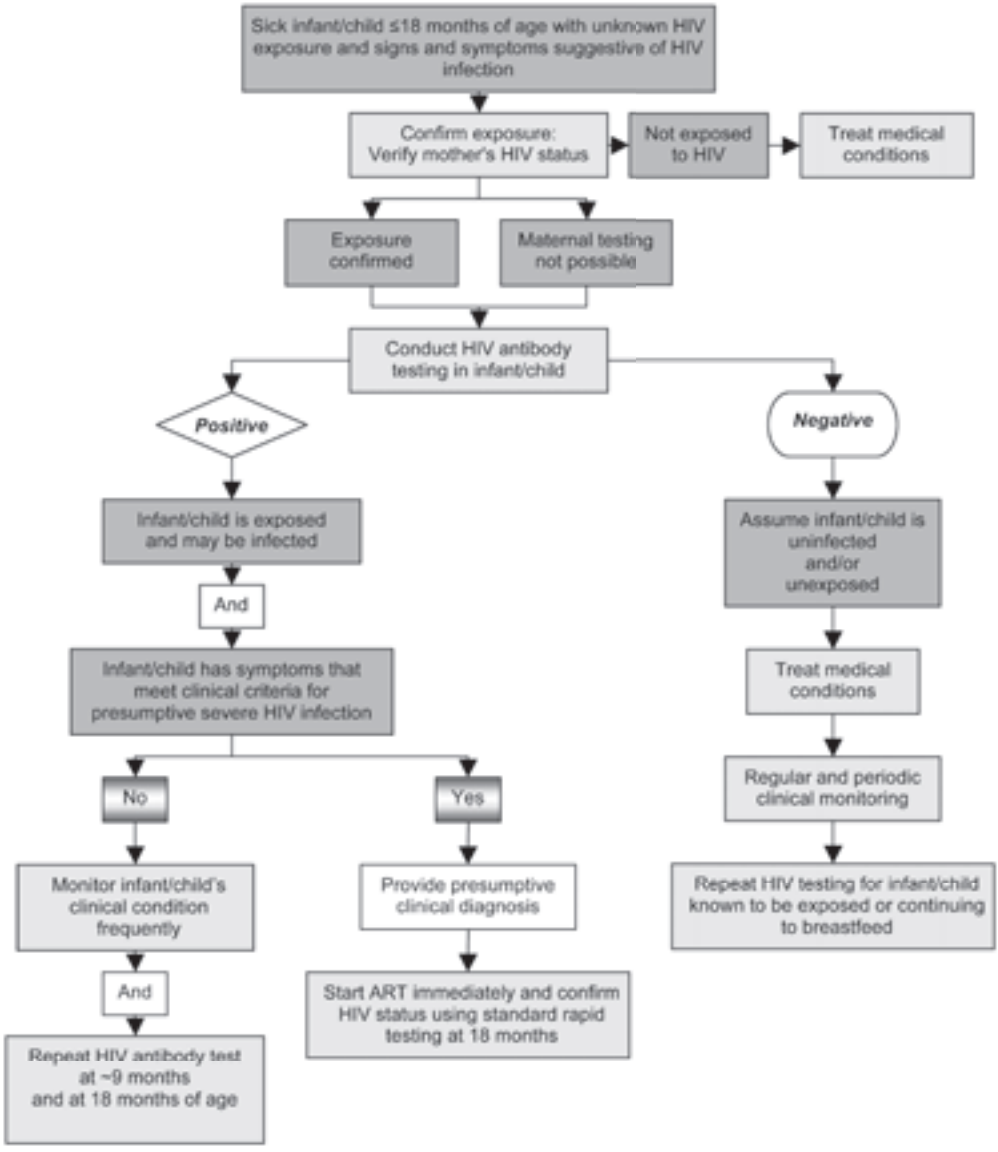


Figure 4. Initiating ART for infants and children

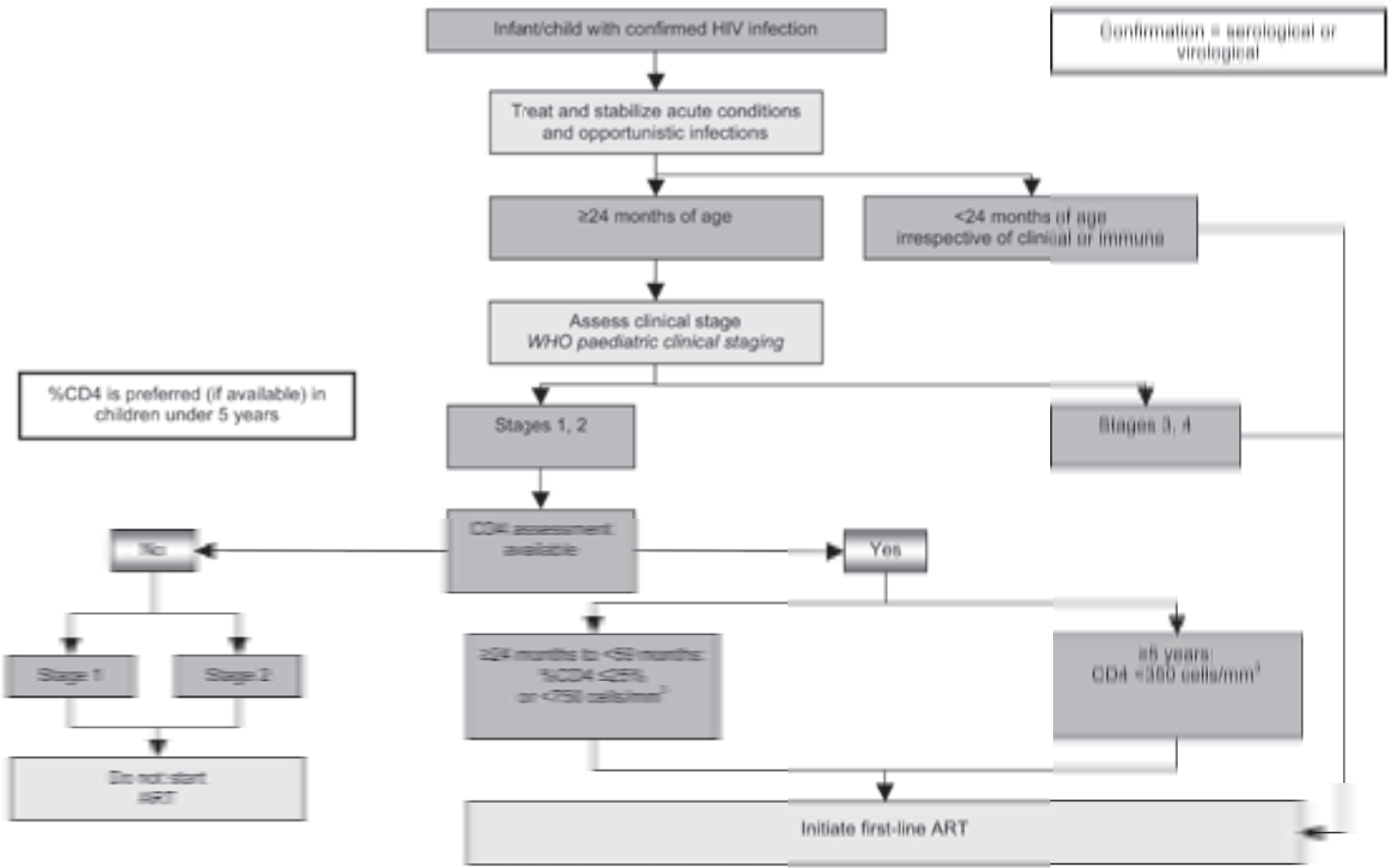


Figure 5. First-line ART for infants and children <24 months

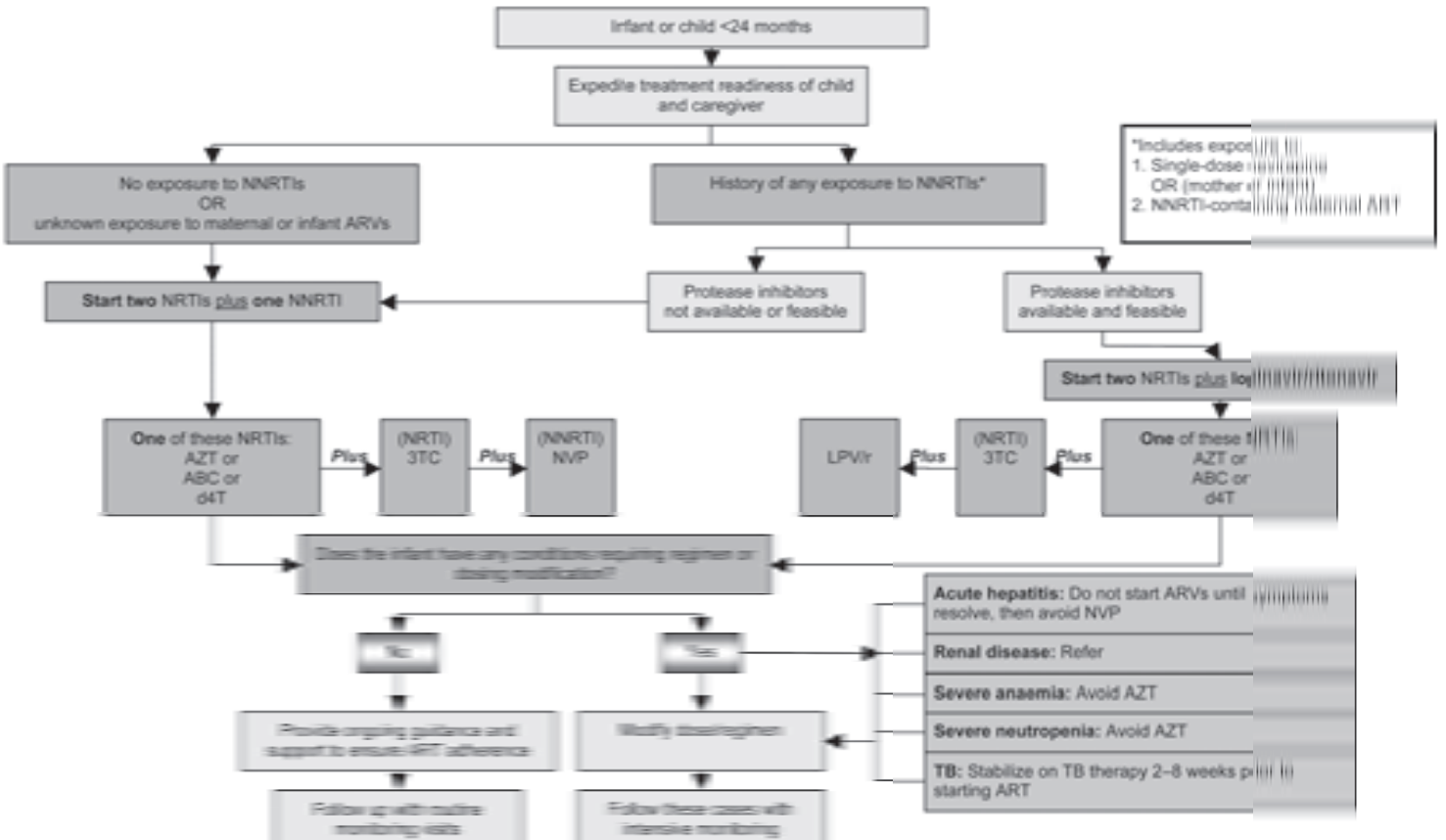


Figure 6. First-line ART regimens for children

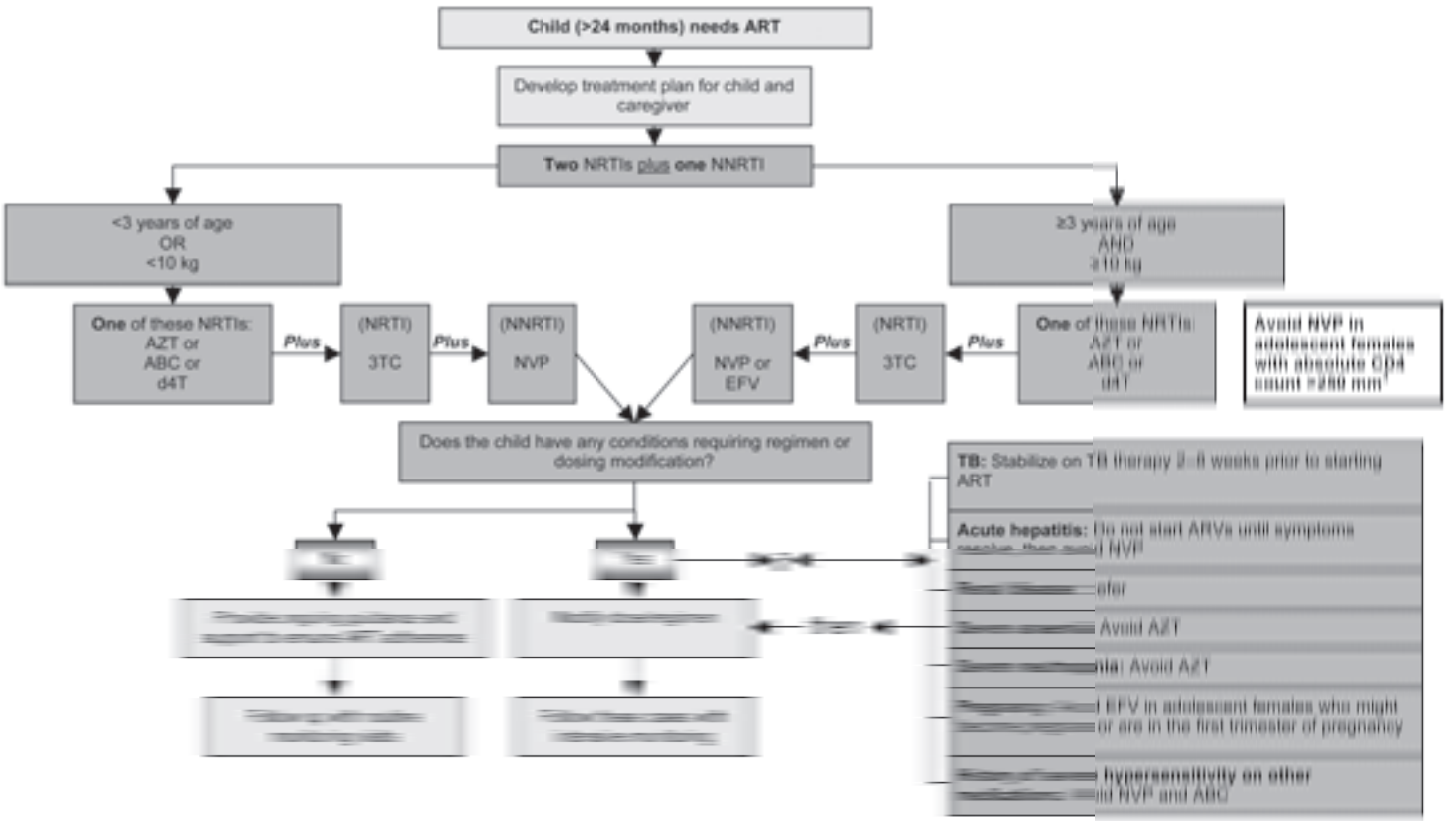
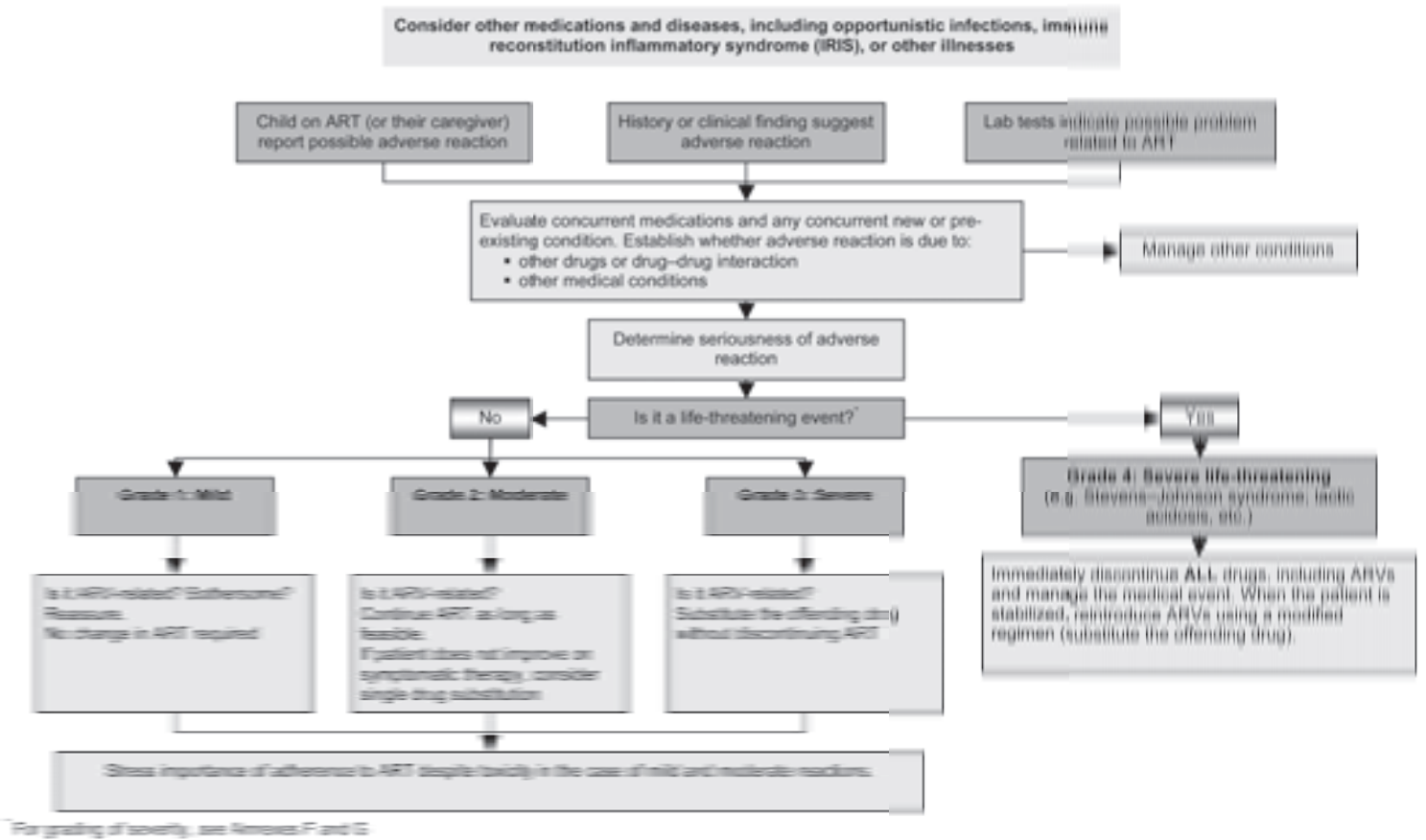


Figure 7. Routine follow-up visit

Figure 8. Managing ARV toxicity



* For grading of toxicity, see Annexes F and G.

Figure 9. Managing treatment failure when CD4 testing is available

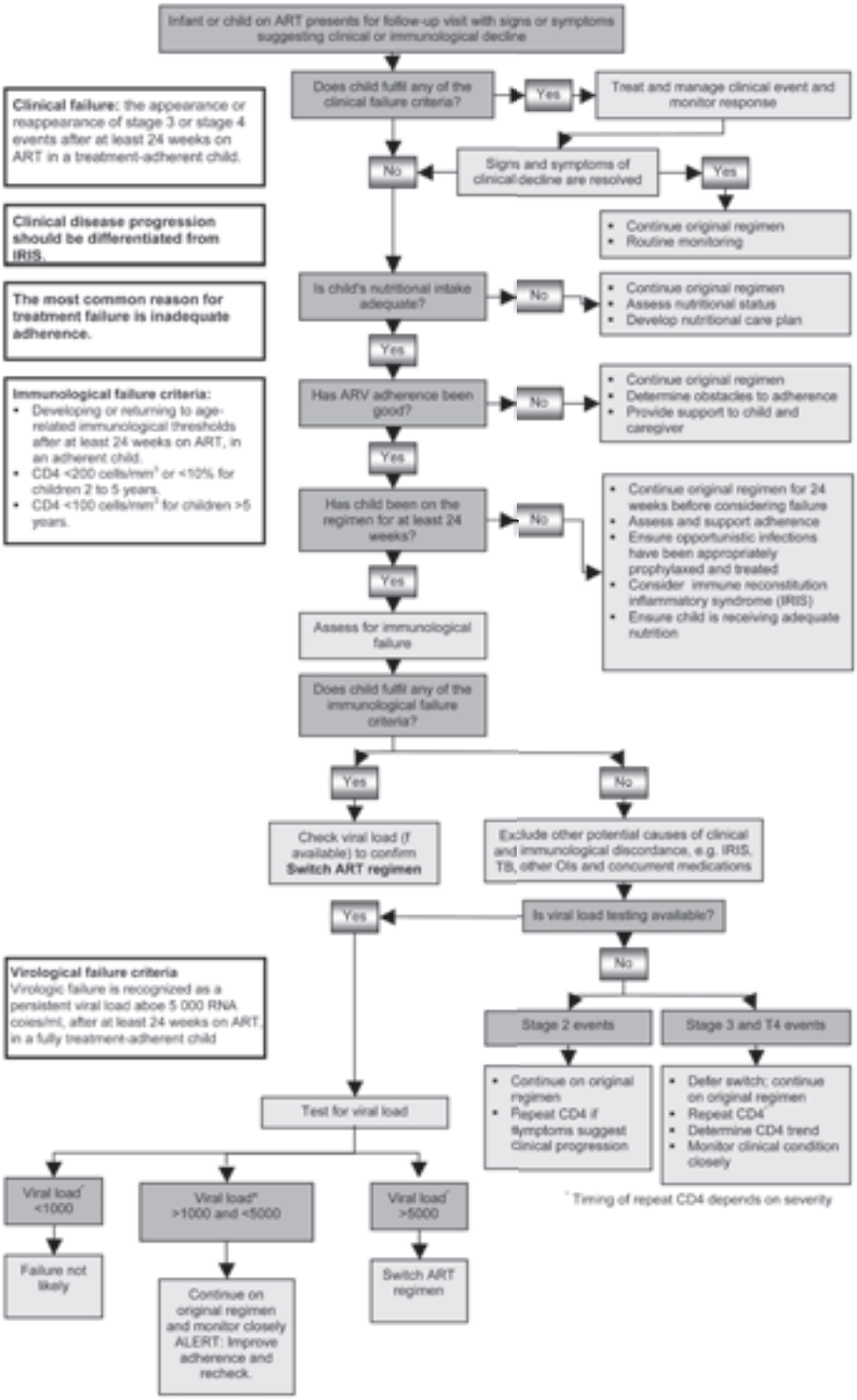


Figure 10. Managing treatment failure when CD4 testing is not available

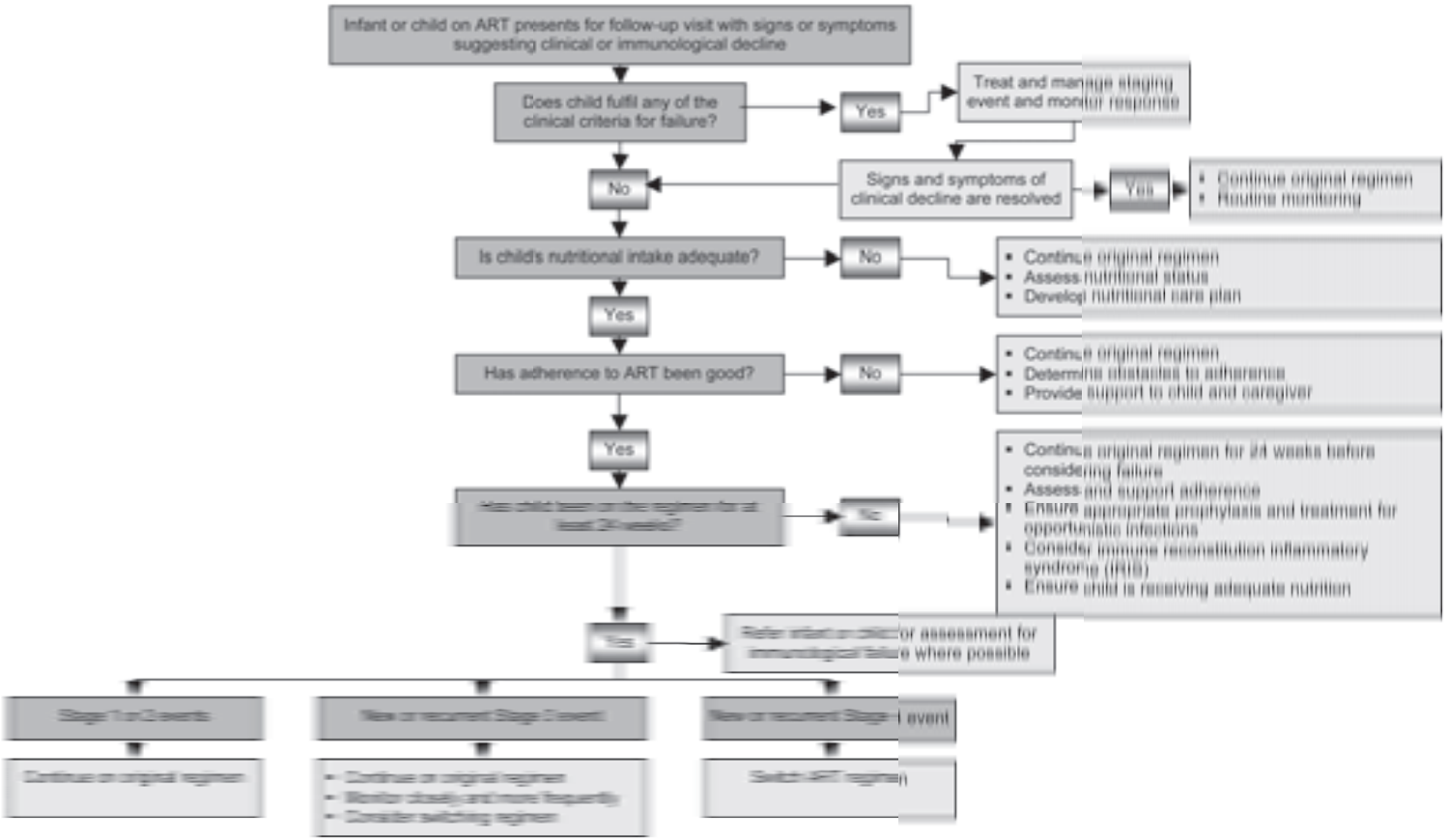
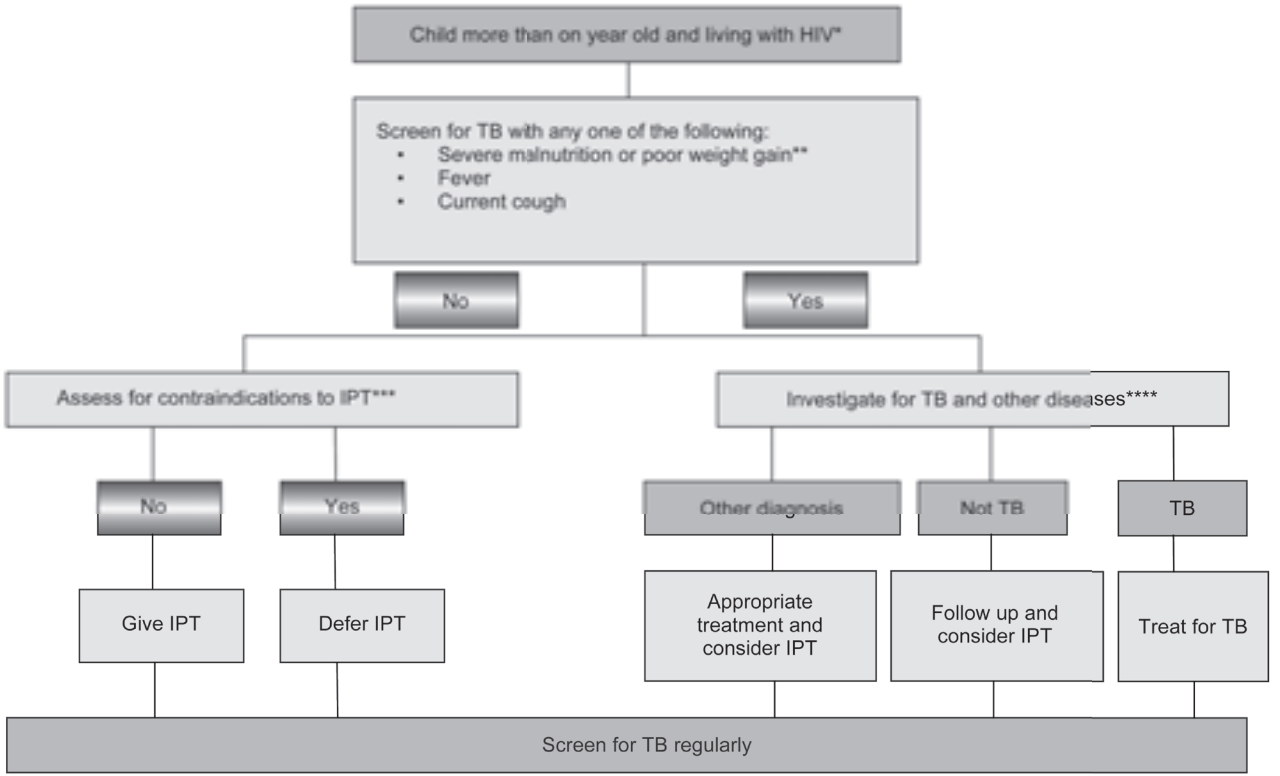


Figure 11. TB screening and IPT initiation among children living with HIV in resource-limited settings



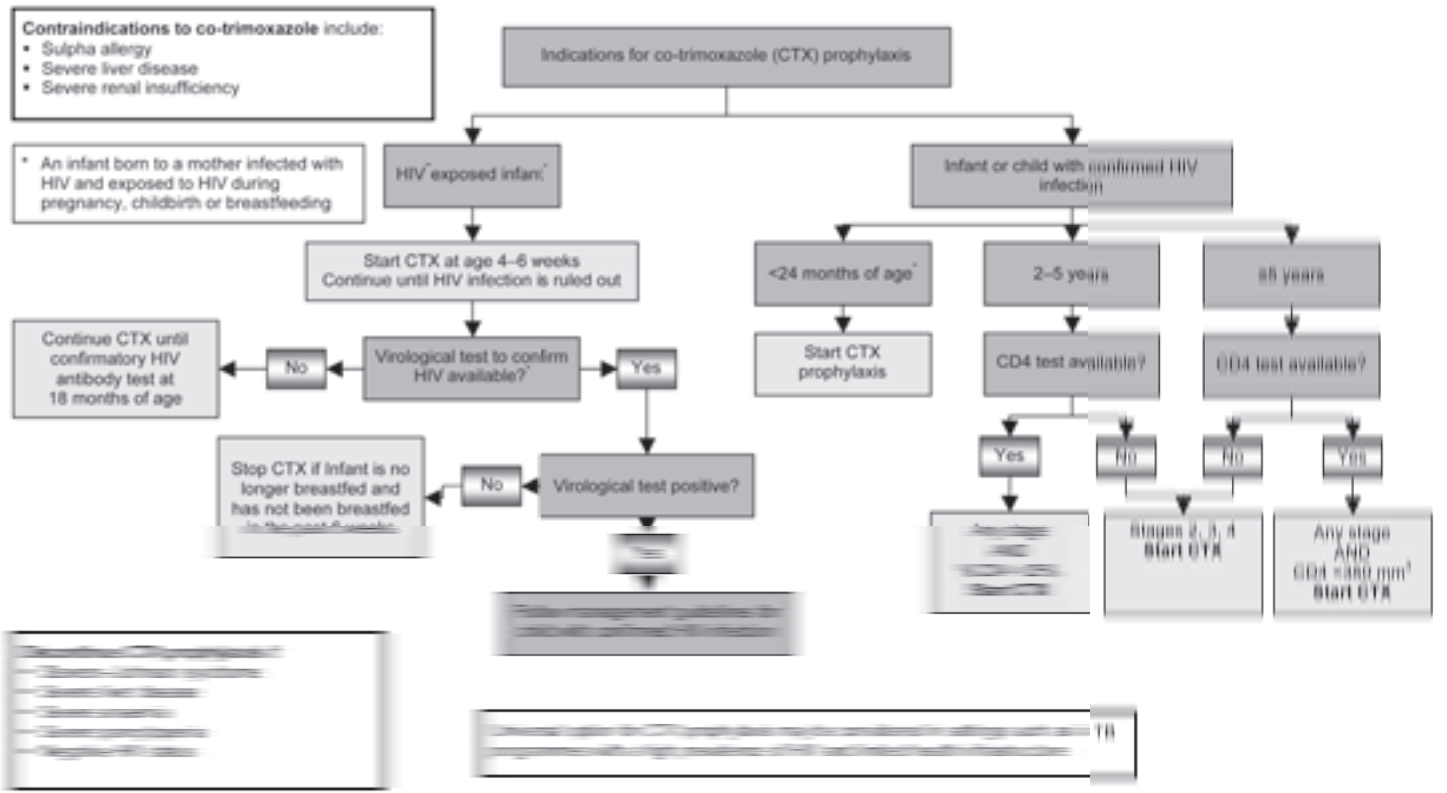
* *See* section 13.2

** Severe malnutrition as noted by signs of severe wasting, or oedema present in both feet, or weight-for-height less than -3 Z-score, or mid-upper arm circumference (MUAC) less than 115 mm in infants and children 6 – 60 months; 129 mm in children 5 – 9 years; 160 mm in children 10 – 14 years. Poor weight gain. [140] (*See* Section 13.2)

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

**** Per existing national guidelines.

Figure 12. Initiating co-trimoxazole prophylaxis



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