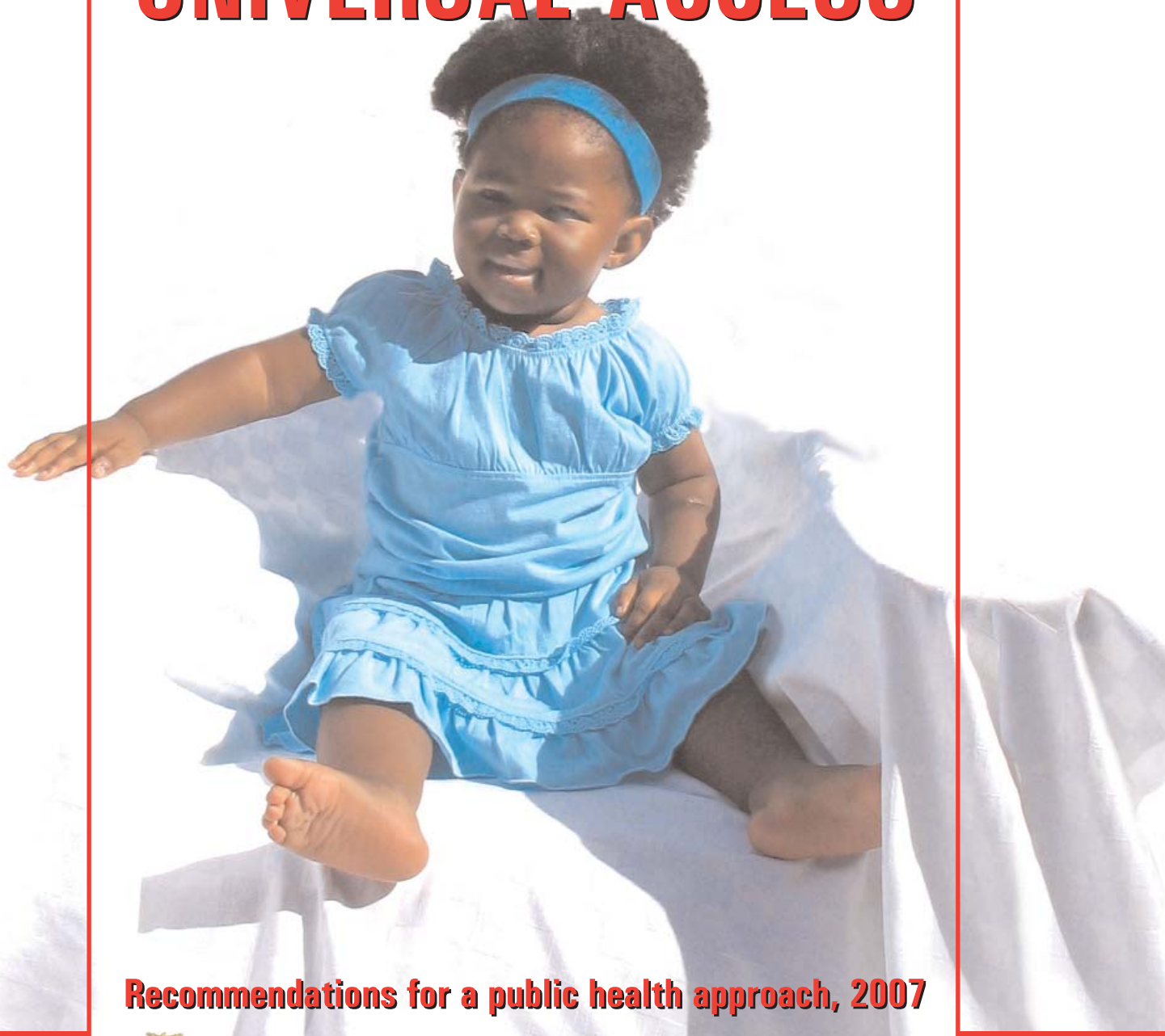
Zambian Guidelines for Antiretroviral Therapy of HIV infection in Infants and Children:

TOWARDS UNIVERSAL ACCESS



Recommendations for a public health approach, 2007

Government of the Republic of Zambia,
Ministry of Health

unicef

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Foreword

Globally about 1800 children under 15 years of age are infected with HIV everyday; more than 90% of these infections are occurring in the developing world and Mother-to-Child Transmission (MTCT) is by far the largest source of HIV infection in these children. According to` UNAIDS estimates, more than 90 percent of children acquire the virus through Mother-to-Child Transmission. Therefore the most efficient and cost effective way to tackle paediatric HIV is to reduce mother-to-child transmission of HIV. Therefore, there is a need to rapidly scale up the Prevention-of Mother-toChild-Transmission (PMTCT) programme in Zambia so that it reaches every woman who needs it. Antiretroviral therapy (ART) should be offered a timely manner to infants and children who become infected with HIV inspite of on going preventive efforts.

Zambia is one of the countries hardest hit by the HIV/AIDS epidemic, has a very high HIV prevalence among pregnant women, but the magnitude of HIV infection among infants and children remains unknown, although it is estimated to be about 10% of that of infected adults.

The Government of the Republic of Zambia has an obligation, and is committed to provide the country with equitable access to cost effective and quality health care, as close to the family as possible. It is against this background that the Ministry of Health is committed to achieve universal access to ART for both adults and children by 2010.

This can only be achieved through the expansion and integration of ART services into maternal and child health (MCH) and related health care services. The paediatric ART intervention entails, among other approaches, the establishment of linkages to other support programmes within the framework of a continuum of care for HIV positive people. Paediatric ART services will be linked to PMTCT interventions, to adult care, and along with other child survival programmes will ensure a reduction in maternal and childhood morbidity and mortality.

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This document has been adapted for use by health care providers in Zambia, and it gives guidelines on how to implement paediatric ART services at health facilities. It is hoped that these guidelines will provide guidance and help accelerate efforts towards universal access to ART by Zambian children. It will be periodically updated as paediatric ART management evolves with changing times, and as need dictates.

Dr. Simon Miti,
Permanent Secretary
Ministry of Health

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Acronyms and Abbreviations

Ab . . . . . antibody

ABC. . . . . abacavir

ACTG . . . . . AIDS clinical trials group

AFB . . . . . acid-fast bacilli

AIDS . . . . . Acquired Immunodeficiency Syndrome

ALT . . . . . alanine aminotransferase

ART. . . . . antiretroviral therapy

ARV. . . . . antiretroviral (drug)

AST . . . . . aspartate aminotransferase

AUC . . . . . area under the curve

AZT . . . . . zidovudine (also known as ZDV)

BAL . . . . . bronchoalveolar lavage

bid. . . . . twice daily

CD4. . . . . T-lymphocyte CD4+

CHAP . . . . . children with HIV antibody prophylaxis (clinical trial)

CMV . . . . . cytomegalovirus

CNS. . . . . central nervous system

CPK. . . . . creatinine phosphokinase

CPT . . . . . cotrimoxazole preventive therapy

CRAG . . . . . cryptococcal antigen

CSF . . . . . cerebrospinal fluid

CT . . . . . computerized tomography

CTX. . . . . cotrimoxazole

CXR. . . . . chest x-ray

d4T . . . . . stavudine

DART . . . . . development of antiretroviral therapy (in Africa)

ddI. . . . . didanosine

DBS. . . . . dried blood spot

DNA . . . . . deoxyribonucleic acid

DOT. . . . . directly observed therapy

EFV . . . . . efavirenz

EIA . . . . . enzyme immunoassay

ELISA . . . . . enzyme-linked immunosorbent assay

FBC . . . . . Full blood count

FDC. . . . . fixed-dose combination

GI. . . . . gastrointestinal

GRZ. . . . . Government of the Republic of Zambia

HDL. . . . . high density lipoproteins

Hgb . . . . . haemoglobin

HIV . . . . . Human Immunodeficiency Virus

HIVDR. . . . . HIV drug resistance

HIVNET HIV Network for Prevention Trials

HIVResNet global HIV drug resistance network

HPPMCS . . HIV Paediatric Prognostic Markers Collaborative Study

HSV. . . . . herpes simplex virus

ICD . . . . . immune complex dissociated

IDV . . . . . indinavir

Acronyms and Abbreviations

IMCI . . . . . integrated management of childhood illness

INH . . . . . isoniazid

IRS. . . . . immune reconstitution syndrome

LIP. . . . . lymphocytic interstitial pneumonia

LDS . . . . . lipodystrophy

LGE . . . . . lineal gingival erythema

LPV . . . . . lopinavir

LTB . . . . . laryngotracheal bronchitis

MRI . . . . . magnetic resonance imaging

MTCT . . . . . mother-to-child transmission (of HIV)

NFV. . . . . nelfinavir

NNRTI. . . . . non-nucleoside reverse transcriptase inhibitor

NPA. . . . . nasopharyngeal aspirate

NRTI . . . . . nucleoside reverse transcriptase inhibitor

NVP. . . . . nevirapine

OHL. . . . . oral hairyleukoplakia

PACT. . . . . pediatric AIDS clinical trials group

PCP. . . . . pneumocystis pneumonia

PCR. . . . . polymerase chain reaction

PENTA . . . . Paediatric European Network for Treatment of AIDS

PGL. . . . . persistent generalized lymphadenopathy

PI . . . . . protease inhibitor

PML. . . . . progressive multifocal leukoencephalopathy

PMTCT . . . . Prevention of mother-to-child transmission (of HIV)

/r . . . . . low dose ritonavir

RDA. . . . . recommended daily allowances

RNA . . . . . ribonucleic acid

RT . . . . . reverse transcriptase

RTI. . . . . reverse transcriptase inhibitor

RTV-PI. . . . . ritonavir-boosted protease inhibitor

sgc . . . . . soft gel capsule

SD . . . . . standard deviation

SJS . . . . . Stevens-Johnson syndrome

SQV. . . . . saquinavir

STI. . . . . structured treatment interruption

TB . . . . . tuberculosis

TDF . . . . . tenofovir disoproxilfumarate

TEN . . . . . toxic epidermal necrolysis

TLC . . . . . total lymphocyte count

ULN. . . . . upper limit of normal

URTI . . . . . upper respiratory tract infection

WBC . . . . . white blood cell count

WHO . . . . . World Health Organization

I. Introduction

The most efficient and cost effective way to tackle paediatric HIV is to reduce mother-to-child transmission of (MTCT) HIV. However, every day there are nearly 1800 new infections in children under 15 years of age globally, more than 90% occurring in the developing world and mostly associated with mother-to-child transmission of HIV (MTCT) (1). There is thus a critical need to provide antiretroviral therapy (ART) for infants and children who become infected despite on going efforts to prevent infection in infants and children.

ART has substantially changed the face of HIV infection in countries where it has been successfully introduced. HIV-infected infants and children now survive to adolescence and adulthood. The challenges of providing HIV care have therefore evolved to become those of chronic as well as acute care. In resource-limited settings, many of which are in countries hardest hit by the epidemic, unprecedented efforts made since the introduction of '3 by 5' targets and global commitments to rapidly scale up this access to ART have led to remarkable progress. However, this urgency and intensity of effort have met with less success in extending the provision of ART to HIV-infected children. Significant obstacles to scaling up paediatric care remain, including limited screening for HIV, lack of affordable simple diagnostic testing technologies, lack of human capacity, insufficient advocacy and understanding that ART is efficacious in children, limited experience with simplified standardised treatment guidelines, and a lack of affordable practicable paediatric antiretroviral (ARV) formulations. Consequently, to date far too few children have been started on ART in Zambia. The need to treat increasing numbers of HIV-infected children also highlights the primary importance of preventing the transmission of the virus from the mother to her child in the first place.

"ART HAS SUBSTANTIALLY CHANGED THE FACE OF HIV INFECTION IN COUNTRIES WHERE IT HAS BEEN SUCCESSFULLY INTRODUCED. HIV-INFECTED INFANTS AND CHILDREN NOW SURVIVE TO ADOLESCENCE AND ADULTHOOD."

These "stand alone" comprehensive national guidelines for the use of ART in children are the local adaptation of the WHO paediatric guidelines (2006)2. They have been adapted to support and facilitate the management and scale-up of ART in infants and children based on a public health approach and are long overdue. The present guidelines are part of WHO's and Zambia's commitment to achieve universal access to ART by 2010.

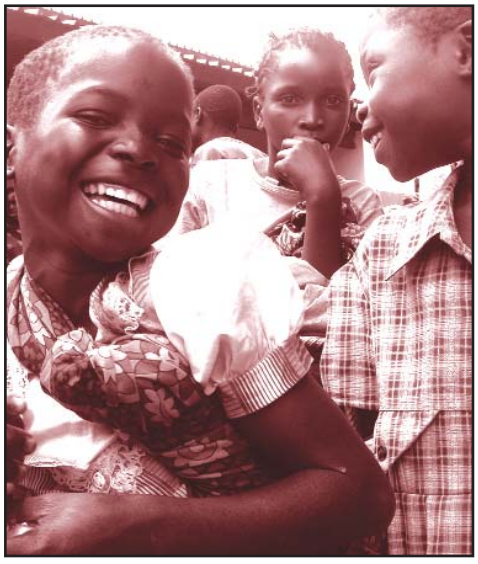
II. Objectives of the Guidelines

These stand alone paediatric treatment guidelines serve as a framework for selecting the most potent and feasible first-line and second-line ARV regimens as components of the expanded national response for the care of HIV-infected infants and children. Recommendations for diagnosing HIV infection in infants and children; when to start ART, including situations where severe HIV disease in children less than 18 months of age has been presumptively diagnosed; and for clinical and laboratory monitoring of ART as well as for substitution of single drugs for toxicities are provided.

The guidelines consider ART in different situations, such as where infants and children are co-infected with HIV and TB for example, or have been exposed to ARVs either due to prevention of MTCT (PMTCT) or because of breastfeeding from an HIV-infected mother on ART. The guidelines address the importance of nutrition in the HIV-infected child and of severe malnutrition in relation to provision of ART. Adherence to therapy and viral resistance to ARVs are both discussed with a particular focus on issues related to infants and children. A section on ART in adolescents briefly outlines key issues related to treatment and care in this age group. It also highlights management of common conditions seen in HIV positive children

Training the health worker and provision of guidelines alone are not enough. The Government does realise that there is a need to strengthen health systems, including human resources capacity and evaluation and monitoring capabilities, with a view to maximising the quality and long-term benefits of therapy. Improved access to HIV diagnostic testing as well as to immunological assays for measuring %CD4 or absolute CD4 cell count for infants and young children is important to assist in decision-making on initiation and optimising maintenance of ART. The inability to diagnose HIV infection early in children, especially through programmes for PMTCT, severely limits access to ART and/or its timely initiation.

This publication is primarily intended for use by everyone involved in planning and management of national HIV care strategies of ART related pediatric health care; Ministry of Health (MOH), its partners, treatment advisory boards, National AIDS programme managers, senior policy-makers and all health workers implementing ART both in public and private health facilities.



III. Recommendations for the Paediatric ART Programme

Advances in diagnosis and treatment of HIV have occurred and data on resistance, drug-drug interactions and the long-term toxicities of ART based upon use in resource-limited settings have emerged since the original guidance by WHO on ART for infants and children in 2004. An expert WHO Technical Reference Group on Paediatric HIV Care and Treatment and ART & HIV care met in Geneva in 2005 and in their recommendations considered the following overarching principles:

- ART programmes should be scaled-up with a view to universal access, i.e., all persons, including infants and children, requiring treatment as indicated by medical criteria should have access to it, and the treatment of infants and children in need of ART as per national guidelines should initiate treatment as soon as practicable.

"ADVANCES IN DIAGNOSIS AND TREATMENT OF HIV HAVE OCCURRED AND DATA ON RESISTANCE, DRUG-DRUG INTERACTIONS AND THE LONG-TERM TOXICITIES OF ART BASED UPON USE IN RESOURCE-LIMITED SETTINGS HAVE EMERGED SINCE THE ORIGINAL GUIDANCE BY WHO ON ART FOR INFANTS AND CHILDREN IN 2004."

- To support the efficient implementation of treatment programmes in resource-limited settings, ARV regimens need to be standardised and simplified; the recommendations in these guidelines are harmonised with the WHO guidelines for treatment in adults, ARV drugs for treating pregnant women and preventing HIV infection in infants, and post-exposure prophylaxis.

- ART recommendations should be based on the best available scientific evidence, avoiding the use of substandard protocols that compromise the outcomes of individual patients and creating a potential for the emergence of drug-resistant virus, and are based upon simplified standardised regimens that offer both a durable response and preserve future treatment options.

- Recommendations made are based on evidence from randomised controlled trials, high quality scientific studies for non-treatment related options, or observational cohort data or, where insufficient evidence is available, on expert opinion, and they have been identified as such.

- Cost-effectiveness is not explicitly considered as part of these recommendations, although the realities with respect to the availability of human resources, health system infrastructures and socio-economic contexts have been taken into account.

- Revisions to previous recommendations should not disrupt the scale-up efforts already underway in countries; adaptations according to the prevailing local situation may be necessary to facilitate implementation.

IV. Goals and Targets

1. Long term goal

(target date end of 2010)

Achievement of the highest quality of life for HIV infected children and their families through delivery of a comprehensive package of care. This will entail:

a. Equipping all Primary Health Care Centres to manage children pre-ART and to follow-up children after stabilisation.

b. Provide health centres in each district, capacity to provide ART

c. Develop tools to ensure long-term continuum of care

d. Improve Government capacity to support ART, including provision of flow cytometers for CD4, RNA, PCR and if possible resistant testing

2. Short term goals

a. 25% of HIV infected children admitted to hospitals nation-wide and 75% by the end of 2007 should have an antibody test performed.

b. 25% of all HIV infected children should receive CPT by December 2006 and 50% by December 2007

c. 7.5% of ART recipients in Zambia should be children less than 15 years of age by December 2006 and 12.5% by December 2007

To achieve the above goals there is need to:

1. Decentralise care to district level

- **a.** ART initiation and maintenance should extend to all district hospitals and clinics with an ART trained health care provider (MO/CO/nurse)
- **b.** Pre-treatment HIV care (CPT) be extended to all MCH sites
- **c.** Keep stocks of CTX and ARVs at point of service
- **d.** Recommend against routine distribution of d4T in liquid form at sites where refrigeration is not available

2. Referral systems from lower to higher health facilities and vice versa will be defined and disseminated

3. Institute mechanisms for laboratory analysis where available utilising DBS and related transport mechanisms.

4. Increase capacity of health care workers to provide paediatric HIV care, starting with those trained in managing adults, and provide a preceptorship approach to training (trainer from the original training team remains on for a certain period of time to provide on site mentoring). A preceptor will rotate to different clinics within a district.

5. Roll-out "Family Approach": A family centred approach should be institutionalised at all health facilities by December 2007. Services to promote in family centred clinics are:

- **a.** Couple counselling and testing
- **b.** Psychosocial problem solving
- **c.** Discussion of child's treatment plan with the principal caregiver and other members of the family.

IV. Goals and Targets

6. Advantages of family-based approach include:

a. Stigma reduction within family, and family support harnessed

b. Family members mutually support each other's adherence, which promotes better clinical outcomes.

c. All family members can be seen and clinically managed at the same clinic on the same day

7. Key entry points into family based care - PMTCT, ART, MCH clinics

MOH will establish a district and team approach to management and coordination activities for paediatric care at the DHMTs by December 2007. Responsibilities of this body will include

a. Program implementation oversight including training, supply management and monitoring and evaluation (M&E)

b. Update district health providers and facilities with current policies and revised guidelines

c. Establish mechanisms of providing oversight for each level of care

- Develop site reviews and supervisory review tools
- Utilise M&E data reporting to review progress
- Utilise quality improvement methods to improve care

MOH WILL ESTABLISH A DISTRICT AND TEAM APPROACH TO MANAGEMENT AND COORDINATION ACTIVITIES FOR PAEDIATRIC CARE AT THE DHMTS BY DECEMBER 2007.

V. Establishing Diagnosis of HIV Infection

The definitive diagnosis of HIV infection in children at any age requires diagnostic testing that confirms the presence of Human Immunodeficiency Virus. Antibody testing identifies the HIV antibody. However, as maternal HIV antibodies transferred passively during pregnancy can persist for as long as 18 months in a child born to an HIV-infected mother (6), interpretation of a positive HIV antibody test result is difficult in children under 18 months of age. In order to definitively diagnose HIV infection in children less than 18 months of age, assays that detect the virus or its components (i.e., virological tests) are therefore required. Virological tests that can be used in children include:

- assays to detect plasma proviral HIV DNA (7);
- assays to detect plasma HIV RNA (8-12);
- Assays to detect Immune Complex Dissociated (ICD) p24 antigen, (13-15).

Real-time PCR detects HIV RNA and DNA and several automated platforms are commercially available, and currently available at the University Teaching Hospital and Lusaka DHMT reference laboratories. HIV infant diagnosis will soon be introduced on a wider scale in Zambia, and the reliability of the above mentioned laboratories should be continuously ensured with standard quality assessments. Real-time PCR has become cheaper and easier to standardise than PCR, providing several advantages in the early diagnosis of HIV infection in children and the monitoring of ART effectiveness (11). ICD p24 assays are promising future alternatives for use in smaller district laboratories (16).

Blood can be difficult to collect from young infants and has to be sent immediately to the laboratory.

More recently, use of dried blood spots (DBS) for both HIV DNA and RNA testing and ultra sensitive p24 antigen assay have proved robust and reliable (17-24). DBS do not require venipuncture but can be obtained using blood from a finger-stick or heel-stick. They carry less of a biohazard risk than liquid samples, the samples are stable at room temperature for prolonged periods, and are easier to ship, facilitating centralised laboratory testing (17).

The National PMTCT and ART programmes are striving to ensure that diagnostic protocols are in place for systematic testing of HIV-exposed infants and children, including availability of virological tests that allow early diagnosis of HIV infection in young children.

The identification and follow-up of infants born to HIV-infected women are a necessary first step to infant diagnosis.

It needs to be emphasised that children less than18 months of age known or suspected to have been exposed to HIV should be closely monitored and benefit early in life from interventions such as CPT, even in situations where virological testing is not available to definitively diagnose HIV infection.

While HIV antibody testing cannot be used to definitively diagnose HIV infection in infants under 18 months of age,

It can be used to exclude HIV infection as early as 9 to 12 months of age in infants who have not breastfed or who ceased breastfeeding 6 weeks or more prior to the antibody test, as most uninfected HIV-

exposed infants will lose maternal antibody by the age of 12 months. In children 18 months of age or older, HIV antibody tests can be used reliably to definitively diagnose HIV infection in the same manner as they're used in adults.

Additional investment by MOH and its partners to improve access to earlier HIV diagnosis for infants will lead to a notable increase in the efficiency of PMTCT programmes in identifying HIV-infected children, facilitating medical management, reducing morbidity and mortality and improving quality of life. In addition, early diagnosis offers societal benefits that extend beyond economic savings (25).

Children may be with or without a legal parent or guardian and issues of consent, competency to consent, disclosure, confidentiality and counselling need to be considered.

If HIV infection is diagnosed in a young child or infant, usually the mother herself is also HIV infected and other siblings may also be infected. Appropriate counselling and support therefore needs to be provided when testing for HIV in children.

Children Less Than 18 Months of Age

Definitive laboratory diagnosis of HIV infection in children less than18 months of age can only be made by conducting virological testing.

Positive tests performed using one of the virological tests recommended above establish the diagnosis of HIV for purposes of clinical management. Although earlier virological testing, during the first 48 hours of life of an HIV-exposed infant, identifies those infants infected in utero, those infants infected during late pregnancy and intrapartum will have negative virological tests at that time. By the age of 4 weeks, virological testing approaches 98% sensitivity (29). *Therefore, it is considered more programmatically efficient to perform initial virological testing at the time of the first postnatal visit, usually at age 6-8 weeks,* at which time infants infected during the intrapartum period and early postpartum can be identified. *A positive virological test at any age is considered diagnostic of HIV infection.* A repeat virologic test on a separate specimen is not routinely recommended to confirm an initial positive test.

Therefore, within a public health approach, for purposes of clinical management, including initiation of ART, positive virological testing at any age is viewed as sufficient to diagnose HIV infection. In these situations, the reliability of the laboratory (determined by standard quality assessment) is fundamental to ensure reliable test results. In children diagnosed with HIV infection based on one positive virological test, HIV antibody testing should be performed after 18 months of age to confirm HIV infection (Figure 1).

Diagnosing HIV infection in breastfeeding infants

If an infant or child is breastfeeding, he or she remains at risk of acquiring HIV infection throughout the breastfeeding period, and therefore a negative virological test in an infant who is breastfeeding does not rule out HIV infection. The national recommendation is therefore, that virological assays to detect HIV infection should be conducted at least 6 weeks or more after complete cessation of breastfeeding. If the child is between 9-18 months of age at the time of discontinuation of breastfeeding, HIV antibody testing should be performed prior to virological testing because HIV antibody testing is less expensive and often

easier to perform than virological testing. Only children who have HIV antibody present (i.e., those infants and children who have either persisting maternal antibodies or who acquired HIV during breastfeeding) are likely to be HIV-infected and therefore need further virological testing for definitive diagnosis of infection (Figure 1).

HIV-exposed symptomatic infants and children

Where virological testing is not routinely available, any child younger than 12 months of age known to be HIV-exposed and developing signs and symptoms of HIV infection should be referred for virological testing. Positive virological results at any stage indicate HIV infection.

HIV-exposed asymptomatic infants and children

By the age of 12 months, most uninfected HIV-exposed children will have lost maternal antibody and HIV antibody positive testing in a child at this age can be considered indicative of probable HIV infection in the child (i.e., 94.5% seroreversion at age 12 months; 96% specificity), and should be confirmed by a second antibody test after age 18 months.

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

HIV DNA remains detectable in the peripheral blood mononuclear cells of HIV-infected children who have received ART and have undetectable viral replication as measured by HIV RNA assays, so testing (i.e. DNA PCR) can be conducted in infants born to mothers who received ART. However, there are concerns about the effect of maternal and infant ARV prophylaxis of MTCT on the sensitivity of HIV **RNA or ICD** p24 antigen assays when RNA or ICD p24 antigen assays are used for early diagnosis. Based on expert opinion, it is however *recommended that the assays may be used at any time from 6 weeks of age.*

Diagnosing infection when the mother is on ART:

It is not known whether during breastfeeding maternal ART affects HIV RNA or p24 detection in the infant in light of the relatively high ART levels found in the infants of breast feeding mothers (32). *DNA detection remains unaffected by maternal ART.* Experts recommend that the other methods of virological testing can be used from 6 weeks of age even if the mother is breastfeeding and on ART.

Children 18 Months of Age or Older

Definitive HIV diagnosis in children 18 months of age and older (with known or unknown HIV exposure) *is made with antibody tests, following standard testing algorithms used for adults* (Figure 1). Confirmation of the positive antibody test result should follow standard national testing algorithms, and at a minimum, should be confirmed by duplicate testing using a different HIV antibody test (26, 33). The use of rapid antibody tests for diagnosis has the advantage that test results become available the day of the clinic visit.

**To optimise Early Infant Diagnosis and institutionalise care for HIV exposed children*

we will standardise the documentation of the mother's HIV status on the under-five card and provide guidance and necessary training to all healthcare workers in MCH clinics to routinely review the card for HIV status and provide clinical care accordingly.

V. Establishing Diagnosis of HIV Infection

Presumptive Clinical Diagnosis of HIV Infection

No single clinical diagnostic algorithm has proved to be highly sensitive or specific for diagnosis of HIV infection. Clinical algorithms are rarely more than 70% sensitive for accurate diagnosis of infection (34) and vary considerably with age; they are less reliable in particular in children aged less than 12 months (35). *However, there are situations where the use of a clinical algorithm may require initiating appropriate, life-saving treatment of a seriously ill child under age 18 months.* There are currently insufficient data available to make firm recommendations of the use of clinical algorithms combined with measurement of CD4 or other parameters to establish HIV infection. *It should be emphasised that WHO clinical staging of HIV disease can only be conducted where HIV infection has been established.*

Children Less Than 18 Months of Age

For infants and children aged less than 18 months where access to virological testing is not yet available, yet a child has symptoms that are suggestive of HIV infection, *a presumptive clinical diagnosis* of severe HIV infection may be necessary in order to permit decision-making on the need for the initiation of potentially life-saving ART (annex B).

Children 18 Months of Age and Older

For children 18 months of age and older with signs and symptoms suggestive of HIV, the use of antibody testing is strongly recommended following the testing protocol to diagnose HIV infection (Figure 1). *Presumptive clinical diagnosis of severe HIV disease is therefore not indicated in this age group because standard HIV antibody testing is diagnostic of HIV infection at this age.* Some clinical conditions are very unusual without HIV infection (i.e., pneumocystis pneumonia, esophageal candidacies, lymphoid interstitial pneumonitis, Kaposi's sarcoma and cryptococcal meningitis), and the diagnosis of these conditions would thus suggest HIV infection and indicate a need to perform an HIV antibody test.

V. Establishing Diagnosis of HIV Infection

Table 1: summarises the recommended methodologies for establishing the presence of HIV infection in different situations

<table>
<tr><th>Method of diagnosis</th><th>Recommendations for use</th><th>Strength of recommendation/ level of evidence</th></tr>
<tr><td>Virological methods</td><td>To diagnose infection in infants under age 18 months; initial testing is recommended from 6-8 weeks of age</td><td rowspan="3">HIV DNA -A (I)
HIV RNA -A(II)
U p24 ag -C(II)</td></tr>
<tr><td rowspan="3">HIV antibody testing</td><td>To diagnose HIV infection in mother or identify HIV exposure of infant</td></tr>
<tr><td>To diagnose HIV infection in children 18 months of age or older</td></tr>
<tr><td>To identify HIV positive children under 18 months of age in whom HIV infection is likely</td><td>A (IV)a</td></tr>
<tr><td>To exclude HIV infection where HIV antibody negative in children aged under 18 months who are HIV exposed and:
• Never breast fed
• Discontinued breast-feeding for more than 6 weeks</td><td></td></tr>
<tr><td colspan="3">Notes: Children less than 18 months of age who have positive HIV antibody tests include children who are truly HIV-infected, as well as those who still have maternal antibody but are uninfected. By the age of 12 months most uninfected children will have lost maternal antibody and positive antibody testing at this time usually indicates probable HIV infection in the child (96% specificity).</td></tr>
</table>

V. Establishing Diagnosis of HIV Infection

To optimise early diagnosis and follow-up care for HIV exposed infants

It is recommended that the use of DBS be institutionalised for early diagnosis at all **MCH** clinics and will utilize PCR capacity at national level:

a) linkages will be formalised between MCH clinics and laboratories with PCR capacity

b) Personnel responsible for sample collection will be trained

c) Mechanism for sample delivery and retrieval and return of DBS results will be institutionalised.

d) Where DNA PCR is not available, the use of rapid tests at 9-12 months in non-breast feeding infants, or ceased breast-feeding at least 3 months prior to testing is recommended

e) Institutionalise CPT for HIV exposed and infected infants

EPI will be used for maximising follow-up of HIV exposed children by:

a) Linking identification of HIV status (definitive PCR-based diagnosis) to first EPI visit; if the mother is positive and is still breast-feeding, perform antibody test at 3 months or PCR 6 weeks after cessation of breast-feeding

b) Conducting growth monitoring at each EPI visit (monthly in the first year of life if possible) as measured by weight for age, and as much as possible, head circumference.

c) Ensuring status of HIV exposure is reviewed at each EPI visit

d) Conducting neuro-developmental monitoring at each EPI visit as measured by milestones

a. Wall chart regarding milestones will be disseminated and should be used

b. Wall charts summarising neuro-developmental assessment should be used.

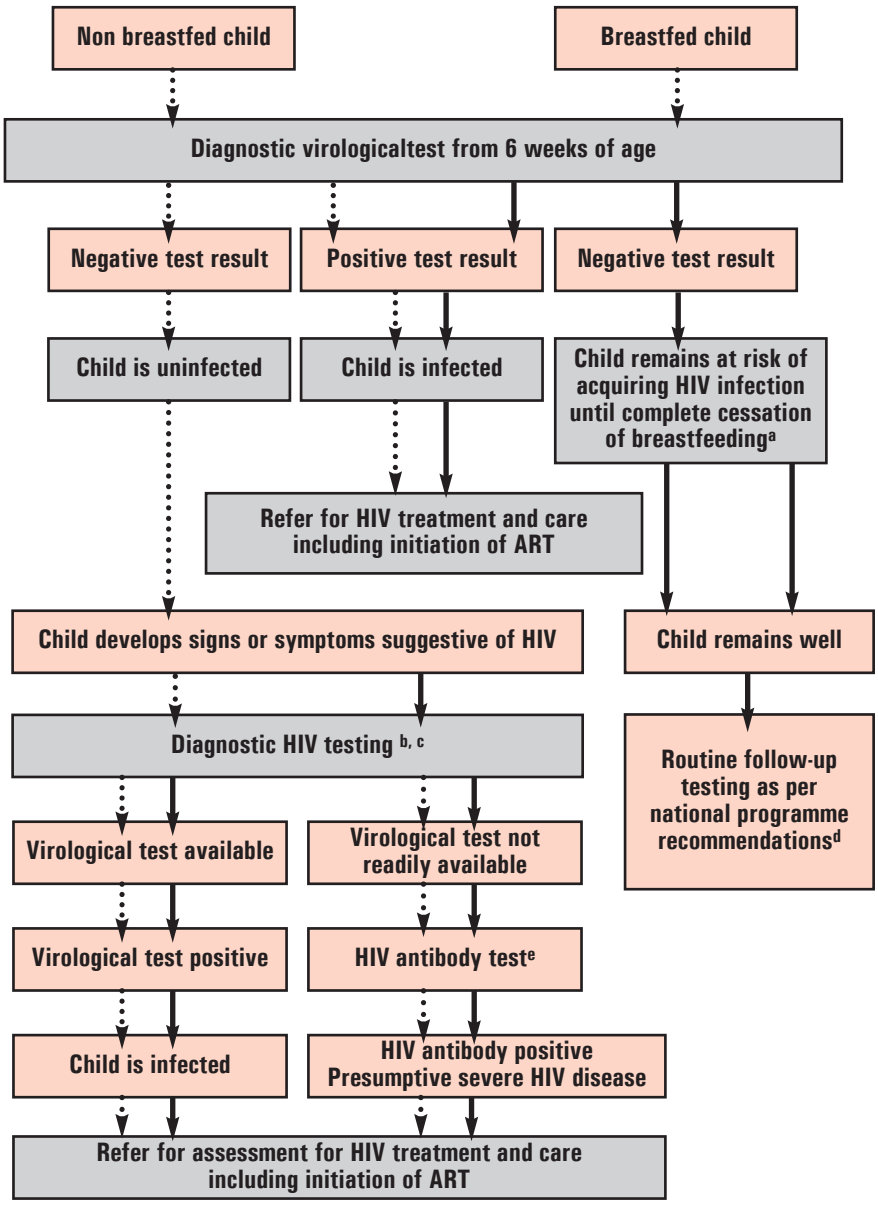
e) It is recommended that the HIV IMCI component be used for every sick child visiting a health facility

To optimise identification of HIV positive children, "routine offer of HIV testing" to all children admitted to a paediatric unit is recommended:

a) Implement routine offer of HIV testing for sick, admitted children for any reason, children of any age with unknown exposure to HIV, sexually defiled children inclusive of all those identified in MCH with growth faltering and delayed milestones.

b) Training in Rapid HIV Testing to all nurses, doctors and other health care will be provided so that opportunities for testing are not missed.

Figure 1. Establishing presence of HIV infection in HIV exposed children aged under 18 months in resource-limited settings to facilitate ART and HIV care



a. The risk of HIV transmission remains if breastfeeding continues beyond 18 months of age.

b. Infants over 9 months of age can be tested initially with HIV antibody test, as those who are HIV ab negative are not HIV infected, although still at risk of acquiring infection if still breastfeeding.

c. In children older than 18 months antibody testing is definitive.

d. Usually HIV antibody testing from 9 - 18 months of age.

e. Where virilogical testing is not readily available HIV antibody testing should be performed, it may be necessary to make a presumptive clinical diagnosis of severe HIV disease in HIV seropositive children (see Box 1). Confirmation of diagnosis should be sought as soon as possible.

V. When to Start: Antiretroviral Therapy in Infants and Children

The decision-making process for initiation of ART in infants and children relies on clinical and/or immunological assessment;

To facilitate scale up to universal access of ART, WHO emphasises the importance of clinical parameters. This approach aims at enabling all children needing treatment to receive it, even if the diagnosis of HIV is presumptive and if CD4 is not available. However, where possible, using the results of CD4 measurements is valuable, particularly for decisions about starting therapy in less sick children (MOH and its partners has increased access to CD4 measurement technologies across the country). Decision-making about starting treatment is particularly important for children aged less than 12 months; because the probability of death in untreated HIV-infected children is high (36, 37), with reported mortality rates of up to 40% by the age of 1 year (35, 38).

The decision about when to start ART should also involve the evaluation of the social environment of the child needing therapy.

This should include the identification of a clearly defined caregiver who understands the prognosis of HIV and the implications of ART (i.e., the fact that it is a life-long therapy; implications of non-adherence; administration, toxicities and storage of drugs). Access to nutritional support (see section XIV) and family support groups, including identification of a secondary (back up) informed caregiver, are important when making decisions about the initiation of ART.

Clinical Assessment of HIV Infected Children

The WHO Paediatric Clinical Classification of HIV related disease has recently been revised and is now harmonised with the adult classification system (Table 2).

Table 2. WHO classification of HIV-associated clinical disease[a]

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

Notes: Annex A & B provides further details on staging events and criteria for recognising them.

Box 1: WHO staging for children with established HIV infection

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 infection (otitis media, otorrhea, sinusitis, tonsillitis) Fungal nail infections
Clinical stage 3
Unexplained moderate malnutrition not adequately responding to standard therapy Unexplained persistent diarrhea (14 days or more) Unexplained persistent fever (above 37.5 intermittent or constant, for longer than one month) Persistent oral Candida (outside first 6-8 weeks of life) Oral hairyleukoplakia Acute necrotizing ulcerative gingivitis/periodontitis Lymph node TB Pulmonary tuberculosis Severe recurrent presumed bacterial pneumonia Symptomatic lymphoid interstitial pneumonitis Chronic HIV-associated lung disease including bronchiectasis Unexplained anemia (<8g/dl), neutropenia (<05 x 109) or chronic thrombocytopenia (<50 x 109/l3)
Clinical stage 4
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 >one month' s duration or visceral at any site) Extra pulmonary tuberculosis Kaposi sarcoma Esophageal candidacies (or Candida of trachea, bronchi or lungs) Central nervous system toxoplasmosis (outside the neonatal period) HIV encephalopathy Cytomegalovirus (CMV) infection; retinitis or CMV infection affecting another organ, with onset at age >1 month. Extra pulmonary cryptococcosis including meningitis Disseminated endemic mycosis (extra pulmonary histoplasmosis, coccidiomycosis, penicilliosis) Chronic Cryptosporidiosis Chronic Isosporiasis Disseminated non-tuberculous mycobacteria infection Acquired HIV-associated rectal fistula Cerebral or B cell non-Hodgkin lymphoma Progressive multifocal leukoencephalopathy HIV-associated cardiomyopathy or HIV-associated nephropathy
Notes: a. Diagnosis of HIV infection according to recommendations in Section IV b. All clinical events or conditions referred to are described in Part B of this Annex

V. When to Start: Antiretroviral Therapy in Infants and Children

Clinical staging is for use where HIV infection has been confirmed (i.e. serological or virological evidence of HIV infection).

It is informative for assessment at baseline or entry into HIV care and can also be used to guide decisions on when to start CPT in HIV-infected children over age 1 year. *(**note:** all HIV-exposed children and HIV-infected children under age 1 year should receive CPT from 6 weeks of age, which should ideally be started prior to the child having a clinical need for ART)* and other HIV-related interventions including when to start, switch or stop ART in HIV-infected children, particularly in situations where CD4 is not available. Annex B provides further details of the specific staging events and the criteria for recognising them.

A preliminary analysis of WHO staging based on clinical signs at baseline and disease history in children enrolled in the Children with HIV Antibody Prophylaxis (CHAP) trial(39) showed that clinical stage without ART can predict mortality; however, this was heavily dependent on the malnutrition criteria in the staging definitions (D. Gibb, unpublished observations, 2005). *Therefore, the clinical stage indicates the urgency with which to start ART* (Table 4). Treatment with a potent and efficient ARV regimen improves clinical status and effectively reverses the clinical stage.

Immunological Assessment of HIV Infected Children

It is also possible to measure the immunological parameters of the HIV-infected child and assess the severity of HIV-related immunodeficiency to guide decision on initiation of ART; *results of CD4 measurement should be used in conjunction with clinical assessment.* The CD4 and the total lymphocyte count (TLC) 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 about 6 years of age. *In considering the results of immunological parameters age must therefore be taken into account as a variable.* In children less than 5 years of age, the absolute CD4 count tends to vary within an individual child more than the %CD4. Therefore, the measurement of the %CD4 is more valuable in children less than 5 years of age. Absolute CD4 counts (and less so % CD4) fluctuate with intercurrent illness, physiological changes, or test variability. Serial measurements are therefore more informative than individual values and also reflect trends over time. Where possible, these assessments should be based on the same parameter; i.e., either absolute CD4 count or %CD4. As with clinical status, immunological recovery occurs with successful ART. Because of the variability of both CD4 (% and absolute count), *if possible, two values below threshold should be obtained prior to initiation of ART based on immunological criteria alone, particularly before starting a child on ART with no or mild symptoms of HIV* (i.e., Clinical Stage 1 and 2) (3, 40-42). Results of CD4 measurement are also useful to monitor responses to treatment.

The threshold CD4 levels for severe immunodeficiency (i.e., <25% for infants ≤11 months, <20% for children aged 12-35 months, or <15% for children aged 3 years and older) (see Table 3) are derived from longitudinal data on HIV-infected infants and children, and, except in children aged less than1 year, correspond to a 12 month mortality risk of 5% or less (43), (D. Dunn, unpublished observations, 2006). *It should be noted that in young infants (under 6 months of age), %CD4 or absolute CD4 count is less predictive of mortality, as there is a high risk of death even at high %CD4* (e.g., CD4 >25% or 1500 cell s/mm3).

V. When to Start: Antiretroviral Therapy in Infants and Children

These thresholds also indicate the level at or below which ART is indicated. Where %CD4 is not available, absolute CD4 count thresholds may be used (i.e., <1500 cells/mm for infants aged ≤11 months, <750 cells/mm for children aged 12-35 months, or <350 cells/mm for children aged 36-59 months). For children 5 years of age and older, the same cut-off value as in adults, i.e., <200 cells/mm, can be used (Table 3). *Asymptomatic HIV-infected children (i.e. those with Clinical Stage 1 and 2 diseases) should be considered for ART when immunological values begin to drop to values close to the described threshold values.* A drop below threshold values should be avoided.

It needs to be emphasised that *severe HIV-related disease always requires ART irrespective of whether defined clinically or immunologically.* Advanced HIV disease also requires initiation of ART, whether defined clinically or immunologically (see Table 2). However, in children aged 12 months and older with clinically advanced HIV disease who have specific Clinical Stage 3 conditions, including tuberculosis, lymphocytic interstitial pneumonia, thrombocytopenia and oral hairy leukoplakia, CD4 measurements are useful in determining the immediate need for therapy: a CD4 level >20% in children aged 12 to 35 months of age or >15% in 36 to 59 months and >200 cells/mm in children 5 years of age and older may suggest that it is reasonable to delay the start of ART. For children with pulmonary or lymph node tuberculosis, the result of CD4 measurement and clinical status should guide whether ART is urgently required or can be delayed (Section XIII). The table below provides an overview of the WHO revised immunological classification.

As in HIV-infected adults, the total lymphocyte count (TLC) significantly predicts the risk of mortality in HIV-infected children (44). The recommended thresholds (i.e., a TLC of <4000 cells/mm^3 for children aged ?11 months, <3000 cells/mm^3 for children aged 12-35 months, <2500 cells/mm^3 for children 3-5 years of age, <2000/mm for children 5-8 years of age) (Table 6) define similar mortality risks as the CD4 thresholds (45). As for %CD4 and absolute CD4 count, the predictive value of TLC for mortality in very young children (i.e., less than 6 months of age) is poor, where high mortality can occur even at high TLC values. Therefore, in situations where CD4 measurements are not available, TLC maybe used as an indication for the need to initiate ART in infants or children up to 8 years of age with WHO Paediatric Clinical Stage 2 disease. There are less data available to make recommendations on the use of TLC for decision-making in children older than 8 years of age.

Table 3: WHO Classification of Human Immune Deficiency Virus Associated Immunodeficiency in Infants and Children

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

Source: Based on WHO global and regional consultation & data [3]

V. When to Start: Antiretroviral Therapy in Infants and Children

As stated above, it is desirable that an abnormal TLC or CD4 (% or absolute count) be confirmed with a second test before therapeutic decisions are made but it is recognised that this may not always be possible. The figure in Annex D illustrates the 12 month mortality risk at selected thresholds for %CD4, absolute CD4 count and TLC.

Table 4 summarises the recommendations for initiating ART in HIV infected infants and children according to clinical stage and availability of immunological markers. Table 5 lists the CD4 criteria for severe immunodeficiency and Table 6 the TLC criteria for initiating ART in infants and children.

Table 4. Recommendations for initiating ART in HIV infected infants and children according to clinical stage and availability of immunological markers

<table>
<tr><th rowspan="2">WHO Paediatric Stage</th><th rowspan="2">Availability of CD4 cell measurements</th><th colspan="2">WHO</th></tr>
<tr><th>Age Specific Treatment Recommendation
<12 months</th><th>≥12 months</th></tr>
<tr><td rowspan="2">4[a]</td><td>CD4</td><td colspan="2" rowspan="2">Treat all</td></tr>
<tr><td>NoCD4[b]</td></tr>
<tr><td rowspan="2">3[a]</td><td>CD4</td><td rowspan="2">Treat all</td><td>Treat all CD4 guided in those children with TBc, LIP, OHL, thrombocytopenia</td></tr>
<tr><td>NoCD4[b]</td><td>Treat all[c]</td></tr>
<tr><td rowspan="2">2</td><td>CD4</td><td colspan="2">CD4-guided[d]</td></tr>
<tr><td>NoCD4[b]</td><td colspan="2">TLC-guided</td></tr>
<tr><td rowspan="2">1</td><td>CD4</td><td colspan="2">CD4-guided[d]</td></tr>
<tr><td>NoCD4[b]</td><td colspan="2">Do not treat</td></tr>
</table>

LIP -lymphocytic interstitial pneumonia; OHL-Oral hairy leukoplakia; TB-tuberculosis
* Strength of recommendation/level of evidence Notes:

a) Stabilise any opportunistic infection prior to initiation of ARV therapy.
b) Baseline CD4 is useful to monitor ART even if it is not required to initiate ART.
c) In children with pulmonary or lymph node tuberculosis, the CD4 level and clinical status should be used to determine the need for and timing of initiation of ART in relation to tuberculosis treatment (see section XIII).
d) d. For CD4 or TLC values, refer to Tables 5 and 6, respectively.

V. When to Start: Antiretroviral Therapy in Infants and Children

Table 5: Criteria for Severe HIV Immune Deficiency

Immunological Marker[a]	Age specific recommendation to initiate ART			
	≤11 months	12 months-35 months	36 months - 59 months	≥5 years
CD4 %[c]	**<25%**	**<20%**	**<15%**	**<15%**
CD4 count[c]	<1500 cells/mm3	<750 cells/mm3	<350 cells/mm3	<200 cells/mm3

Notes:
* Strength of recommendation/level of evidence

a) Immunological markers supplements clinical assessment and should therefore be used in combination with clinical staging; ideally, CD4 is measured after stabilisation of acute presenting conditions.

b) ART should be initiated by these cut-off levels, regardless of clinical stage; a drop of CD4 below these levels significantly increases the risk of disease progression and mortality.

c) % CD4 is preferred for children<5 years of age.

Table 6: TLC criteria of severe HIV immunodeficiency requiring initiation of ART; suggested for use in infants and children with clinical stage 2 and where CD4 measurement is not available

Immunological Marker[a] [C(II)]*	Age specific recommendation to initiate ART			
	≤11 months	12 months-35 months	36 months - 59 months	≥5 years
TLC	<4000 cells/mm^3	<3000 cells/mm^3	<2500 cells/mm^3	<2000 cells/mm$^{3(e)}$

Notes:
* Strength of recommendation/level of evidence

a) Immunological markers supplement clinical assessment and should therefore be used in combination with the clinical staging.

b) A drop of TLC below these levels significantly increases the risk of disease progression and mortality.

c) There are fewer data available to make recommendations on the use of TLC for decision-making in children older than 8 years of age.

An assessment of viral load (e.g. using plasma HIV-1 RNA levels) is not considered necessary before starting therapy.

Because of the cost and complexity of viral load testing, its routine use is not currently recommended to assist with decisions on when to start therapy. It is hoped, however, that increasingly affordable methods of determining viral load will become available so that this adjunct to treatment monitoring can be more widely employed.

V. When to Start: Antiretroviral Therapy in Infants and Children

Criteria for Starting ART in Infants and Children with Presumptive Diagnosis of Severe HIV Disease:

For situations where access to virological testing is not yet available, WHO has developed clinical criteria to diagnose presumptively severe HIV disease in a child less than18 months of age to allow appropriate management of the potentially HIV-infected child (annex B).

Presumptive clinical diagnosis of severe HIV-related disease warrants the appropriate management of the presenting acute illnesses first and institution of, or referral for, management of presumed HIV infection, which may include initiation of ART.

Use of a presumptive clinical diagnosis of infection in a child under the age of 18 months for initiation of ART should be accompanied by immediate efforts to establish the HIV diagnosis with a DNA PCR, but at the latest with HIV antibody testing at 18 months of age. Decisions on further treatment should be adjusted at that time by the results. Infants and children started on ART based on a presumptive clinical diagnosis of severe HIV disease, therapy should be closely monitored. Those infants and children who are no longer exposed to HIV (i.e., through breastfeeding from an HIV-infected mother) and where HIV infection can be confidently ruled out ART should be stopped.

Initiation of ART based on presumptive clinical diagnosis of severe HIV disease is not recommended for use by clinical care providers who are not appropriately trained in HIV care or administration of ART.

Use of clinical criteria to make a presumptive diagnosis of HIV infection is not needed in children18 months of age and older as antibody testing establishes HIV infection status. It is recommended that children <18 months of age be referred to a level I or II hospital for initiation of ART.

V. When to Start: Antiretroviral Therapy in Infants and Children

Box 2 lists the criteria for presumptive clinical diagnosis and Box 3 summarises the WHO recommendations for starting ART in infants and children.

Box 2. Clinical criteria for presumptive diagnosis of severe HIV disease in infants and children less than 18 months of age requiring ART in situations where virological testing is not available [B (IV)]*

A presumptive diagnosis of severe HIV disease should be made if:

- the infant is confirmed HIV antibody positive;

and

- diagnosis of any AIDS-indicator condition(s)a can be made;

or

- the infant is symptomatic with two or more of the following
  - o Oral thrushb
  - o Severe pneumoniab
  - o Severe sepsis b

Other factors that support the diagnosis of severe HIV disease in an HIV seropositive infant include:

- Recent HIV-related maternal death; or advanced HIV disease in the mother;
- CD4 < 20%c

Confirmation of the diagnosis of HIV infection should be sought as soon as possible.

Notes:

- *Strength of recommendation/level of evidence

a. AIDS indicator conditions include some but not all HIV paediatric clinical stage 4 conditions, such as PCP, cryptococcal meningitis, HIV wasting, KS & extra pulmonary TB

b. As per IMCI definition:

° Oral thrush: Creamy white to yellow soft small plaques on red or normally colored mucosa which can often be scraped off (pseudo membranous), or red patches on tongue, palate or lining of mouth, usually painful or tender. Not responding to topical antifungal treatment.

° Severe pneumonia: Cough or difficult breathing in a child with chest in-drawing, 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 such as fast breathing, chest in-drawing, bulging fontanel, lethargy, reduced movement, not feeding or sucking breast milk, convulsions etc

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

V. When to Start: Antiretroviral Therapy in Infants and Children

Box 3. Summary of WHO recommendations for ART initiation in infants and children

a. Infants and children with established HIV infection should be started on ART if they have:

- WHO Paediatric Clinical Stage 4 disease (irrespective of CD4)
- WHO Paediatric Clinical Stage 3 disease (irrespective of CD4 although it may add guidance); for children aged older than12 months with tuberculosis or lymphocytic interstitial pneumonia or oral hairy leukoplakia or thrombocytopenia, if CD4 is available, ART initiation maybe delayed if CD4 is above threshold valuesa to initiate ART;
- WHO Paediatric Clinical Stage 2 disease and CD or TLCb value at or below threshold
- WHO Paediatric Clinical Stage 1 disease and CD4 value at or below threshold.

b. Where virological testing is not available to confirm HIV infection HIV antibody positive infants and children less than18 months of age should be considered for ART if they have clinically diagnosed Presumed Severe HIV diseasec .

Notes:

a. Threshold values for CD4 are provided in Table 5.

b. Threshold values for TLC are provided in Table 6. TLC is most useful for decisions in infants and children with clinical stage 2 and should only be considered where CD4 measurement is not available.

c. Criteria for clinical diagnosis of Presumptive Severe HIV Disease are provided inbox 1.

VI. What to Start - Recommended Firstline ARV Regimens in Infants and Children

Considerations for Treatment Using a Public Health Approach

Zambia has adopted a public health approach to support and facilitate wider access to ART. Among the key tenets of this approach are standardisation and simplification of ARV regimens. A limited number of first-line regimens and suitable second-line regimens have been selected, recognising that *individuals who cannot tolerate or fail the first-line and second-line regimens may require input from more experienced physicians.* The use of three ARV medications is currently the standard treatment for HIV infection for best suppression of viral replication and to arrest the progression of HIV disease. Maximising the durability and efficacy of any first-line regimen by incorporating approaches that support adherence is important when designing a treatment plan.

When selecting appropriate ARV regimens, programme level factors were taken into consideration. These include

- Ability to treat all ages;
- Suitability of drug formulation, partic larly for infants and young children, including where possible licensing approval by national drug regulatory authority for the product and recommended dose;
- Toxicity profile, including teratogenicity;
- Laboratory monitoring requirements;
- Potential for maintenance of future treatment options;
- Anticipated patient adherence (including consideration of drug regimens taken by parents or caretakers, as appropriate);
- Prevalent co-existent conditions (e.g. co-infections, malnutrition, malaria, TB and Hepatitis B);
- Availability and cost effectiveness.
- Capacity of drug procurement and supply systems

Access to a limited number of ARV drugs in forms suitable for treatment of infants and young children may be further influenced by; limited health service infrastructures (including human resources); the high prevalence of malnutrition; other frequently occurring infections such as Malaria, TB and possibly hepatitis B and C in infants and children; and the presence of varied HIV may further influence the choice of an appropriate ARV regimen.

Considerations for Drug Formulations and Doses for Children

Quality-assured ARV drugs in fixed-dose combinations (FDCs) or as blister packs, are mostly used in adults and older children and hopefully will be available in the future for administration to younger children. Once daily dosing becomes available for some adult ARV combinations it will further simplify drug regimens. Advantages of FDCs and once daily dosing include improved adherence which, in turn, limits emergence of drug resistance as well as simplifies ARV storage and distribution logistics. *WHO strongly encourages the development of formulations appropriate for paediatric use, particularly solid formulations (e.g. crushable, dispersible, granular, scored tablets or capsules that can be opened) in doses that can be used by paediatric patients.* Syrups and solutions remain necessary for treating infants and very young children who cannot swallow whole tablets or capsules but they have shortcomings; these may include limited availability, increased cost, storage difficulties, reduced shelf life, unsuitable excipients and poor palatability. As the child gets older, it is preferable to give solid formulations (parts of scored tables

VI. What to Start - Recommended Firstline ARV Regimens in Infants and Children

or combination preparations). For some ARVs, capsules and tablets are available in sufficiently low doses to enable accurate dosing for children. The pharmacokinetics of some crushed tablets or sprinkled capsule contents have been evaluated. However, many drugs do not have solid formulations in doses appropriate for paediatric use; some solid formulations do not have all drug components evenly distributed in the tablets or others do not have pharmacokinetic data to enable accurate dosing.

While satisfactory virological and immunological benefits in children receiving an adult fixed-dose combination of stavudine/lamivudine/nevirapine (d4T/3TC/NVP) tablet in fractions were reported from Thailand (46), and Uganda (47), the use of tablets that require cutting up, particularly unscored tablets, can result in the underdosing or overdosing of children, which can lead to an increased risk of resistance or toxicity. Moreover, the doses cannot easily be adjusted as the children grow which may further contribute to underdosing. The splitting of adult-dose solid formulation ARVs, while sub-optimal, may however be the best currently available option when no alternatives are available for treatment of children as soon as feasible (usually by weight 13-15 kg), and may be considered. The use of pill cutters will improve this but ideally pills should not be cut below fractions of a half. Pharmacokinetic studies in Malawian children confirm that single drug liquid formulations are better than splitting adult FDCs for smaller children (48). *Therefore it is recommended that children <12kg be prescribed liquid formulations.*

Dosing in children is usually based on either body surface area or weight (49). As these change with growth, drug doses must be adjusted in order to avoid the risk of under dosage.

Standardisation is important and it is desirable to provide health care workers with a table of simplified drug doses that can be administered according to weight bands. Health care providers should be aware that current fixed-dose combination formulations for use in adults may not contain the appropriate doses of each of the component drugs for children on a weight basis. This is a specific problem for the NVP component of some adult-size fixed-dose formulation of zidovudine/lamivudine/nevirapine (AZT/3TC/NVP) and stavudine/lamivudine/nevirapine (d4T/3TC/NVP), and additional NVP may be necessary if tablets are used to treat younger children (Annex E). Fixed dose formulations for children became available in late 2005 and include d4T/3TC/NVP in different strengths.

i. Quality-assured medicines assembled in fixed-dose combinations (FDCs)-products which have been deemed to meet or exceed international standards for quality, safety and efficacy.

ii. FDCs include two or more active pharmacological products in the same pill, capsule, granules, tablet or solution.

iii. A blister pack is a plastic or aluminum blister containing two or more pills, capsules or tablets.

VI. What to Start - Recommended Firstline ARV Regimens in Infants and Children

Considerations for the Choice of a First-line Regimen

Studies of antiretroviral therapy in children demonstrate that similar improvements are seen in morbidity, mortality and surrogate markers with many different potent ARV regimens as in adults (37, 50-53). The preferred option when choosing a first line regimen for infants and children is a reverse transcriptase inhibitor (RTI)-based regimen which consists of two nucleoside reverse transcriptase inhibitors (NRTIs) plus one non-nucleoside reverse transcriptase inhibitor (NNRTI) (Box 4). NRTI/NNRTI-based regimens are efficacious, generally less expensive, generic formulations are more often available and a cold chain is not required. In addition, they preserve a potent new class (i.e., protease inhibitors [PI]) for second-line. Disadvantages include different half lives, the fact that a single mutation is associated with the resistance to some drugs (e.g., lamivudine [3TC], NNRTIs), and for the NNRTI drugs a single mutation can induce resistance to all currently available drugs in the class.

Active components of these regimens may include a thymidine analogue NRTI (i.e., stavudine [d4T] or zidovudine [AZT]) or a guanosine analogue NRTI (i.e., abacavir [ABC]), combined with a cytidine NRTI, (i.e., 3TC), and an NNRTI (i.e., efavirenz [EFV] or nevirapine [NVP]). A caveat is that EFV is not currently recommended for use in children less than 3 years of age or weighing less than 10kg because of a lack of appropriate dosing information, although these matters are under study. Consequently, for children aged less than 3 years or weighing less than 10 kg, NVP is the recommended NNRTI. Additional concerns of NNRTIs as components of first-line regimens relate to their use in adolescents (see Section XV); these include the teratogenic potential of EFV in the first trimester of pregnancy and the hepatotoxicity of NVP in adolescent girls with CD4 absolute cell counts >250/mm. Available data in infants and children indicate a very low incidence of hepatic toxicity with NVP without association with CD4 count (54).

The use of a triple NRTI regimen (i.e., AZT/d4T plus 3TC plus ABC) can be considered as an option for simplifying initial therapy in special circumstances (Box 4), but has somewhat lower virological potency compared to a two-class triple drug combination in adult studies (55-58) and therefore its use is currently recommended for use in *restricted special circumstances, in particular for infants and children receiving TB treatment, a situation where NVP may not be an optimal choice because of drug interactions with rifampicin* (see Section XIII). *Another possible indication for the use of a triple NRTI regimen is treatment of pregnant adolescent girls* with CD4 absolute cell counts >250/mm in which both NVP and EFV have contraindications. This regimen, especially where combined in a single pill, could also be considered in adolescents with anticipated or documented poor adherence (see Section XV).

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Box 4. Summary of recommended preferred first-line ARV regimens for infants and children

Regimen of 2 NRTI plus 1 NNRTIa: [A (II)]*
AZTb +3TCc +NVPd/ EFVe
d4Tb +3TCc +NVPd/ EFVe
ABC +3TCc +NVPd/ EFVe

Notes:

* Strength of recommendation/level of evidence

a) The use of AZT, d4T, ABC with 3TC results in several possible dual nucleoside combinations including AZT +3TC; d4T +3TC; ABC +3TC.

b) AZT should not be given in combination with d4T.

c) Where available, FTC can be used instead of 3TC in children older than 3 months of age.

d) NVP should be avoided in post pubertal adolescent girls (considered as adults for treatment purposes) with baseline CD4 absolute cell counts >250/mm3.

e) EFV is not currently recommended for children <3 years of age or < 10kg, and should be avoided in post pubertal adolescent girls who are either in 1st trimester of pregnancy or are sexually active and not receiving adequate contraception

Box 5. Recommended alternative ARV regimen for infants and children to simplify management of toxicity, co morbidity and drug-drug interaction

Regimen of Triple NRTI: [C (III)]*
AZT/ d4Ta +3TCb +ABC

Notes:

* Strength of recommendation/level of evidence

a. AZT should not be given in combination with d4T

b. Where available, FTC can be used instead of 3TC.

VI. What to Start - Recommended Firstline ARV Regimens in Infants and Children

Choice of NRTIS

The NRTIs were the first class of antiretroviral drugs available for the treatment of HIV infection. Once they are converted intracellular to active nucleoside metabolites they are potent inhibitors of the HIV reverse transcriptase enzyme which is responsible for the reverse transcription of viral RNA into DNA. The drugs from the NRTI class used within the public health approach are described below.

Lamivudine (3TC) a cytidine analogue, 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 therapy. It is usually given twice daily in children and has been incorporated into a number of fixed-dose combinations.

Emtricitabine (FTC) is a newer cytidine analogue 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 but is not available in Zambia and therefore not recommended for use as of now. FTC is structurally related to 3TC and shares its resistance profile (59). Where available, it can be used in children older than 3 months of age as an alternative to 3TC.

Stavudine (d4T) is a thymidine analogue NRTI that is initially better tolerated than AZT and does not require haemoglobin or laboratory monitoring. However, among the NRTIs, it has been consistently most associated with lipoatrophy (60) and lactic acidosis. In addition, elevated hepatic transaminases and pancreatitis have been observed. d4T can also cause peripheral neuropathy, though these complications are less common in children than in adults (61, 62).d4T liquid formulations require a cold chain and capsule size starts at 15 mg only. While less laboratory monitoring requirements may be a good reason to favor d4T over AZT as the chosen NRTI component, in particular during rapid scale-up of programmes, the risk of widespread lipoatrophy in children treated with d4T-containing regimens remains. It is worth emphasising that d4T and AZT should never be used together because of proven antagonism between them (63, 64) (Box 5).

Zidovudine (AZT) is a thymidine analogue in the NRTI class. Although AZT is generally well tolerated in children, it has also been associated with metabolic complications of therapy but to a lesser extent than d4T. Initial drug-related side-effects are more frequent with AZT and the drug can cause severe anemia and neutropaenia; hemoglobin monitoring before and during treatment with AZT is thus useful. This is particularly important in Zambia a country with stable malaria where anaemia is highly prevalent in young children. Large volumes of AZT liquid formula are often poorly tolerated. d4T can be substituted for AZT in the event of intolerance to the latter and vice versa, except in cases of suspected lactic acidosis in which instance neither drug should be restarted. As noted above, AZT should not be administered in combination with d4T.

Abacavir (ABC) a guanosine analogue, has been included in these paediatric guidelines as an alternative NRTI in first-line therapy and ABC is available in a paediatric formulation. Reports from a randomised, partly blind multi-centre trial comparing dual NRTI regimens (PENTA-5) (65) have shown that ABC-containing dual NRTI regimens (ABC/3TC or ABC/AZT) are more effective than AZT+3TC-containing regimens in children with HIV-1 who have not been previously treated. The results have also suggested a similar safety profile in children to that in

VI. What to Start - Recommended Firstline ARV Regimens in Infants and Children

adults, with very little haematological toxicity. NRTI combinations containing ABC therefore provide a good NRTI backbone for use with NNRTI or as part of a triple nucleoside regimen. Of all the NRTI drugs, ABC has the least effect on mitochondrial DNA (66), ***and is the preferred substitute for d4T in a child who developed lactic acidosis while receiving a d4T-containing regimen. ABC could also be substituted for AZT in the event of intolerance.*** However, ABC is associated with a potentially fatal hypersensitivity reaction in a small proportion of children (about 3%) who receive the drug (65). In infants and children suspected of having a hypersensitivity reaction, ABC should be stopped and not restarted (see Section VIII). ***Children and/or their caregivers should be advised about the risk of this serious hypersensitivity reaction and the need to immediately consult their care provider if signs or symptoms of a hypersensitivity reaction occur.***

Tenofovir (TDF) an adenosine nucleotide analogue, is another drug that has been incorporated by WHO as an effective option for first-line regimens in adults. Due to concerns about the limited data on safety (i.e., bone mineralisation and potential renal toxicity), ***the use of TDF in children is not encouraged until further data becomes available.*** TDF is generally well tolerated (67) although there have been reports of renal insufficiency in adult patients receiving TDF (68-70). There are conflicting studies on whether tenofovir does or does not impair bone mineral accrual while demonstrating a good immunological response to ART (71, 72).

Didanosine (ddI) is an adenosine nucleoside analogue-NRTI usually reserved for second-line regimen.

Box 6. NRTI drug combinations to be avoided[a],

D4T + AZT - both drugs work through common metabolic pathways

D4T + ddIb - these drugs have overlapping toxicities

TDF +3TC +ABCc - associated with high incidence of virologic failure

TDF +3TC +ddI - associated with high incidence of virologic failure + K65R mutation

TDF +ddIb -NNRTI - associated with high incidence of virologic failure

Notes:

a. Based on data from studies performed in adults.

b. Didanosine (ddI) is an adenosine analogue NRTI which is generally reserved for second-line regimens

c. Data from 3 clinical trials involving the combination of TDF +ABC +3TC demonstrated high rates of virologic failure and drug resistance; in light of these concerns and the lack of clinical data, this NRTI backbone should not be used in treatment-naive patients. Another report confirms that ABC and TDF select for K65R mutation which reduces susceptibility to both drugs.

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Choice of NNRTIS

NNRTI-based regimens are now the most widely prescribed combinations for initial therapy. They are potent, i.e. rapidly reduce viral load, but are inactive with respect to HIV-2 and group O of HIV-1 and a single mutation can induce cross-class resistance. The NNRTIs efavirenz (EFV) and nevirapine (NVP) both have demonstrated clinical efficacy when administered in appropriate combination regimens in children. However, differences in toxicity profile, the potential for interaction with other treatments, lack of dosing information for EFV in young children, and cost, are factors that need to be taken into consideration when choosing an NNRTI (75-81).

Efavirenz (EFV) is metabolised via the cytochrome P450 pathway. ***It is not currently recommended for use in infants and children younger than 3 years of age or weighing less than 10 kg 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 adults, is generally mild, and usually does not require discontinuation of therapy. The CNS symptoms typically abate after 10 to 14 days in the majority of patients; observational studies reported the transient CNS disturbance in 26%-36% of children receiving EFV (53, 82). EFV should be avoided in children with a history of severe psychiatric illness, when there is a potential for pregnancy (unless effective contraception can be assured) and during the first trimester of pregnancy. In these situations, NVP maybe the better choice (see below). EFV should be considered as the NNRTI of choice in children with TB/HIV co infection (see Section XIII).

Nevirapine (NVP) is highly lipophylic and widely distributed in the body. As with EFV, NVP is metabolised via cytochrome P 450. ***NVP should only be given in combination with other retroviral drugs, except when used as single-dose prophylaxis as an interim measure 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 above, NVP is also associated with a rare but potentially life-threatening risk of hepatotoxicity. In these situations, NVP should be permanently discontinued and not restarted (see Sections VIII and IX). ***This makes the drug less suitable for treating children who use other hepatotoxic medications, or drugs that can cause rash, or both, such as rifampicin for the treatment of tuberculosis.*** NVP is currently the only NNRTI syrup available for infants. It also exists as part of the three-drug FDC (triomune, duovir-N) used to treat older children.

NVP may be the preferred choice in adolescent girls when there is potential for pregnancy or during the first trimester of pregnancy when EFV cannot be used because of its teratogenic effect. However, symptomatic NVP-associated hepatic or serious rash toxicity, while uncommon, is more frequent in women than in men, and more likely to be seen in antiretroviral-naïve women with higher CD4 cell count (>250 cells/mm3). Thus, NVP should be used with caution in adolescent girls with CD4 count between 250-350 cells/mm3; if used in such adolescent girls, careful monitoring is needed during the first 12 weeks of therapy, ideally including liver enzyme monitoring.

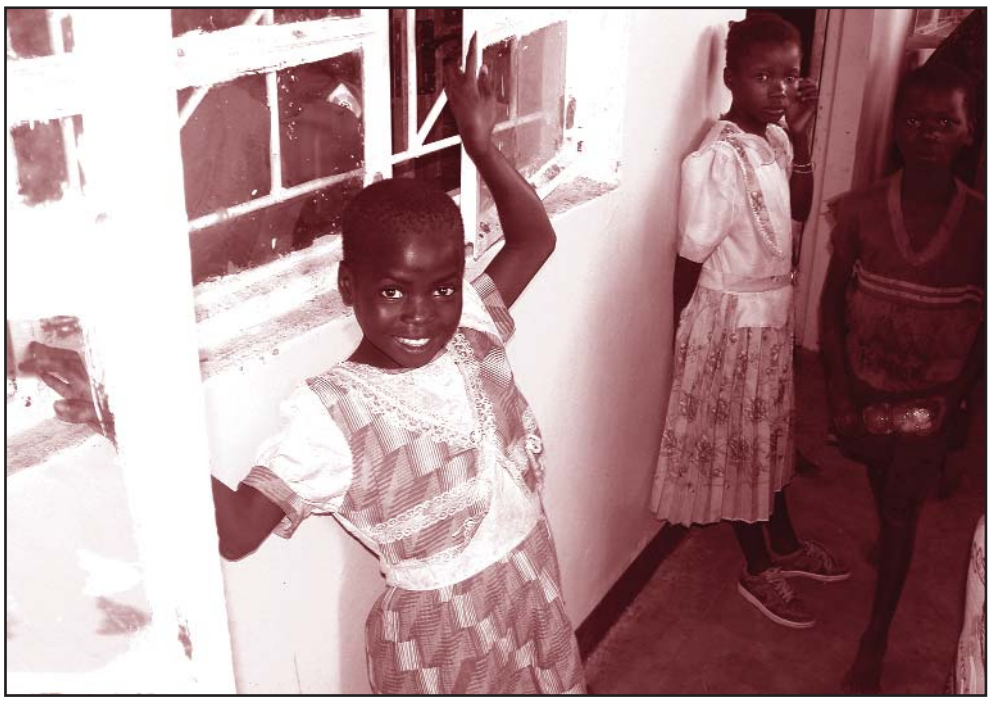
Limited data indicate that both EFV and NVP may interact with oestrogen-based

VI. What to Start - Recommended Firstline ARV Regimens in Infants and Children

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. It is not known if use of preparations such as medroxyprogesterone acetate depot injection, which provide higher blood hormone levels than oral contraceptive, would compromise contraceptive efficacy; studies are under way to evaluate interactions between medroxyprogesterone acetate and selected PI and NNRTI drugs.

Use of Protease Inhibitors (PIS) in Initial Therapy

It is recommended that the PI-class of drugs should be reserved for second-line therapy because their use in an initial treatment regimen compromises any subsequent second-line regimen.



VII. Considerations for ART in Infants Previously Exposed to ARV Drugs

ART in Infants Exposed to ARVs Through Prevention of Mother-to-Child-Transmission

If a mother has received ARVs during pregnancy, either for prophylaxis of transmission of the virus to her infant or for her own disease, there is a possibility that the infant may become infected with drug-resistant virus. Additionally, resistance could be induced de novo in an infected infant who is exposed to an ARV drug being used for prophylaxis (i.e. the infant-portion of prophylaxis for MTCT) before the infection status of the infant is known. This is a particular problem if NVP or 3TC has been used, either alone or as a component of a two-drug regimen, for prophylaxis of MTCT, because a single point mutation is associated with resistance to each of these drugs (83, 84). In HIVNET 012, following single-dose NVP, 46% of infected infants had NNRTI-associated mutations (primarily the Y181C mutation, which may not always be associated with cross-resistance to EFV). As has been observed in mothers, these mutations fade with time but may persist as minor viral subpopulations (83). It is not known whether ARV choices should be modified for infants who have been exposed to ARVs used for PMTCT. Studies in children are in progress, however, until there are data allowing these questions to be definitively answered, *children who require ART and who have previously received single-dose NVP or 3TC as part of PMTCT should be considered eligible for NNRTI-based regimens and should not be denied access to life-sustaining therapy.*

Ongoing Exposure to Anti-retroviral Drugs Due to Maternal ART in Breast Feeding Infants

The penetration of ARVs into human breast milk in lactating women has not been quantified for most ARVs. Although some ARVs, such as NVP, AZT and 3TC, are known to be present in breast milk, the concentration and quantity of drug ingested by infants would be less than those needed to achieve therapeutic levels (32, 85). Consequently, ***if a breastfeeding infant is ill enough to require ART, the administration of ARVs at standard paediatric doses should be initiated regardless of whether the mother is receiving ART,*** but closer monitoring of the infant for potential toxicity should be considered. In addition, it is possible that the ingestion of sub-therapeutic levels of some ARVs by breastfeeding infants could lead to the development of drug resistance in the infant's virus, diminishing the efficacy of the prescribed paediatric regimen, but there are currently no data to address this issue.

Box 7. Summary of recommendations on ART infants and children exposed to ARV drugs [B(IV)]*

- Infants who were exposed to ARVs through prevention of mother-to-child-transmission, either during the maternal or infant portion
- Breastfeeding infants who are exposed to antiretroviral drugs due to maternal ART

Should be considered eligible for the standard 2 NRTI + 1 NNRTI firstline ARV regimen using the same doses and criteria as outlined in Sections V and VI.

Research is urgently needed to identify the efficacy of ART in infants with prior or ongoing exposure to ARVs

Notes: * Strength of recommendations

VIII. Antiretroviral Drug Toxicity

Differentiating between complications of HIV disease and toxicity (i.e., also known as adverse events) secondary to ARV drugs used for the management of HIV infection is sometimes difficult. Alternative explanations for the toxicity must be excluded before it is concluded the toxicity is secondary to the ARV drug. Alternative explanations for an observed toxicity could include a concurrent infectious process (for example, common childhood illnesses including hepatitis A virus infection in a child with symptoms of hepatitis, or malaria in a child with severe anaemia), or a reaction to a non-ARV drug that is being given concurrently with the ARV drugs (such as isoniazid-induced hepatitis in a child on tuberculosis treatment or cotrimoxazole-induced rash in a child receiving cotrimoxazole preventive therapy). Adverse reactions that have a non-ARV drug etiology do not require change of the ARV drug. However, because of the risk of potentially life threatening hepatotoxicity associated with NVP, hepatic dysfunction of any etiology requires careful consideration of discontinuation of NVP.

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 (86). However, the full spectrum of ARV toxicities observed in adults are less common in children (e.g., NVP-related symptomatic hepatotoxicity is rare in children), while others are more common in children than adults (e.g., EFV-related rash) or occur only in children (e.g., TDF-related loss of bone density). More attention needs to be paid to pharmacovigilance and post-marketing surveillance hence the need to develop an adverse event form and reporting system.

Drug-related adverse events can be **acute**, occurring soon after the drug was administered; **sub acute**, occurring within 1-2 days of administration; or **late**, occurring after prolonged drug administration. Additionally, adverse events can vary in severity from mild to severe and life-threatening, they include:

- *Haematologic adverse events* from drug induced bone marrow suppression, most commonly seen with AZT therapy (anaemia, neutropenia, and more rarely thrombocytopenia.
- *Mitochondrial dysfunction*, primarily seen with the NRTI drugs, including lactic acidosis, hepatic toxicity, pancreatitis, and peripheral neuropathy (the NRTIs differ in their ability to affect mitochondrial function, with d4T having greater toxicity than AZT, and 3TC or ABC even less so);
- *Lipodystrophy and metabolic abnormalities*, primarily seen with d4T and the PI class, and less, but also with, certain other NRTI drugs (abnormalities include fat maldistribution and body habitus changes; hyperlipidaemia; hyperglycemia, insulin resistance, and diabetes mellitus; and osteopenia, osteoporosis, and osteonecrosis);
- *Allergic reactions* such as skin rashes and hypersensitivity reactions, more common with the NNRTI drugs but also seen with certain NRTI drugs, such as ABC.

Toxicity can be monitored clinically on the basis of child/guardian reporting and physical examination, and assessed also through a limited number of laboratory investigation tests, depending on the specific ARV combination regimen that is utilised and the health care setting. Routine laboratory monitoring, although desirable, is not required and cannot be carried out in many decentralised facilities.

VIII. Antiretroviral Drug Toxicity

The management of the patient and the decision about the potential need to stop drugs or to substitute a new ARV drug for the drug associated with the toxicity largely depends on the ability to attribute the toxicity to a specific ARV drug in the treatment regimen and on the severity of the toxicity symptoms (Box 5). Given the limited number of ARV drugs and drug combinations currently available in Zambia, it is preferable to pursue drug substitutions where feasible, so that premature switching to completely new alternative regimens is minimised, and also to restrict drug substitutions to situations where toxicity is severe or life-threatening.

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). Some *moderate or severe toxicities* may require substitution of the ARV drug associated with toxicity with a drug in the same ARV class but with a different toxicity profile, but do not require discontinuation of all ART. Severe *life threatening toxicity* may require discontinuation of all ARV drugs and initiation of appropriate supportive therapy (such as intravenous fluids) depending on the toxicity, with substitution of another drug for the drug associated with the toxicity once the patient is stabilised and the toxicity is resolved (see Annex E). NNRTI drugs have a much longer half-life than NRTIs, leading to a concern that stopping all drugs simultaneously leads to exposure to drugs from the NNRTI class only. However, if the child has a life-threatening toxicity, all ARV drugs should be stopped simultaneously until the patient is stabilised.

Clinical examination can also detect toxicities that are not life-threatening and that may appear late (months to years after therapy has been started), such as lipodystrophy. In such cases, referral to district or regional hospital centers or consultation with an HIV expert is recommended for management.

Regardless of their severity, adverse events may affect adherence to therapy and a "proactive approach" to managing toxicity is recommended. Discussing the potential side effects of the ART regimen prior to therapy initiation and during the early stages of treatment with the child and his/her caregiver, as well as support during minor and moderate adverse events, can increase the likelihood of adherence to therapy (see Section XVII). Most ARV drug toxicities are time-limited and symptoms resolve while ART is being continued. Nevertheless, the child and his/her caregiver should be familiar with signs of toxicities that are serious and require immediate contact with the provider and potential drug discontinuation. This is particularly important for toxicities that can be life-threatening if the ARV drug is not discontinued, such as NVP-associated Stevens Johnson Syndrome or symptomatic hepatitis or ABC-associated hypersensitivity reaction.

VIII. Antiretroviral Drug Toxicity

Box 8. Guiding principles in the management of ARV drug toxicity

1. Determine the seriousness of the toxicity.
2. Evaluate concurrent medications, and establish whether the toxicity is due to (an) ARV drug(s) or due to another non-ARV medication taken at the same time.
3. Consider other disease processes (e.g., viral hepatitis in a child who develops jaundice on ARV drugs) because not all problems that arise during treatment are due to ARV drugs.
4. Manage the adverse event according to severity. In general:
   - Severe life-threatening reactions (Annex E):Immediately discontinue all ARV drugs, manage the medical event (i.e. symptomatic and supportive therapy); reintroduce ARV drugs using a modified regimen (i.e. with an ARV substitution for the offending drug) when patient is stabilised;
   - Severe reactions: Substitute the offending drug without stopping ARTa;
   - Moderate reactions: Consider continuation of ART as long as feasible; if patient does not improve on symptomatic therapy, consider single drug substitutions;
   - Mild reactions are bothersome but they do not require change in therapy.
5. Stress maintaining adherence despite toxicity for mild and moderate reactions.
6. If there is a need to discontinue ART because of life-threatening toxicity, all ARV drugs should be stopped until the patient is stabilised.

Notes:

a. For substitution options, refer to Table 7

IX. Substituting Within a First-line Antiretroviral Drug Regimen in Infants and Children for Drug Toxicity

When the toxicity is related to an identifiable drug in the regimen, the offending drug can generally be replaced with another drug from the same class that does not have the same adverse effect, e.g. substitution of d4T for AZT (e.g., for anaemia) or NVP for EFV (e.g., for CNS toxicity or in the event of pregnancy in adolescent girls). ***Given the limited number of ARV drug options available in Zambia, drug substitutions should be limited to situations where toxicity is severe or life-threatening,*** and substitution of drugs from the PI class for toxicity reasons should be avoided if possible. Table 7 lists the usual ARV substitution options for adverse events for the recommended combination first-line regimens.

For some life-threatening toxicity, it may not be possible to identify an optimal substitute drug. For example, for NVP-associated Stevens Johnson Syndrome, avoid substituting with another NNRTI drug due to the potential for class-specific toxicity. This would require a change to either a triple NRTI regimen (e.g., substituting a third NRTI, such as ABC, for NVP), or substituting a protease inhibitor ARV drug for NVP, thereby introducing a drug class usually reserved for second-line regimens.

Table 7. Severe toxicities in Infants and children associated with specific first-line antiretroviral drugs and potential first-line drug substitutions

First-line ARV drug[a]	Most frequent significant toxicity for the ARV drug	Suggested first-line ARV drug substitution
ABC	Hypersensitivity reaction	AZT
AZT	Severe anemia or neutropaenia[b,c]	d4T or ABC
	Lactic acidosis	ABC
	Severe gastrointestinal intolerance[d]	d4T or ABC
d4T	Lactic acidosis	ABC[e]
	Peripheral neuropathy	AZT or ABC[e]
	Pancreatitis	
	Lipoatrophy/metabolic syndrome[f]	
EFV	Persistent and severe central nervous system toxicity[g]	NVP
	Potential teratogenicity (adolescent girl in1st trimester pregnancy or of childbearing potential not receiving adequate contraception)	

Table continued on following page

IX. Substituting Within a First-line Antiretroviral Drug Regimen in Infants and Children for Drug Toxicity

Table 7. Severe toxicities in Infants and children associated with specific first-line antiretroviral drugs and potential first-line drug substitutions

First-line ARV drug[a]	Most frequent significant toxicity for the ARV drug	Suggested first-line ARV drug substitution
NVP	Acute symptomatic hepatitis[h]	EFV[i]
	Hypersensitivity reaction Severe or life-threatening rash (Stevens-Johnson Syndrome[j]	• a third NRTI (disadvantage, maybe less potent) *or* • PI (disadvantage, premature start of 2nd line ARV drug)[k]
Notes:	**a.** 3TC/FTC -associated pancreatitis has been described in adults but is considered very rare in children. **b.** Exclude malaria in areas of stable malaria. **c.** Defined as severe haematological abnormality that can be life-threatening and that is refractory to supportive therapy. **d.** Defined as severe, refractory gastrointestinal intolerance that prevents ingestion of ARV drug regimen (e.g., persistent nausea and vomiting). **e.** ABC is preferred in this situation; however, where ABC is not available AZT maybe used. **f.** Substitution of d4T typically may not reverse lipoatrophy. In children, ABC or AZT can be considered as alternatives. **g.** Defined as severe central nervous system toxicity such as persistent hallucinations or psychosis. **h.** Symptomatic NVP-associated hepatic toxicity is very rare in HIV-infected children prior to adolescence. **i.** EFV is not currently recommended for children<3 years of age or <10kg, and should not be given to post pubertal adolescent girls who are either in 1st trimester of pregnancy or are sexually active and not using adequate contraception. **j.** Severe rash is defined as extensive rash with desquamation, angioedema, or serum sickness-like reaction; or a rash with constitutional findings such as fever, oral lesions, blistering, facial oedema, conjunctivitis; Stevens-Johnson Syndrome can be life-threatening. For life- threatening rash, most clinicians would not substitute EFV due to the potential for NNRTI-class specific toxicity. **k.** The premature introduction of the PI class of drugs in first-line regimens leads to limitations in the choice of drugs in the event of treatment Failure (i.e. second-line regimens; see Section XI).	

Table carried over from following page

X. Switching an ARV Regimen in Infants and Children: Treatment Failure

Poor adherence, inadequate drug levels, prior existing drug resistance or inadequate potency of the drugs chosen can all contribute to ARV treatment failure (87-90). Genetic differences in drug metabolism may also be important (91, 92). It is recommended that we should primarily use clinical criteria, supported, where possible, with CD4 criteria, in order to define treatment failure. When treatment failure is confirmed, switching to a new second-line regimen becomes necessary[i].

It should **not** be concluded, on the basis of clinical criteria, that an ***ARV regimen is failing until the child in question has had a reasonable trial on the therapy, i.e. the child should have received the regimen for at least 24 weeks, and adherence to therapy assessed and considered to be optimal and any intercurrent opportunistic infections treated and resolved.*** Additionally, before considering changing treatment due to growth failure, it should be ensured that the child is receiving adequate nutrition.

Clinical Definition of Treatment Failure

The WHO Paediatric Clinical Staging System (3) is suggested as a tool to support assessment of disease progression prior to or at start of ART as well as to guide decision-making in the event of suspected treatment failure. The classification of the clinical stage of treatment is designated T1 -T4. ***Treatment failure is defined as the detection of recurrent clinical events classified within the same WHO clinical staging and may reflect progression of disease in a child on ART (either new or recurrent stage 3 or 4 clinical events develop)*** (Table 9). However, pulmonary or lymph node tuberculosis alone, although Clinical Stage 3 conditions (T3), may not be an indication of treatment failure, and thus may not necessitate change to second-line therapy. Response to anti-tuberculosis therapy should be used to evaluate the need for switching therapy (Section XIII).

In children on ART, the main clinical indications to switch therapy are the development of new or recurrent stage 3 or 4 events (i.e., WHO Clinical Stage T3 or T4) at least 24 weeks after starting therapy with a first-line regimen.

Clinical indications to switch therapy:

- Lack of, or decline in growth rate in children who showed an initial response to treatment (WHO Paediatric Clinical Stage T3 or T4 - moderate or severe unexplained malnutrition not adequately responding to standard therapy despite adequate nutritional support and without other explanation) (93, 94); *or*
- Loss of neurodevelopmental milestones (94) or development of encephalopathy (WHO Paediatric Clinical Stage T4) (95); *or*
- Occurrence of new opportunistic infections or malignancies, or recurrence of infections, such as oral candidacies that are refractory to treatment, or oesophageal candidacies (WHO Paediatric Clinical Stage T3 or T4).

i Switching a regimen for a failure should not be confused with substitution of a single drug for toxicity (see Section IX).

X. Switching an ARV Regimen in Infants and Children: Treatment Failure

Immune reconstitution syndrome

Clinical disease progression should be differentiated from the immune reconstitution syndrome (IRS), an entity that has been observed in adults, and less frequently in children starting ART, particularly those with very low CD4 values (96-101). Symptoms are similar to those seen in opportunistic infections. They usually occur within the first 3 months after the start of a potent ART (102), concurrent with a rapid rise of CD4 values. It is also possible that this immunological reconstitution may lead to the development of atypical presentations of some opportunistic infections.

Table 8. Using the WHO Paediatric Clinical Staging System to guide decision-making for switching to second-line therapy for treatment failure

WHO Clinical Stage on ART[a]	Management options[b]
T1 No new event or PGL	• **Do not switch to other regimen** • Maintain scheduled follow up visits including CD4
T2 Stage 2 events	• **Treat and manage staging event** • **Do not switch to new regimen** • Assess and offer adherence support • Assess nutritional status and offer support • Schedule earlier visit for clinical review and consider CD4
T3 Stage 3 events	• **Treat and manage staging event and monitor response c, d, e** • Check if on treatment 24 weeks or more • Assess and offer adherence support • Assess nutritional status and offer support • Check CD4 -where available • Institute more frequent follow up • **Consider switching regimen**
T4 Stage 4 events	• **Treat and manage staging event** • Check if on treatment 24 weeks or more • Assess and offer adherence support • Assess nutritional status and offer support • Document CD4[f] where available • **Switch regimen**

Notes:

a. Clinical stages in this table refer to a new or recurrent stage at the time of evaluating the infant or child on ART. Annex B provides more details about the revised WHO Paediatric Clinical Staging System.

b. It must be ensured that the child has had at least 24 weeks of treatment trial; adherence to therapy has been assessed and considered to be adequate prior to considering switching to second-line regimen.

c. Differentiation of opportunistic infections from immune reconstitution syndrome is important.

d. In considering changing treatment because of growth failure, it should be ensured that the child is not failing to grow due to lack of adequate nutrition, and that any intercurrent infections have been treated and resolved.

e. Pulmonary or lymph node TB, Clinical Stage 3 conditions, may not be an indication of treatment failure, and thus not require consideration of second-line therapy; response to tuberculosis therapy should be used to evaluate the need for switching of therapy (Section XIII).

f. CD4 is best performed once acute phase of presenting is resolved.

X. Switching an ARV Regimen in Infants and Children: Treatment Failure

Immunological Definition of Treatment Failure

Immunological treatment failure can be identified by examining baseline CD4 and the initial immunological response to ART. ***Treatment failure is usually characterised by a drop in the CD4 to values at or below their age-related CD4 threshold for initiation of treatment after initial immune recovery*** following initiation of ART. It is also possible that children on ART may persist at or below their age-related CD4 threshold for initiation of treatment despite an adequate trial of therapy (e.g. at least 6 months of ART). Thus, ***defining treatment failure based on immunological values relies on previous CD4 values.*** Immunological criteria for defining treatment failure are supplemental to clinical criteria (Box 7 and Table 9).

Box 9: CD4 criteria to guide decision-making on switching to a second-line regimen

a. Development of age-related severe immunodeficiency after initial immune recovery c;

b. New progressive age related severe immunodeficiency, confirmed with at least one subsequent CD4 measurement c;

c. Rapid rate of decline to at or below threshold of age-related severe immunodeficiency c.

a) It must be ensured that the child has had at least 24 weeks of treatment trial; adherence to therapy has been assessed and considered to be adequate prior to considering switching to second-line regimen.

b) At least two CD4 measurements should be available.

c) Age-related severe immunodeficiency values as defined in Table 5; use of %CD4 in children less than 5 years of age and absolute CD4 count after 5 years of age is preferred. If serial CD4 values are available, the rate of decline should be taken into consideration.

Use of Clinical and Immunological findings for Decision-making Regarding Switching ART

CD4 values supplement clinical findings when making decisions about switching therapy (Box 10 and Table 9). Although children with new Clinical Stage T4 conditions should be considered for switching therapy regardless of CD4 value, for children who develop Clinical Stage T3 conditions, CD4 values are useful in determining the need for switching ART. In such children, ***if CD4 values are at or below the age-related threshold for severe immunodeficiency following previous immune response to ART, it is recommended to switch to a second-line regimen.*** In children on ART who are clinically well (***i.e. Clinical Stage T1 and T2***), switching a regimen should only be considered ***if two or more CD4 values below the age-related threshold*** for severe immunodeficiency are obtained. In such children, if the CD4 value begins to approach the age-related threshold for severe immunodeficiency, increased clinical and CD4 follow-up is warranted. A regimen switch is not recommended in children at Clinical Stages T1 - T3 where CD4 values drop but remain above their age-related threshold (Box 9 and Table 9).

Decision-making Regarding Switching ART in the Absence of CD4 Measurement

In situations where CD4 values are not available, a simplified approach is needed when making decisions on the need to switch to a second-line regimen (Tables 8 and 9). Clinical Stage T4 is sufficient criteria to consider switch regardless of CD4. ***In children developing signs of Clinical Stage T3 and where CD4 measurements are not available, switching regimen may be considered.*** However, it is recommended

that a child with Clinical Stage 3 defining pulmonary or lymph node TB or with severe recurrent presumed bacterial pneumonia should receive appropriate TB or antibacterial therapy before switching regimens, with re-evaluation of the child after adequate trial of TB or antibacterial therapy to determine the need to switch the ART regimen. In children who are clinically well (i.e. Clinical Stage T1 and T2), a regimen should not be switched if CD4 measurements are not available.

Table 9. Decision-making regarding switching to second line therapy for treatment failure based on availability of CD4 measurement [a]

WHO Paediatric Clinical Stage on ART[a]	Availability of CD4 measurements[b]	Management options[c]
T1 and T2[d] Event(s)	No CD4	• Do not switch regimen
	CD4	• Consider switching regimen **only if 2 or more values** below age-related threshold for severe immunodeficiencyd are available • **Increase clinical and CD4 follow up** if CD4 approaches age-related threshold for severe immunodeficiencye
T3[d] Event(s)	No CD4	a. Consider switching regimen[e,f]
	CD4	b. Switching regimen is recommended if CD4 at or below age-related threshold for severe immunodeficiency and particularly if child initially had good immune response to ART
T4 Event(s)	No CD4	c. Switch regimen, regardless of CD4
	CD4	d. Switching is generally recommended, but it may not be necessary where CD4 is above age related threshold for severe immune deficiency

Notes:

a) It needs to be ensured that the child had at least 24 weeks of treatment trial; adherence to therapy has been assessed and considered to be adequate prior to considering switching to second-line regimen. Additionally, in considering changing treatment because of growth failure, it should be ensured that the child has adequate nutrition, and that any intercurrent infections have been treated and resolved.

b) Clinical stages in this table refer to a new or recurrent stage at the time of evaluating the infant or child on ART.

c) Where CD4 is available, at least two CD4 measurements should be compared.

d) Do not switch regimen if CD4 values are above age-related threshold for severe immunodeficiency.

e) Age-related severe immunodeficiency values as defined in Table 5; switching should particularly be considered if values are <15% (12-35 months of age), <10% (36-59 months of age), <100 cells/mm^3 (?5 years of age); use of %CD4 in children less than5 years of age and absolute CD4 count after 5 years of age is preferred; if serial CD4 values are available, the rate of decline should be taken into consideration.

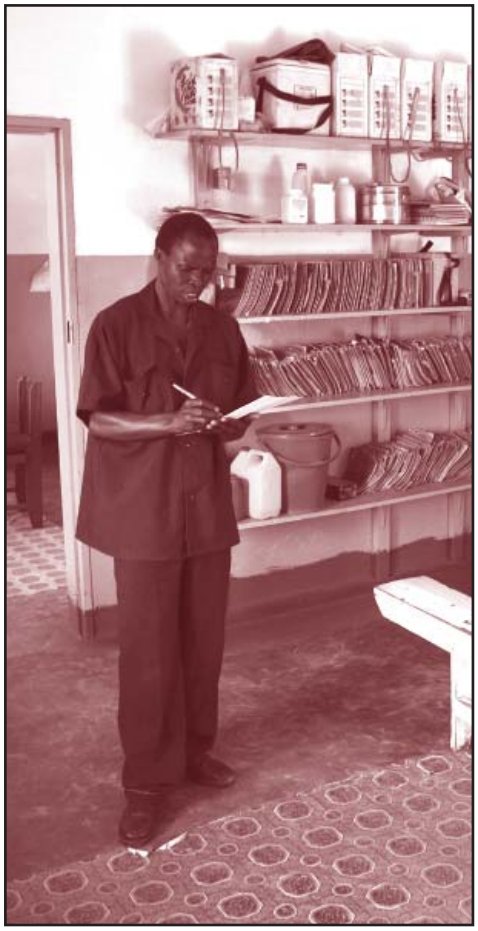
f) Some T3 conditions (i.e. pulmonary or lymph node tuberculosis and severe recurrent presumed bacterial pneumonia) may need to be treated and do not always indicate the need to switch regimens.

g) Viral load determination may be useful to support recognition of treatment failure

X. Switching an ARV Regimen in Infants and Children: Treatment Failure

Use of Other Laboratory Parameters for Decision-making Regarding Switchin ART

The definition of virological failure is more complex and a consensus has not yet been reached. ***Therefore the use of routine viral load in decision making on treatment failure is currently not recommended.*** In addition, TLC, while useful in the absence of CD4 measurement to guide when to initiate therapy, ***should not be used for the evaluation of response*** to ARV therapy as change in TLC is a poor predictor of treatment success (103). Similarly, drug resistance testing will not become a routine part of clinical care at this point, but will be used in future and so is not considered in these recommendations. However, ***it should be noted that basing the recognition of treatment failure solely on clinical criteria may provide a greater opportunity for drug resistance mutations to appear*** before regimen change. Finally, it is critically important to develop and implement less costly and complex methods for monitoring CD4, HIV RNA levels and drug resistance in HIV-infected children (and adults) in resource-limited settings as soon as possible.



XI. Choice of ARV Regimens in the Event of Treatment Failure of First-line Regimens in Infants and Children Second-line Regimens

The entire regimen should be changed from a first-line to a second-line combination in the event of treatment failure. The new second-line regimen should preferably include at least three new drugs, one or more of them from a new class, in order to increase the likelihood of treatment success, minimise the risk of cross-resistance, and be based upon drugs that retain activity against the child's virus strain. Designing potent and effective second-line regimens for infants and children is particularly difficult because of the current lack of experience with use of second-line regimens in children and the limited formulary available in the country today. This highlights the importance of choosing potent and effective first-line regimens and maximising their durability and effectiveness by optimising adherence.

Choice of Second-line Regimen Following a Preferred First-line Regimen of Two NRTI Plus One NNRTI

A regimen based on a protease inhibitor (PI), boosted where possible with ritonavir (RTV), combined with two new NRTI agents (usually based upon the NRTI didanosine [ddI]) is recommended as the second-line treatment for children failing a regimen of 2 NRTIs with a NNRTI (Table 10).

Choice of NRTIs

NRTI cross-resistance, especially in the presence of long-standing virological failure allowing accumulation of multiple drug resistance mutations, may compromise the potency of alternative dual NRTI components. Given the cross-resistance that exists between d4T and AZT, ***a second-line regimen for a child receiving a first-line d4T or AZT-containing regimen that might offer more activity includes ABC plus ddI,*** although high level AZT/3TC resistance can confer diminished susceptibility to ABC. If ABC plus 3TC were used as a first line nucleoside combination, ***AZT plus ddI*** would be the choice for an alternative regimen. An enteric-coated ddI formulation is better tolerated than the buffered tablet form and is therefore the preferred formulation to enhance tolerability and promote treatment adherence. ***Administration constraints for ddI in adults (i.e. administration one hour before or two hours after meals due to reduced bioavailability of ddI with food) does not apply in paediatric patients*** as the systemic exposure to ddI in children is similar in the presence or absence of food (49, 104).

Choice of PIs

Because of the diminished potential of almost any second-line nucleoside component, a low dose RTV-enhanced PI (PI/r) component, i.e. lopinavir (LPV)/r is generally preferable to nelfinavir (NFV) alone for second-line regimens (105). ***Advantages of PI-based regimens include proven clinical efficacy and well-described toxicities.*** However, the use of PIs other than LPV/r (which is available in co-formulation) and NFV is more problematic in children because there are no suitable paediatric formulations for indinavir (IDV) and SQV and a lack of appropriate dosing information, therefore, RTV-boosted PIs other than LPV/r can be considered as an alternative in children weighing more than 25 kg (who therefore can receive the adult dose) and who are able to swallow tablets/capsules. Other limitations related to the use of RTV-boosted PIs include the requirement for the presence of a cold chain for most products and poor tolerability of RTV. ***Therefore, LPV/r (kaletra syrup) remains the preferred PI for use in children if there is a secure cold chain.***

Data from small studies have shown that

XI. Choice of ARV Regimens in the Event of Treatment Failure of First-line Regimens in Infants and Children Second-line Regimens

use of NFV in children receiving SQV resulted in 2 to 3 (in PI naïve children) (106, 107, 108), or 4 to 20-fold increased SQV exposure, compared with SQV alone (49). In addition, the majority of children receiving SQV/NFV combinations achieved threshold SQV concentrations that appear more likely to maintain virological response for 48 weeks or more.

A regimen combining NFV with full-dose RTV assessed by the Paediatric AIDS Clinical Study Group (PACTG) Protocol 403 found that therapy with NFV (30 mg/kg bid) and RTV (400 mg/m2 bid) and ddI (buffered, 240 mg/m2 daily) is more efficacious in ***NRTI- experienced*** children than a regimen containing NFV and NVP and d4T (109). However, full-dose liquid RTV is unpalatable, has significant gastrointestinal intolerance and hence is poorly tolerated by children, and data on the concomitant use of NFV and RTV is insufficient to make firm recommendations for practice.

NFV alone can be considered as an alternative for the PI component if a RTV-enhanced PI is not available, if a cold chain cannot be secured or if there is a clinical contraindication to the use of another PI. Mild diarrhea, high dose requirements [i.e. infants younger than one year of age need at least 150 mg/kg/day to achieve NFV concentrations close to minimum therapeutic doses of older children and adults (110, 111)], poor tolerance of NFV powder, the need to crush tablets particularly for infants and young children, a high pill burden for older children and lower potency compared with RTV-boosted agents are considerable disadvantages of NFV (91). Several new PIs have become available for use in adults (e.g. tipranavir and atazanavir) but are currently not licensed for use in children or there are insufficient data to guide use in children.

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 9).

NRTI/NNRTI/PI combination regimens have been studied in treatment-experienced children, and were well tolerated (114). Thus a NNRTI +/-alternative NRTIs plus a RTV-boosted PI can be considered if drug availability permits. Following a first-line regimen containing ABC, ddI would be the NRTI of choice in a second-line regimen. Because EFV and NVP are potent inducers of enzymes required to metabolise some PIs, dose adjustments may be needed and use of a RTV-boosted PI is recommended to ensure adequate PI drug levels.

The clinical efficacy of continuing 3TC in a child who fails an initial first-line regimen that included 3TC has not been proven. Some data in adults suggest that continuing 3TC therapy even in the presence of multi-drug resistance (including the M184V mutation associated with 3TC resistance) may continue to provide additional antiviral activity, potentially due to decreased viral replicative fitness and increasing thymidine analogue susceptibility (115).

Choice of a Second-line Regimen Following a PI-Based Initial Regimen

Although not recommended, if for some reason PIs had been used as initial therapy where the NNRTI was substituted with a PI because of severe toxicity, it is not considered safe to reintroduce the NNRTI class. If PIs had been used as first line with

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NRTIs, in this situation, NNRTIs remain the only new drug class that can be introduced but the durability of such a regimen will be compromised by the inevitable and potentially rapid development of single point mutations with high-grade NNRTI resistance.

In both of these circumstances, ***referral*** of the patient to a setting where specialised and individualised HIV care is provided is warranted, however this may not be an option open to all patients. Any subsequent regimen will have to be based on the limited available formulary, including NNRTIs and NRTIs. It is for these reasons that premature use of the PI drug class in first-line regimens is not recommended.

Table 10: Recommended second-line regimens in infants and children in the event of treatment failure of first-line regimens

Recommended 2nd line regimen: boosted PI component +2 RTI components (NRTI/NNRTI)			
1st line regimen at failure	**Preferred 2nd line regimen**		
	RTI components (NRTI/NNRTI)		**PI component[b]**
2 NRTI[b] +1 NNRTI AZT *or* d4T containing	ddI[c]+ABC[d]	**Plus**	LPV/r[f] or NFV[g]
ABC - containing	ddI[c] + AZT		
Triple NRTI	ddI[c] + EFV[e]		

Notes:

a) Continuation of 3TC in second line may be considered

b) PI components are listed in order of potency/acceptability;

c) ddI may not need to be taken on an empty stomach in children;

d) It is not recommended to introduce AZT after use of d4T or vice versa;

e) EFV is not currently recommended for children<3 years of age or <10kg, and should be avoided in post pubertal adolescent girls who are either in1st trimester of pregnancy or are sexually active and not using adequate contraception;

f) LPV/r is available co-formulated as solid and liquid;

g) Unboosted NFV may need to be used where no cold chain in place for liquid LPV/r or SQV/r; it should be taken with food to improve bioavailability and high doses are needed in young children (e.g., >150 mg/kg per day).

XII. Strategies in the Event of Failure of Second-line Regimens

Currently, multi drug resistance may not be a big problem in Zambia, but is an increasing problem in paediatric treatment in Western countries in children who have received multiple antiretroviral regimens. Limited data are available to make recommendations about treatment options. Different strategies that balance benefits for the child might be explored to maintain CD4, reduce adverse events, and enhance prevention of opportunistic infections.

Considerations for the use of ARV Salvage Regimens

A number of treatment approaches have been looked at in clinical trial settings, although largely in adults and where virological monitoring is possible. These include addition or substitution of new drugs (such as enfurvirtide/T20); mega-HAART (combining of 5 or more drugs, including 2 or more protease inhibitors); strategic recycling of drugs; structured treatment interruptions (STI); and continuing current therapy until additional drugs become available. Analysis of 13 HIV cohorts involving adult patients who had three-class virological failure indicate 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 10000 copies per ml or at least 1.5 log10 below the off-treatment value may not be associated with CD4 cell-count decline (116). Immunological and clinical benefit has been reported even among patients who have partial viral response or virological rebound, presumably as a result of decreased viral fitness due to the presence of multiple resistance mutations (114, 115, 117-120). Decisions about therapy in such situations are complex and require, at a minimum, consultation with an HIV specialist.

Considerations for Stopping ART and Palliative Care

At some stage the option to stop ART may need to be considered, although prevention of opportunistic infections, symptom relief and pain management need to continue. Symptoms and pain are a major cause of discomfort 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 major challenge in Zambia because there is a paucity of experience and replicable models of planned terminal care, both institutional and community-based. At the end of life there are typically more symptoms that must be addressed, and there are polypharmacy guidelines to control multiple syndromes and treatment for multiple conditions. Terminal care preparation for children and their families is a long-term process and requires continuity in care providers and services. Critical factors in effective long-term planning include early and active communication and involvement with 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 which may not be best for the child's needs, 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 the child has end-stage HIV disease.

XIII. Considerations for Infants and Children Co-infected with Tuberculosis and HIV

Tuberculosis (TB) represents a significant threat to child health; HIV infection increases susceptibility to infection with M. tuberculosis and the risk of rapid progression to TB disease and in older children with latent TB reactivation. Increasing levels of co-infection with TB and HIV in children have been reported from resource-limited countries with dual epidemics (122), with prevalence of HIV in TB infected children ranging from 10-60% (121). ***Isoniazid (INH) preventive therapy is recommended for HIV-infected children if living in high TB prevalence areas or who are household contacts of TB patients (123).*** INH preventive therapy has shown early and significant survival benefits and reduction in TB incidence in HIV-infected children (124).

Considerations for the Diagnosis of TB

The primary disease in children presents with a broader range of non-pulmonary and pulmonary manifestations and diagnosis is difficult. In addition, problems obtaining sufficient sputum from infants and young children for smear microscopy and culture complicate making a definite diagnosis of TB. In many cases, particularly in young children, diagnosis is presumptive and based on a constellation of clinical signs and symptoms, known contact with a household member with TB disease, and the child's response to empiric anti-TB therapy. ***The principles for treatment of TB in HIV-infected children are the same as in HIV-uninfected children although treatment duration may be longer.*** While all HIV-exposed infants and children should benefit from CPT, this intervention is particularly important in children co-infected with TB and HIV as studies in adults have indicated improvement in survival in patients co-infected with HIV and TB who received cotrimoxazole prophylaxis compared to those receiving no prophylaxis.

Considerations for the Choice of First-line ARV Regimens in Children Receiving Rifampicin-containing Treatment

The co-management of TB and HIV is complicated by the potential for multiple drug interactions, particularly rifampicin drug interactions with the NNRTI and PI class. These drugs have similar routes of metabolism and elimination, and extensive drug interactions may result in sub-therapeutic antiretroviral drug levels. ***Overlapping toxicity profiles may result in increased risk of toxicity as well as interruption or change in the HIV or TB regimens, with a potential risk of TB microbiological or HIV treatment failure.*** The choice of ART regimen in TB/HIV co-infected children is also complicated by the limited options for paediatric drug formulations and/or dosing information (particularly for children less than 3 years of age) for antiretroviral drugs (EFV), which further limits ART options for co-infected children.

The preferred first-line treatment recommendation for children above 3 years of age (>10kg) with TB and HIV co-infection is a standard first-line regimen of 2 NRTIs plus EFV (i.e., the NNRTI component). For infants and young children <3 years old, the triple NRTI (i.e. d4T or AZT + 3TC + ABC) is recommended. ***Thus for children less than 3 years of age, a triple NRTI regimen is the preferred choice in this situation*** because information on EFV formulation and appropriate dosing for this age group is currently unavailable. Use of a standard first-line regimen of 2 NRTIs plus NVP (i.e., as NNRTI component) can be considered, although NVP levels are reduced with concurrent rifampicin, with larger reductions in AUC of 31-37% (125, 127); and ***the use of higher doses of nevirapine with rifampicin has not been evaluated.*** In a study in HIV-infected adults, a

XIII. Considerations for Infants and Children Co-infected with Tuberculosis and HIV

regimen of AZT/3TC/ABC had lower virological potency than an EFV-based regimen (79% versus 89% efficacy at 32 weeks). (57) However, because of concern for the potential for sub-therapeutic dosing of NNRTIs with concomitant rifampicin, triple NRTI regimen is the preferred choice.

Additionally, NVP, like rifampicin and isoniazid, has potential hepatic toxicity. However, because NVP levels are reduced more than EFV levels, a regimen of 2 NRTIs plus NVP should only be considered when no other options are available and when careful clinical and laboratory monitoring can be assured (i.e., monitoring for potential liver toxicity clinically and with liver function tests). More data are needed to determine rifampicin and NVP interactions and exact NVP dose requirement in children receiving rifampicin. EFV should be avoided in adolescent girls of childbearing potential (without adequate contraception) or who are in the first trimester of pregnancy.

Considerations for the Timing of ART Initiation Following Initiation of Rifampicin-Containing TB Treatment

In HIV-infected children with confirmed or presumptive TB disease, initiation of TB treatment is the priority. However, the optimal timing for 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 possible immune reconstitution syndrome versus the risk of further progression of immune suppression with its associated increase in mortality and morbidity.

ART is indicated for children with Clinical Stage 3 pulmonary TB and Clinical Stage 4 extra pulmonary TB. However, ***results of CD4 measurements*** - if available - are important in making decisions about ***the urgency of initiation of ART***. Because the degree of immunodeficiency in TB/HIV co-infected children is highly correlated with mortality (122), ***earlier initiation of ART is more critical in co-infected children with low CD4 values.***

Studies of HIV-infected children without TB infection indicate an inverse association of the CD4 value with the short-term risk of death (43). ***Thus, in children who have WHO Paediatric Clinical Stage 4, regardless of immunological criteria, and in children with Clinical Stage 3 and concurrent severe or advanced immunodeficiency,[I] ART should be started between 2 to 8 weeks after the start of TB therapy, after the child has stabilised on TB therapy.*** In children with Clinical Stage 3 who are classified as having either not significant or mild immunodeficiency i (and therefore have a lower short-term risk of HIV disease progression or death) clinical response to TB therapy can guide the decision whether ART needs to be initiated urgently or can be delayed.

Clinical response to TB treatment should be expected within the first few weeks of receiving anti-TB therapy. ***In a child with clinical response to TB therapy, initiation of ART may be delayed until after completion of TB therapy, provided that response to TB therapy is closely monitored*** and the need for ART is re-assessed after TB therapy has been completed. ***If an appropriate clinical response is not observed, then it may be necessary to start ART earlier rather than later*** (e.g. before the 2-month induction phase of TB therapy is completed). ***The potential for immune reconstitution syndrome (see below) should be considered in all children starting ART, particularly those starting ART with very low %CD4.***

i Advanced immune deficiency can be assumed to be 5% above age-specific CD4 threshold for severe immunodeficiency as listed in Table 5 or CD4 200-349 cells/mm 3 for children ≥ 5 years of age (See Annex C)

XIII. Considerations for Infants and Children Co-infected with Tuberculosis and HIV

In situations where CD4 measurements are not available in children with Paediatric Clinical Stage 3, except for those with lymph node TB, ART should be initiated with the same urgency as in children with Paediatric Clinical Stage 4 (Table 10).

Considerations for Children on First-line ARV Regimens Diagnosed with TB

In children already on a first-line ARV regimen and who are diagnosed with TB ART should be continued. However, the ARV regimen should be reviewed and may need adjustment to ensure optimal treatment of both TB and HIV and to decrease the potential for toxicities and drug-drug interactions. In children receiving a standard first-line regimen of two NRTIs plus one NNRTI and where TB has occurred due to primary infection or as part of IRS (see below), a change to a triple NRTI (simplification) first-line regimen can be considered in children <3years of age or <10kg. Alternatively, children >3years could remain on their standard regimen of two NRTI plus one NNRTI which is more optimal for children receiving EFV-based regimens rather than NVP-based regimens. In those children and adolescents for whom EFV is not recommended and who are taking NVP, standard doses should in this case be administered.

Because of overlapping toxicities and drug-drug interactions, children who are given rifampicin and NVP concomitantly should be followed-up more frequently and laboratory parameters checked if available. Where TB is being considered a sign of treatment failure of the first-line regimen, switch to a second-line regimen can be considered if the child has received an adequate trial of ART (i.e. more than 24 weeks) and initially responded to it and the child has not responded to anti-TB treatment. Because concurrent use of rifampicin and any PI is not recommended, consultation is suggested for construction of a second-line regimen.

Considerations for Children on Second-line ARV Regimens Diagnosed with TB

For children who are receiving a second-line regimen with RTV-boosted PIs and are diagnosed with TB, ***the choice of ARV regimens is more difficult*** because of likely resistance to first-line NRTI drugs and varying interactions between rifampicin and the PIs. ***Single PIs and PIs given with low-dose RTV(r) boosting are not recommended to be administered with rifampicin due to the decrease in PI drug levels.*** Significant hepatocellular toxicity was observed in adults receiving concomitant administration of rifampicin with RTV-boosted SQV as part of ART and therefore is not recommended. Although there are no data, LPV/r could be administered with additional RTV dosing to provide standard therapeutic doses of RTV; a dose increase to the same level as the LPV dose in mg may be considered (i.e. LPV/RTV-Kaletra)). However, presence of a cold chain should be ensured. Use of other boosted protease inhibitor combinations is discouraged until further data becomes available. ***NFV should not be administered with rifampicin*** (129, 130). Construction of other salvage regimens in this situation may need to be considered. In children where TB is a sign of failure of a second-line regimen, ***stopping ART until TB therapy has been completed maybe an option.*** Reassessment and referral for construction of a salvage regimen, as appropriate, is indicated.

Tables 10 and 11 summarise the WHO recommendations for ART in HIV-infected children diagnosed with TB. Research is

XIII. Considerations for Infants and Children Co-infected with Tuberculosis and HIV

urgently needed to evaluate the pharmacokinetics and clinical outcome of NNRTI and PIs with rifampicin in children to enable evidence-based recommendations to be made.

Immune Reconstitution Syndrome in the Context of Co-therapy

An immune reconstitution syndrome has been observed in patients receiving anti-TB therapy that were initiated on ART. This syndrome has primarily been reported in adults (but has also been reported in children), ***and is characterised by worsening of disease after initial clinical improvement,*** with new onset of systemic symptoms, especially fever, worsening of pulmonary infiltrates, development of peripheral and mediastinal adenopathy, and expanding CNS lesions in patients with tuberculomas. These reactions may occur during the first 3 months of ART, are generally self-limiting and last 10-40 days, although some reactions can be severe and require a short course of treatment with a glucocorticoid (122) (see also Section X).

Table 11. Recommendations for the timing of ART following initiation of TB treatment with 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 ARV Regimen [B (IV)]*
WHO Paediatric Clinical Stage 4[b]	• **Start ART soon after TB treatment** (between 2 and 8 weeks following start TB treatment)	In children<3 years:[d] • **Preferred:** triple NRTI first-line regimen (d4T or AZT +3TC +ABC) *or* • Alternative: standard first-line regimen of 2 NRTI +NVPc In children>3 years:[d] • **Preferred:** triple NRTI first-line regimen (d4T or AZT +3TC +ABC) *or* • Standard first-line regimen of 2 NRTI +EFVe Following completion of TB treatment it is preferable to remain on the ART regimen if well tolerated
WHO Paediatric Clinical Stage 3[c]	With clinical management alone: • **Start ART soon after TB treatment** (between 2 and 8 weeks following start TB treatment) • If excellent clinical response to TB treatment in first 2 to 8 weeks of TB therapy, and child is stable and on co-trimoxazole preventive therapy (CPT)a, it maybe reasonable to delay initiation of ART	
	Where CD4 available: • **Evaluate possibility to delay initiation of ART depending on assessment of clinical status and CD4,and clinical and immunological response to TB therapy**	• Regimens as recommended above • Where ART can be delayed until after completion of TB treatment, initiation with a standard 2 NRTI +NNRTI first line regimen (Table 4) is recommended.

Table continued on following page

i Not significant or mild immune deficiency can be assumed at CD4 levels above those levels defining advanced immune deficiency (see note i, above and Annex C).

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Table 11. Recommendations for the timing of ART following initiation of TB treatment with rifampicin-containing regimen in HIV-infected infants and children

Table carried over from following page

	Where CD4 available: • **Evaluate possibility to delay initiation of ART depending on assessment of clinical status and CD4,and clinical and immunological response to TB therapy:** - Severe and advanced immunodeficiency:[g] initiate ART soon after TB treatment (between 2-8 weeks following start TB treatment) - Mild or no immunodeficiency [h]: Initiation of ART maybe delayed until after completion of TB therapy;[h] monitor closely response to TB therapy and re-assess for ART after TB therapy; if no improvement, consider starting ART.	• Regimens as recommended above • Where ART can be delayed until after completion of TB treatment, initiation with a standard 2 NRTI +NNRTI first line regimen (Table 4) is recommended.

Notes: * Strength of recommendation/level of evidence

a) Administration of CPT is important in children with TB/HIV co-infection.

b) All children with Paediatric Clinical Stage 4 should be initiated on ART regardless of CD4 criteria.

c) Careful clinical monitoring with laboratory support if available is recommended where NVP is administered concurrently with rifampicin.

d) Due to lack of data the ranking of preferred or alternative ARV regimen is not possible

e) EFV is not currently recommended for children <3 years of age or <10kg, and should not be given to post pubertal adolescent girls who are either in1st trimester of pregnancy or are sexually active and not using adequate contraception.

f) Severe immunodeficiency as per Table 5; advanced immunodeficiency is assumed to be up to 5% above age-specific CD4 threshold for severe immunodeficiency or CD4 200-349 cells/mm 3 for children?5 years of age (Annex C).

g) Mild or not significant immunodeficiency is assumed at CD4 levels above those levels defining advanced immunodeficiency (see above and Annex C).

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Table 12: Recommendations for the co-management of TB and HIV in infants and children diagnosed with TB while receiving first or second-line ARV regimens

Time of TB diagnosis in relation to ART	Underlying cause of TB	Underlying cause of TB[a]	ARV Regimen [B (IV)]*
Child on standard 2 NRTI + NNRTI first-line regimen diagnosed with TB	TB due to primary infection (consider at anytime during ART, depending on exposure to TB)	Continue ART but assess for need for change in ART regimen - response to TB therapy should be used to evaluate need for change	• Continue on standard 2 NRTI +NNRTI first-line; if on NVP[b] substitute to EFV[c] if the child is 3 years or older *Or* • Substitute NNRTI to triple NRTI first-line regimen
	TB as part of the immune reconstitution syndrome consider in first 6 months of ART		
	TB as a sign of treatment failure of first-line regimen (consider after at least 24 weeks of ART		• Consider consultation with experts for construction of second-line regimen[d]
Child on standard second-line regimen(NRTI + boosted PI) diagnosed with TB	TB due to primary infection (consider at any time during ART, depending on exposure to TB)	Assess the need for changing or stopping ART regimen-response to TB therapy should be used to evaluate need for change or stop	• Continue same regimen, consider adding RTV to achieve full therapeutic RTV dose (same dose as LPV) until completion of TB therapy
	TB as a sign of treatment failure of second-line regimen		• Consider consultation with experts for construction of salvage regimen[d]

Notes:

a) Administration of cotrimoxazole preventive therapy (CPT) is important in children with TB/HIV co-infection.

b) Ensure careful clinical and laboratory monitoring where NVP is administered concurrently with rifampicin.

c) EFV is not currently recommended for children<3 years of age or <10kg, and should not be given to post pubertal adolescent girls who are either in the first trimester of pregnancy or are sexually active & not using adequate contraception

d) Little data are available to guide ART recommendations. Research is urgently needed

XIV. Considerations for Nutrition in HIV-Infected Infants and Children

Malnutrition is a common condition in HIV infected children, and a major contributor to mortality in both HIV-uninfected and infected children. In HIV-infected children, wasting (i.e. low weight for height/length) has been associated with reduced length of survival (131) while weight loss resulted in increased infectious complications in children with AIDS. Conversely, HIV has been associated with nutritional disorders, and immune status and level of viral replication may be important in predicting growth outcomes (132-134).

Growth (i.e. a composite of weight, length or height, and head circumference) is a sensitive indicator of optimal nutrition and of HIV disease progression. ***In HIV-infected children severe growth problems (i.e. growth failure and severe malnutrition as criteria for Paediatric Clinical Stage 3 and 4 Disease respectively) not attributable to inadequate nutritional intake may point to the need for initiation of ART.*** Growth is also useful in the evaluation of response to ART. Conversely, potential adverse effects of ARV drugs or opportunistic infections may affect food intake and nutrition in general, with limited improvements in growth and/or adherence to therapy as a consequence. These guidelines provide a brief summary of key nutritional interventions relevant to the care of HIV-infected infants and children prior to or while on ART. For more details the users of these guidelines are encouraged to refer to existing manuals and guidelines (IMCI) on clinical or nutritional management of the HIV-infected child (135-142).

Nutritional Assessment and Support

In view of the close interrelation of HIV infection, nutritional status and growth, it is recommended that ***early nutritional intervention (i.e. nutritional assessment and support) should be an integral part of the care plan of HIV-infected children.***

Nutritional assessment i.e. the systematic evaluation of current nutritional status, diet, and nutrition-related symptoms, is critical in early identification of malnutrition and poor growth as well as for monitoring of HIV disease progression and treatment efficacy for children on ART. Nutritional assessment should be part of the routine clinical monitoring of HIV-infected children whether or not they are receiving ART. ***All HIV-infected infants should be measured monthly, ideally using standardised growth curves. Thereafter, children should be weighed at each review and full nutritional assessments performed every month for infants and every three months for older children unless the child requires particular attention due to growth problems or special nutritional requirements.***

A proactive approach to nutritional support in HIV infected children is important because of increased energy needs that are associated with HV infection. ***In asymptomatic HIV-infected children, resting energy expenditure is increased by about 10%, while in HIV-infected children who experience growth failure; increased energy needs between 50% and 100%*** have been reported. Increased utilisation and excretion of nutrients in HIV infection can lead to micronutrient deficiencies (143). Nutritional support should thus include early efforts to ensure adequate nutrient intake based on locally available and affordable foods and ensure intake of micronutrients equivalent to one Recommended Daily Allowance (RDA) (140, 141, 144). It is recommended to ***increase the energy intake of HIV-infected infants and children by 10% of the***

RDA for their age and sex where asymptomatic and by 20-30% of RDA when symptomatic or recovering from acute infections (142). These requirements are considered minimal and more may be needed in children with nutritional deficiencies (145). ***Increased protein*** requirement over and above that required in a balanced diet to satisfy the total energy requirements (12 to 15% of the total energy intake) ***are not required*** (142).

Current evidence is inconclusive about the effects of micronutrient supplementation on transmission and progression of HIV infection. However, evidence from randomised clinical trials in HIV-infected children confirms that large-dose vitamin supplementation reduces overall morbidity and diarrhea morbidity as well as all-cause mortality (144, 146, 147). ***Vitamin A supplements should be given according to WHO recommended high-dose prevention schedule for children at high risk of Vitamin A deficiency (138).*** Counselling mothers about breastfeeding and all children and their caretakers about food and water hygiene are further core elements of nutritional support.

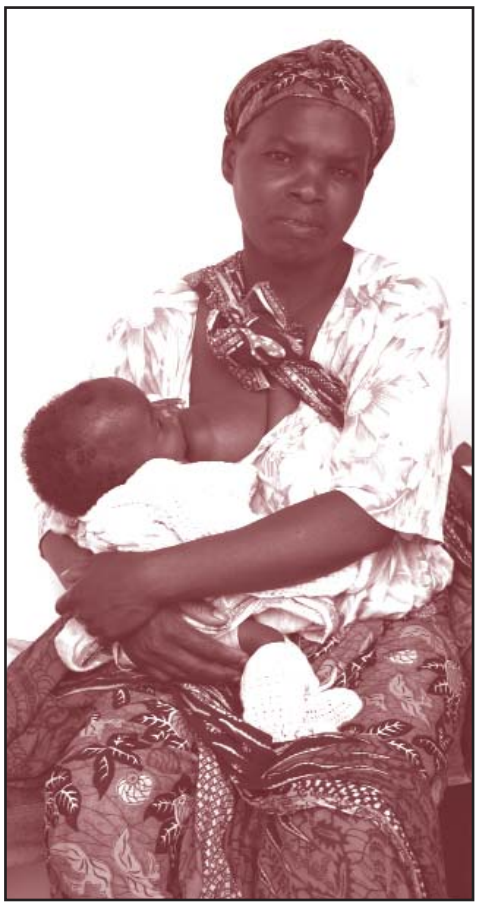
In children experiencing growth failure (i.e., failure to gain weight or weight loss between regular measurements) or feeding difficulties, more targeted support may be necessary. Identification of the underlying cause of growth failure may provide valuable information on further support strategies. This may include the treatment of underlying illness (common illnesses should be managed according to IMCI guidelines), evaluation of the need to start or switch ART, family education about locally available food choices and referral to food programmes, ideally with support for the whole family. In addition, selection of specific, palatable high-energy foods in children with conditions that interfere with normal ingestion or digestion (such as sore throat or mouth, oral thrush or diarrhea) may ameliorate symptoms and at the same time ensure sufficient energy intake.

ART in Severly Malnourished Infants and Children

Severe wasting is a common clinical presentation of HIV infection in children. All children with severe malnutrition are at risk of a number of life-threatening problems and urgently require treatment. The phase of malnutrition treatment at which to start ART is not known. Therefore, ***it is recommended that HIV-infected children with severe malnutrition be stabilised according to IMCI & (140, 141) national guidelines prior to making decisions on initiation of ART.*** Initial treatment of severe malnutrition lasts until the child has stabilised on initial treatment and his or her appetite has returned. While in HIV-uninfected children this initial phase should not take longer than 10 days, ***experts suggest that in HIV-infected children the response to initial treatment of severe malnutrition may be delayed or very limited.*** Following successful initial treatment of severe malnutrition, the child's clinical condition should be re-evaluated; initiation of ART may be considered based on the criteria listed in Section V.

In those HIV-infected children slow to improve on malnutrition treatment, a decision may be taken (either for in-patients or out-patients) at around six to eight weeks if they have not achieved 85% weight for height (i.e. cure). ***However, HIV-infected children readmitted with severe malnutrition may benefit from earlier initiation of ART.*** It needs to be emphasised that where malnutrition is endemic, HIV-infected children may become severely malnourished due to lack of an adequately balanced diet and with restoration of the nutritional sta-

tus initiation of ART may no longer be appropriate. This may be a particularly important consideration for children presumptively diagnosed with severe HIV disease. ***However, in HIV-infected infants and children with unexplained severe malnutrition not due to an untreated opportunistic infection, who do not respond to standard nutritional therapy (i.e. a criteria for HIV Clinical Stage 4 disease), initiation of ART is indicated.***



In children who rapidly gain weight due to adequate nutrition and ART, dosages of ARVs should frequently be revised. The ***recurrence of severe malnutrition not due to lack of food in children receiving ART may indicate treatment failure and the need to switch therapy*** (see Section X).

"MALNUTRITION IS A COMMON CONDITION IN HIV INFECTED CHILDREN, AND A MAJOR CONTRIBUTOR TO MORTALITY IN BOTH HIV-UNINFECTED AND INFECTED CHILDREN. IN HIV-INFECTED CHILDREN, WASTING (I.E. LOW WEIGHT FOR HEIGHT/LENGTH) HAS BEEN ASSOCIATED WITH REDUCED LENGTH OF SURVIVAL"

i WHO defines severe malnutrition as severe wasting (i.e. less than 70% of weight for height/length of the average child or less than minus three standard deviations from the median) or oedema of both feet (reference 140): Guidelines for the care at the first-referral level in developing countries. Geneva, Switzerland: World Health Organisation; 2000.) There are no published studies of effectiveness, pharmacokinetics and safety of ARVs in severely malnourished children; further research is urgently needed.

XV. Considerations for ART in Adolescents

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

There are distinct groups of HIV-infected adolescents who may require ART. In adolescents who were infected around birth and have survived into adolescence, HIV disease may progress slowly and they may present for the first time to ART services during adolescence; their treatment and care needs are similar to those that become infected during adolescence. Adolescents with perinatal infection who began ART during early childhood due to rapid progression of HIV disease have some years of contact with health services and are likely to have experience with different ARV treatments; often, their parents know their HIV status. ***For adolescents with perinatal infection, challenges relate mainly to disclosure of HIV status to the adolescent if the parents have not done so; developmental delays; transition of care from paediatric to adult care, including choice of appropriate ARV regimens, and adherence.***

HIV-infected adolescents (i.e. those infected as infants or young children) often face considerable physical challenges. They may experience delayed growth and development, often resulting in late puberty and delayed or irregular menstrual cycles in girls (148). Stunting and/or wasting caused by progressing HIV illness that is frequently exacerbated by malnutrition, may further complicate the decision whether to follow child-or adult ARV treatment guidelines.

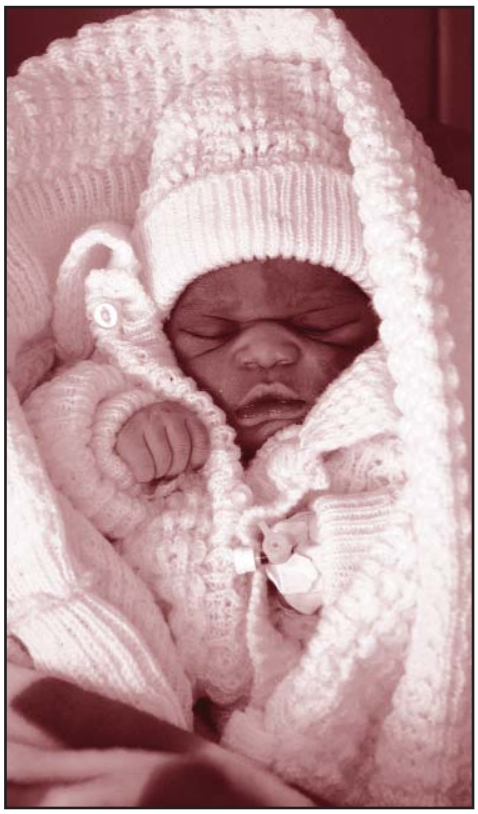
WHO ***recommends basing the choice of ARV regimens and dosages for adolescents on sexual maturity rating (i.e. Tanner Staging, Annex H): adolescents in Tanner stage I, II, or III should be begun on paediatric schedule*** and monitored particularly carefully because they are at the time of growth-spurt hormonal changes. Adolescents in ***Tanner stage IV or V are considered adults*** and the same recommendations and special considerations as for adults, including the use of the WHO clinical and immunological classifications for adults apply[i]. However, in choosing an appropriate ARV regimen and doses there is a need to go beyond considering maturity. Simplification and anticipated long-term adherence are further important criteria. Other considerations relate to the use of EFV and NVP in adolescent girls. EFV should be avoided in adolescent girls who are at risk of pregnancy (i.e. are sexually active and not using adequate contraception) or are in the first trimester of pregnancy.

Symptomatic NVP-associated hepatic or serious rash toxicity, while uncommon, is more frequent in females than in males, and more likely to be seen in antiretroviral-naïve females with higher absolute CD4 cell count (>250 cells/mm3). Therefore, NVP should be used with caution in adolescent girls with absolute CD4 count between 250-350 cells/mm3; if used in such adolescent girls, careful monitoring is needed during the first 12 weeks of therapy, ideally including liver enzyme monitoring. In situations where both EFV and NVP should not be included in first-line regimens for adolescent girls, use of a triple NRTI regimen maybe indicated.

Adherence to long-term therapy is particularly difficult among adolescents. In addition to providing routine adherence assessment and support (see Section XVII), health care providers may want to consider issues that are particularly relevant to adolescents and impair optimal adherence to ART. This may include the adolescents'

i As outlined in the 2006 revision of "Scaling up antiretroviral therapy (for adults and adolescents) in resource-limited settings: Treatment guidelines for a public health approach"; to be published by WHO in 2006.

perception of being immortal, their desire for independence, lack of disclosure of HIV status and stigma. ***Parents of those adolescents who became infected as infants or young children may find it hard to share the diagnosis of HIV with their child because of fear of stigma or blame from their own child.*** However, without this knowledge it is not possible for the adolescent to progress completely through the transition process into adult care. Sharing this diagnosis with peers is difficult for those adolescents who are aware of their HIV status. For these reasons it is especially important that young people: 1) are informed about their HIV status; 2) are well educated about their condition, its treatment and the importance of adhering to care and ART; 3) are confident in their ability to talk about HIV with those who they want to know about their condition; and 4) have a support system, so they know where to get help and advice when they need it. In heavily treatment-experienced adolescents the ease of adherence may be a reason to favor a regimen that is easier to adhere to over a more potent regimen when constructing a second-line or salvage regimen.



"WHO CONSIDERS ADOLESCENCE AS THE PERIOD BETWEEN 10-19 YEARS OF AGE, DURING WHICH HEALTHY ADOLESCENTS PASS THROUGH WELL DESCRIBED STAGES OF PHYSICAL, PSYCHOLOGICAL AND SEXUAL MATURATION THAT HAVE IMPLICATIONS FOR PROVIDING APPROPRIATE TREATMENT AND CARE."

XVI. Clinical and Laboratory Monitoring

Clinical and laboratory assessments are required at baseline (i.e. at entry into HIV care), during care of those patients who are not yet eligible for ART, and for starting and maintaining ART. In settings where CD4 are not available, primarily clinical parameters can be used for monitoring of ART. However, it is highly desirable as a country to develop 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.

Baseline Clinical and Laboratory Assessment

All infants and children who are diagnosed with HIV infection should undergo a baseline clinical and laboratory assessment. This is to determine the clinical stage of HIV disease and, where available, immunological status, as well as eligibility for ART and other interventions. The assessment at baseline also provides an opportunity to initiate cotrimoxazole preventive therapy for all HIV-exposed infants and all infants with known HIV infection who are under 1 year of age. Evaluation for the presence of active opportunistic infections and referral of the infected infant or child to a chronic care setting within the public health system are further objectives. ***The baseline assessment should also serve as a means to provide counselling and support of the child and/or caregiver*** around secondary prevention and around disclosure of HIV diagnosis to others as well as to identify their particular needs.

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

- Clinical staging of HIV disease
- Identification of concomitant medical conditions (TB, pregnancy among adolescent girls);
- Detailing of concomitant medications, including cotrimoxazole and traditional and herbal therapies
- Weight and height; head circumference, and other measures of growth;
- Developmental status
- Nutritional status, including assessment of intake;
- For those eligible for ART, assessment of child's and caregiver's readiness for therapy

The laboratory assessment for infants and children at baseline should include:

- Confirmation of HIV infection status (virological or antibody testing according to age);
- Measurement of CD4, where available;
- Haemoglobin measurement in infants and children initiated on AZT containing regimens;
- White blood cell count (WBC);
- Pregnancy test for sexually active adolescents girls;
- Screening for TB and malaria (and diagnostic testing where clinically indicated), and for the other treatable HIV co-infections and HIV related opportunistic diseases as indicated.

Because of a reasonable correlation between TLC with CD4 levels in symptomatic patients (44, 149-151) and the association of TLC with risk of mortality in paediatric studies (44, 45), the TLC should be used only at baseline assessment for ART if CD4 cell measurements are unavailable.

XVI. Clinical and Laboratory Monitoring

Routine Monitoring of Patients Who are Not Yet Eligible for ART

Clinical evaluation of infants and children who are not yet eligible for ART should be performed ***every 3 months for infants, 3-6 months for older children*** and should include the same parameters used in baseline evaluations. Together with the results of CD4 measurement they are useful to ***update the WHO Paediatric Clinical and Immunological Stage at each visit,*** and determine whether the infant or child in question has become eligible for treatment. Clinical evaluation and CD4 measurements can be obtained more frequently as the clinical or immunological threshold for initiating ART (Table 5) approaches. Also, because of the rapid rate of disease progression in infants and young children, more frequent clinical and laboratory monitoring may be indicated.

Routine Monitoring of Patients on ART

Once on ART, in addition to the same parameters as pre-ART (except for confirmation of HIV infection status), clinical assessment should cover the child's and caregiver's understanding of ART as well as anticipated support and adherence to ART. Observation of the child's response to therapy should also include symptoms of potential drug toxicities or treatment failure (i.e. re-assessment of clinical stage). Particularly important signs of infants' and children's response to ART include the following:

- Improvement in growth in children who have been failing to grow;
- Improvement in neurological symptoms and development in children with encephalopathy or who have been demonstrating delay in the achievement of developmental milestones; and/or
- Decreased frequency of infections (bacterial infections, oral thrush, and/or other opportunistic infections).

The frequency of clinical monitoring will depend upon response to ART, but should be monthly for the first 3 months and every 3 months once the child has stabilised on therapy. In those infants and children who were started on ART based on a presumptive clinical diagnosis of severe HIV disease, HIV-infection status should be confirmed as soon as possible.

Laboratory assessment of CD4 values is desirable every six months or more frequently if clinically indicated (Table 12). The TLC is not suitable for monitoring of therapy as change in TLC value does not reliably predict treatment success (103). ***Haemoglobin measurement in those infants and children initiated on AZT-containing first-line regimens should be performed monthly*** during the first 6 months of treatment or in a symptom-directed approach. Tests for liver function (i.e. liver enzymes) are recommended during the first 3 months of treatment in infants and children receiving nevirapine or who have known co-infection with hepatitis viruses or are on hepatotoxic medications. When choosing other laboratory parameters, clinical symptoms should be taken into consideration for assessing the response to therapy. Some routine monitoring tests may be advisable according to the specific drugs used. However laboratory monitoring of adverse events should largely be directed by clinical symptoms (Annex E and G). ***It should be noted that inability to perform laboratory monitoring should not prevent children from receiving ART.***

Table 13: Laboratory parameters for monitoring infants and children at baseline, prior to ART and during ART

Diagnosis and monitoring laboratory tests		CBaseline (at entry into care)	At initiation of 1st or 2nd-line ARV regimen	Every 6 months	As required (i.e. symptom-directed)
HIV diagnostic testing: virological and Ab testing		✓			
Haemoglobin		✓	✓		✓
WBC and differential[b]		✓	✓		
%CD4 or absolute CD4 cell count[c]		✓		✓	✓
Pregnancy testing in adolescent girls[d]		✓			
Full blood chemistry (including, but not restricted to, ALTe, liver enzymes, renal function, glucose, lipids, amylase, lipase, and serum electrolytes)[f]		✓	✓		✓
Diagnostic tests for treatable co-infections and major HIV/AIDS-related opportunistic diseases	Screening for TB and malaria (basic microscopy, i.e. sputum smear test for TB and thick blood drop smear test for malaria diagnosis)g	✓	✓		✓
	Full cerebral spinal fluid (CSF) aspirate examination (microscopy, India ink, Gram stain, Ziehl-Neelsen), syphilis and other STI diagnostic tests.				✓
	Diagnostic tests for hepatitis B, hepatitis C serology, bacterial microbiology, and cultures and diagnostic tests and procedures for PCP, Crypto-coccus, toxoplasmosis and other major OIs				✓

Table continued on following page

Table 13: Laboratory parameters for monitoring infants and children at baseline, prior to ART and during ART

Table carried over from following page

HIV viral load measurement[h]				✓

Notes:

a) Haemoglobin monitoring during the first weeks of treatment has been recommended by some experts if AZT is used. However, other experts suggest that the haemoglobin level can be monitored in a symptom-directed approach, particularly for AZT-free regimens. Monitoring at week 4, 8 and 12 after initiation of ART is therefore optional.

b. Monitoring at week 4, 8 and 12 after initiation of ART is optional.

c. Children who are not yet eligible for ART should be monitored with measurement of CD4 every 6 months. For infants and children who develop WHO Stage 2 events, or whose CD4 measurements approach threshold values, the frequency of CD4 measurement can be increased. Measurement of % CD4 is preferred in children<5 years of age.

d. Pregnancy testing may be needed for adolescent girls initiating a standard first-line regimen containing EFV.

e. The predictive value of pre-emptive liver enzyme monitoring is considered very low by some experts, WHO recommend liver enzyme monitoring in a symptom-directed approach. However, regular monitoring during the first three months of treatment and symptom-directed measurement of liver enzymes thereafter has been considered by some experts for certain children using nevirapine-based regimens, in particular for adolescent girls with CD4 cell >250 cells/mm 3 and infants and children co-infected with hepatitis B or hepatitis C virus, or other hepatic disease.

f. Regular monitoring (every 6 months) of full chemistry tests, particularly lipid levels, liver enzymes, and renal function, should be considered for infants and children using second-line drugs.

g. In general, active TB infection should be excluded in all patients prior to the initiation of ART, as indicated by symptoms, and according to national TB control protocols.

h. Viral load measurement is currently not recommended for decision-making on initiation or regular monitoring of ART in resource-limited settings. Technology for assessment of viral load can also be used to diagnose HIV infection although it is not yet standardized for this purpose. Source: (152).

Laboratory capability for routine monitoring

Monitoring protocols for the safety and efficacy of ART are important, but in view of the restricted infrastructure for the different tests at different levels in the health system, there are recommendations for a tiered laboratory monitoring 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 locations. Standard quality assessment of laboratories at all levels is important to ensure reliability.

XVII. Adherence to ART

Adherence is related to the clinical and virological response to therapy in infants and children (88, 90, 153). Studies of drug adherence among adult patients in Western countries have suggested that higher levels of drug adherence are associated with improved virological and clinical outcomes and that rates exceeding 90% are desirable in order to maximise the benefits of ART (154, 155). ***Therefore, it is critical to focus on maximising adherence in order to ensure the durability of effect of ARV regimens and to minimise emergence of drug resistance.*** Experience has demonstrated that it can be particularly difficult to adhere to daily medication regimens, particularly over long periods of time, and attention to adherence is equally important. Furthermore, a range of programmatic issues cause barriers to optimal adherence to treatment and may need to be addressed.

Adherence in children is a special challenge because of a variety of factors concerning the child, the caregivers, the medication and their inter-relationships. The lack 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, successful treatment of a child requires the commitment and involvement of a responsible caretaker. This may be more complicated if the family unit is disrupted as a consequence of adverse health or economic conditions. Mothers of HIV-infected children frequently are HIV-infected themselves and the care for their child may be less than optimal due to their own compromised health. Ideally, ***a secondary (back up) informed caregiver should be involved in the care of an HIV infected child.*** In addition, caregivers are often concerned with disclosure of HIV status to other family members, friends or school, thus restricting the child's access to essential support. Finally, an understanding of how the developmental stage of the child influences the extent to which he/she will cooperate with regular administration of medicine will help guide planning and support of the process.

Efforts to support and maximise adherence should begin prior to the initiation of treatment (87). ***The development of an adherence plan*** and education of the patients and their caregivers are important first steps. Initial 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. Where medication is taken mixed with food, consumption of all food is important to ensure administration of the full required dose. The employment of additional methods may be necessary especially for young children, including tasting medications, practicing measuring liquid, and pill swallowing training. When choosing regimens, policymakers and programmers should consider ways to minimise the number of pills and/or volume of liquids as well as the frequency of dosing, avoidance of food restrictions, the feasibility of using FDC and the availability of blister packs or other facilitating presentations of the drugs. 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.

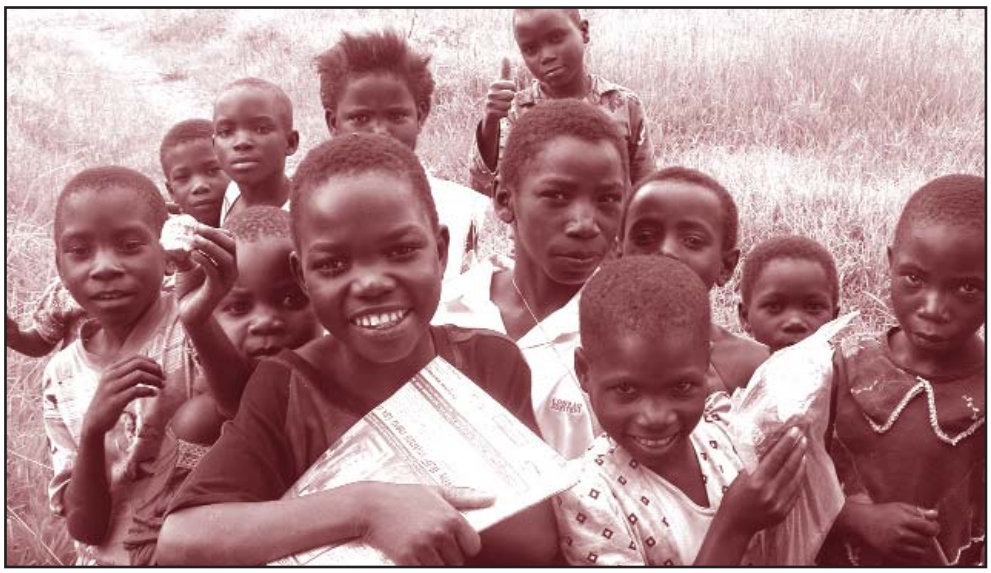
Adherence during the first days and weeks of treatment can be critical to the long term success of the regimen, particularly for some ART combinations that are at higher risk for the development of resistance. Where children stop (either intentionally or unintentionally) ARV drugs within first-line regimens it should be recognized that NNRTI components have half-lives that are several days longer than the half-lives of NRTI components. ***Sudden or periodic interruption of first-line therapy therefore results in persistence of sub therapeutic NNRTI drug levels, and may lead to premature development of NNRTI drug resistant virus.*** Emphasising the need to consistently take the ARV drugs is therefore particularly important with a NNRTI/NRTI based first-line regimen. This also emphasises the importance of an uninterrupted ARV supply in facilities and at household level.

The continuous assessment and support of adherence are vital components of a proactive approach to ART. ***Adherence assessment*** should be the concern of every health care provider participating in the care of the child. It should be performed whenever there is a visit to a health centre in order to identify those children in need of greatest adherence support. The measurement of adherence, however, can be difficult, particularly in children. Quantitative methods are generally employed (asking the child or caregiver how many doses of medication have been missed during the recent past 3, 7 or 30 days) but responses may not reflect their true adherence as they learn the social desirability of reporting complete adherence. ***Qualitative evaluations of adherence can more effectively identify barriers to optimal medication-taking*** but can be more difficult and time consuming for the health care providers as well as the children and/or their caregivers. Qualitative evaluations generally focus on obtaining descriptions of impediments to adherence or problems encountered. Furthermore, the assessment of adherence can be complicated by diverging reports from the child and caretaker as well as the limited availability of information when the caretaker bringing the child to the clinic is not responsible for supervising ART administration (156). ***Review of pharmacy records as well as pill counts can provide valuable information about adherence.*** Viral load measurements can be used to reflect medication adherence, but it is an expensive way to monitor adherence, not readily available in Zambia and therefore not routinely recommended in these guidelines.

In addition to adherence assessment, ***ongoing adherence support*** is a vital component of treatment success. ***Practical aids can be helpful including the use of calendars, pillboxes, blister packs, and labeled syringes.*** Directly observed therapy and the use of treatment buddies or partners have been successful in some settings, but little is known about applicability to the paediatric population. ***Community and psychological support can be critical to the caregiver as well as the child;*** peer support groups may be particularly beneficial for mothers with young children on ART. Adherence may vary with time and families may have periods of time when adherence is excellent and other times when it fails, often due to changing life circumstances. ***Adherence may also suffer as an individual responds to therapy, health improves and the impetus to take daily medication decreases.***

XVII. Adherence to ART

Programmatic issues can also impact on paediatric adherence and must be considered as programmes expand to provide paediatric ART. Problems with adherence for children and their caregivers and adolescents (in particular those who are in transition of care) need to be anticipated and 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 a paediatric treatment programme.*** The limited formulations currently available for children present significant barriers to optimal adherence; development of formulations appropriate for use in infants and young children is therefore strongly encouraged. MOH is committed to the continuous supply and availability of paediatric ART formulations for first-line regimens at all levels.



XVII. Drug Resistance

Considerations for Drug Resistance in Infants and Children

Infants and children may acquire a resistant virus or develop resistance due to ARV exposure for prophylaxis or treatment with ARVs.

In perinatal acquisition, the infant acquires resistant virus from the mother in-utero, intra-partum, or post-partum during breastfeeding. Transmission of a resistant virus can occur: 1) from an ARV-naïve mother infected with HIV already resistant to ARV or 2) from a mother exposed to ARVs before becoming pregnant or, alternatively, 3) from a mother that has been exposed to ARVs during pregnancy either for her own health or for prophylaxis for MTCT. The frequency of transmission by these modes has however not been well documented.

Treatment-related development of resistance in children is, as in adults, frequently related to use of sub-optimal suppressive regimens or sub-therapeutic drug levels, either due to insufficient adherence or pharmacokinetic problems (157) and represents one of the main reasons for treatment failure (158). Children may develop viral resistance as a result of ART, the infant-portion of prophylaxis for MTCT, or exposure to sub therapeutic levels of ARVs (i.e., from mothers receiving ART) during breastfeeding.

Considerations for Minimising the Emergence of Drug Resistance

As the GRZ ART programme scales up, the emergence of HIV drug resistance (HIVDR) is of increasing concern and represents a potential impediment in achieving the long-term success of the rapid scale up of ART. Minimising the emergence and transmission of HIVDR is therefore essential to ensure the efficacy of the limited number of antiretroviral drugs available in the country. ***Optimising adherence is key to minimising resistance, alongside standardised protocols for ARV use for prophylaxis and treatment.*** Specific problems that need to be considered in treating children include the need to switch formulations as children cross weight or age-related thresholds, and the lack of availability of a range of suitable paediatric ARV dose formulations. Staggered stopping of individual drug components in face of toxicity may need to be accommodated.

Development and spread of HIVDR could be minimised through choice of appropriate drug combinations, reliable ARV drug quality and supply as well as culturally-tailored adherence support. ***Furthermore, surveillance and monitoring of HIVDR at country level is recommended as part of the overall monitoring of the effectiveness of antiretroviral programmes.*** These studies are an important public health tool to inform national, regional and global ARV scale-up programmes about trends in drug resistance patterns to enable timely policy development to minimise its impact.

The Global HIV Drug Resistance Network (HIVResNet) has developed an essential package of elements for a national and global HIVDR strategy that complements plans for ART scale-up implementation that is described in more detail on http://www.who.int/hiv/en/ as well as in the 2005/2006 revision of "Scaling up antiretroviral therapy in resource-limited settings: treatment guidelines for a public health approach."

However, because of the described particularities in transmission of resistant virus in infants and children, we intend to adopt surveillance and monitoring protocols that are being developed by WHO specifically

XVII. Drug Resistance

for the paediatric population. The study population for HIVDR surveillance will include pregnant women and newly-infected infants (i.e. infants that may have perinatally-acquired [resistant] virus), and thus identify transmission of resistant virus. Monitoring studies for the emergence of resistance during ART should include cohorts of those infants and children starting ART, on ART, and experiencing treatment failure, in sentinel sites.
As in adults, routine drug resistance testing for individual infant and child management is not recommended.

Paediatric Care & Treatment Indicators

1) Number of children born to HIV positive mothers (MTCT indicator)
2) Number of children given ARV prophylaxis at birth
3) Number of children tested for HIV
4) Number of children with confirmed HIV positive status
5) Number of HIV exposed infants seen in first two months of life for check up
6) Number of HIV exposed children receiving cotrimoxazole prophylaxis
7) Number of children receiving ART

Annex A: WHO Clinical Staging for Children with Established Infection

Primary HIV infection
Clinical Stage 1
• Asymptomatic • Persistent generalised 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 infections (otitis media, otorrhea, sinusitis, tonsillitis)
Clinical stage 3
• Moderate unexplained malnutrition not adequately responding to standard therapy • Unexplained persistent diarrhea (14 days or more) • Unexplained persistent fever (above 37.5 intermittent or constant, for longer than one month) • Persistent oral Candida (outside first 6-8 weeks of life) • Oral hairyleukoplakia • Acute necrotising ulcerative gingivitis/periodontitis • Lymph node TB • Pulmonary tuberculosis • Severe recurrent presumed bacterial pneumonia • Symptomatic lymphoid interstitial pneumonitis • Chronic HIV-associated lung disease including bronchiectasis • Unexplained anaemia (<8g/dl), neutropenia (0.5 x 109 or chronic thrombocytopenia (50 x 109/l)
Clinical stage 4
• Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy Pneumocystis pneumonia • Recurrent severe presumed bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia) • Chronic herpes simplex infection; (orolabial or cutaneous >one month' s duration or visceral at any site) • Extra pulmonary tuberculosis • Kaposi sarcoma • Oesophageal candidacies (or Candida of trachea, bronchi or lungs) • Central nervous system toxoplasmosis (outside the neonatal period) • HIV encephalopathy • Cytomegalovirus (CMV) infection; retinitis or CMV infection affecting another organ, with onset at age >1 month . • Extra pulmonary cryptococcosis including meningitis • Disseminated endemic mycosis (extra pulmonary histoplasmosis, coccidiomycosis, penicilliosis) Chronic Cryptosporidiosis • Chronic Isosporiasis • Disseminated non-tuberculous mycobacteria infection • Acquired HIV-associated rectal fistula • Cerebral or B cell non-Hodgkin lymphoma • Progressive multifocal leukoencephalopathy • HIV-associated cardiomyopathy or HIV-associated nephropathy
Notes: a. Diagnosis of HIV infection according to recommendations in Section IV b. All clinical events or conditions referred to are described in Part B of this Annex

Annex B, Part B: Presumptive and definitive criteria for recognising 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 generalised lymphadenopathy (PGL)	Persistent swollen or enlarged lymph nodes >1 cm at two or more non contiguous sites (excluding inguiral), 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 onchomycosis is uncommon without immunodeficiency.	Clinical diagnosis
Angular cheilitis	Splits or cracks on 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

Annex B, Part B: 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 2 (continued)		
Recurrent oral ulcerations (two or more in six months)	Aphthous ulceration, typically with a halo of inflammation and yellow-grey pseudomembrane.	Clinical diagnosis
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 or 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 (LTB), persistent or recurrent ear discharge.	Clinical diagnosis

Clinical event	Clinical diagnosis	Definitive 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 SDs, 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.

Foreword

				Abacavir			Didanosine (twice daily)			Efavirenz		Lamivudine			Nelfinavir			Nevirapine (maint.)			Stavudine			Zidovudine			Lopinavir/Ritonavir		
Surface area (m^2)		Weight range (kg)		Formulation	Dose (ml or tablets)		Formulation	Dose (ml or tablets)		Formulation	Dose (Caps or tabs)	Formulation	Dose (ml or tablets)		Formulation	Dose (tablets)		Formulation	Dose (ml or tablets)		Formulation	Dose (ml or capsules)		Formulation	Dose (ml or capsules)		Formulation	Dose (ml, capsules or tablets)	
Bottom	Top	Bottom	Top		**AM**	**PM**		**AM**	**PM**	Age 3 years and above. Dose given ONCE daily			**AM**	**PM**		**AM**	**PM**		**AM**	**PM**		**AM**	**PM**		**AM**	**PM**		**AM**	**PM**
0.30	0.34	5.0	5.9	20 mg/ml suspension	2 ml	2 ml	10 mg/ml suspension or 25 mg chew tablets	4 ml 2	4 ml 2			10 mg/ml solution	3 ml	3 ml	250 mg tablets	2	2	10 mg/ml syrup	6 ml	6 ml	1 mg/ml syrup	6 ml	6 ml	10 mg/ml syrup	6 ml	6 ml	80 mg lop/20 mg rit per ml solution	1 ml	1 ml
0.34	0.38	6.0	6.9	20 mg/ml suspension	3 ml	3 ml	10 mg/ml suspension or 25 mg chew tablets	5 ml 2	5 ml 2			10 mg/ml solution	3 ml	3 ml	250 mg tablets	2	2	10 mg/ml syrup	7 ml	7 ml	20 mg capsule	0.5	0.5	10 mg/ml syrup	7 ml	7 ml	80 mg lop/20 mg rit per ml solution	1.5 ml	1.5 ml
0.38	0.40	7.0	7.9	20 mg/ml suspension	4 ml	4 ml	10 mg/ml suspension or 25 mg chew tablets	6 ml 2	6 ml 2			10 mg/ml solution	4 ml	4 ml	250 mg tablets	3	2	10 mg/ml syrup	8 ml	8 ml	20 mg capsule	0.5	0.5	10 mg/ml syrup	8 ml	8 ml	80 mg lop/20 mg rit per ml solution or 133 mg lop/33 mg rit per capsule	1.5 ml 1	1.5 ml 1
0.40	0.43	8.0	8.9	20 mg/ml suspension	4 ml	4 ml	10 mg/ml suspension or 25 mg chew tablets	6 ml 2	6 ml 2			10 mg/ml solution	4 ml	4 ml	250 mg tablets	3	3	10 mg/ml syrup	9 ml	9 ml	20 mg capsule	0.5	0.5	10 mg/ml syrup or 100 mg capsule	9 ml 1	9 ml 1	80 mg lop/20 mg rit per ml solution or 133 mg lop/33 mg rit per capsule	1.5 ml 1	1.5 ml 1
0.43	0.45	9.0	9.9	20 mg/ml suspension	4 ml	4 ml	10 mg/ml suspension or 25 mg chew tablets	6 ml 3	6 ml 2			10 mg/ml solution	4 ml	4 ml	250 mg tablets	3	3	10 mg/ml syrup or 200 mg tablets	9 ml 0.5	9 ml 0.5	20 mg capsule	0.5	0.5	10 mg/ml syrup or 100 mg capsule	9 ml 1	9 ml 1	80 mg lop/20 mg rit per ml solution or 133 mg lop/33 mg rit per capsule	2 ml 1	2 ml 1
0.45	0.49	10	10.9	20 mg/ml suspension	5 ml	5 ml	10 mg/ml suspension or 25 mg chew tablets	6 ml 2	6 ml 2	200 mg capsule	1	10 mg/ml solution	5 ml	5 ml	250 mg tablets	3	3	10 mg/ml syrup or 200 mg tablets	10 ml 0.5	10 ml 0.5	15 mg capsule	1	1	10 mg/ml syrup or 100 mg capsule	10 ml 1	10 ml 1	80 mg lop/20 mg rit per ml solution or 133 mg lop/33 mg rit per capsule	2 ml 1	2 ml 1
0.49	0.53	11	11.9	20 mg/ml suspension or 300 mg tablets	5 ml 0.5	5 ml 0.5	10 mg/ml suspension or 25 mg chew tablets	7 ml 3	7 ml 3	200 mg capsule	1	10 mg/ml solution	5 ml	5 ml	250 mg tablets	3	3	10 mg/ml syrup or 200 mg tablets	10 ml 0.5	10 ml 0.5	15 mg capsule	1	1	10 mg/ml syrup or 100 mg capsule	10 ml 1	10 ml 1	80 mg lop/20 mg rit per ml solution or 133 mg lop/33 mg rit per capsule	2 ml 1	2 ml 1
0.53	0.58	12	13.9	20 mg/ml suspension or 300 mg tablets	6 ml 0.5	6 ml 0.5	10 mg/ml suspension or 25 mg chew tablets	7 ml 3	7 ml 3	200 mg capsule	1	150 mg tablet	0.5	0.5	250 mg tablets	4	4	10 mg/ml syrup or 200 mg tablets	11 ml 0.5	11 ml 0.5	15 mg capsule	1	1	100 mg capsule	1	1	80 mg lop/20 mg rit per ml solution or 133 mg lop/33 mg rit per capsule or 200 mg lop/50 mg rit per tablet	2 ml 2 1	2 ml 1 1
0.58	0.70	14	16.9	300 mg tablets	0.5	0.5	10 mg/ml suspension or 25 mg chew tablets	8 ml 4	8 ml 3	200 mg capsule + 50 mg capsule	1 + 1	150 mg tablet	0.5	0.5	250 mg tablets	4	4	200 mg tablets	1	0.5	20 mg capsule	1	1	100 mg capsule or 300 mg tablets	2 0.5	1 0.5	80 mg lop/20 mg rit per ml solution or 133 mg lop/33 mg rit per capsule or 200 mg lop/50 mg rit per tablet	2 ml 2 1	2 ml 1 1
0.70	0.80	17	19.9	300 mg tablets	0.5	0.5	10 mg/ml suspension or 25 mg chew tablets	9 ml 4	9 ml 4	200 mg capsule + 50 mg capsule	1 + 1	150 mg tablet	0.5	0.5	250 mg tablets or 650 mg tablets	5 or 2	5 or 2	200 mg tablets	1	0.5	20 mg capsule	1	1	100 mg capsule or 300 mg tablets	2 0.5	1 0.5	80 mg lop/20 mg rit per ml solution or 133 mg lop/33 mg rit per capsule or 200 mg lop/50 mg rit per tablet	2.5 ml 2 1	2.5 ml 1 1
0.80	0.95	20	24.9	300 mg tablets	1	0.5	25 mg chew tablets	5	5	200 mg capsule + 100 mg capsule	1 + 1	150 mg tablet	1	0.5	250 mg tablets or 650 mg tablets	5 or 2	5 or 2	200 mg tablets	1	0.5	20 mg capsule	1	1	100 mg capsule or 300 mg tablets	2 0.5	2 0.5	80 mg lop/20 mg rit per ml solution or 133 mg lop/33 mg rit per capsule or 200 mg lop/50 mg rit per tablet	3 ml 2 1	3 ml 2 1
0.95	1.10	25	29.9	300 mg tablets	1	1	25 mg chew tablets	5	5	200 mg capsule + 100 mg capsule + 50 mg capsule	1 + 1 + 1	150 mg tablet	1	1	250 mg tablets or 650 mg tablets	5 or 2	5 or 2	200 mg tablets	1	1	30 mg capsule	1	1	100 mg capsule or 300 mg tablets	2 1	2 0.5	80 mg lop/20 mg rit per ml solution or 133 mg lop/33 mg rit per capsule or 200 mg lop/50 mg rit per tablet	3.5 ml 2 2	3.5 ml 2 1
1.10	1.20	30	34.9	300 mg tablets	1	1	25 mg chew tablets	5	5	200 mg capsule	2	150 mg tablet	1	1	250 mg tablets or 650 mg tablets	5 or 2	5 or 2	200 mg tablets	1	1	30 mg capsule	1	1	100 mg capsule or 300 mg tablets	3 1	3 1	80 mg lop/20 mg rit per ml solution or 133 mg lop/33 mg rit per capsule or 200 mg lop/50 mg rit per tablet	4 ml 3 2	4 ml 3 2
		35	39.9				25 mg chew tablets	5	5	200 mg capsule	2				250 mg tablets or 650 mg tablets	5 or 2	5 or 2										80 mg lop/20 mg rit per ml solution or 133 mg lop/33 mg rit per capsule or 200 mg lop/50 mg rit per tablet	5 ml 3 2	5 ml 3 2
		40	and over							200 mg capsule or or 600 mg tablet	3 1																80 mg lop/20 mg rit per ml solution or 133 mg lop/33 mg rit per capsule or 200 mg lop/50 mg rit per tablet	5 ml 3 2	5 ml 3 2

1st 2nd 3rd 4th

Annex E: Serious acute and chronic toxicities due to ARV drugs that may require therapy modification: Clinical presentation, laboratory abnormalities, and implications for ART management[a]

Possible clinical manifestations (Most common ARV drug(s) associated with the toxicity)	Possible laboratory abnormalities[b]	Implications for antiretroviral drug treatment
Acute Serious Adverse Reactions		
Acute Symptomatic Hepatitis (NNRTI class, particularly NVP, more rarely EFV; NRTIs or PI class)		
• Jaundice • Liver enlargement • Gastro-intestinal 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 ARV until symptoms resolve • If possible, monitor transaminases, bilirubin • If receiving NVP,NVP should NOT be re administered to the patient in future • Once symptoms resolve, either to restart ART with change to alternative ARV (if on NVP regimen, this is required);or • to restart current ART regimen with close observation; if symptoms recur, substitute an alternative ARV[c]
Acute Pancreatitis (NRTI class, particularlyd 4T,ddI;morerarely3TC)		
• 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 [c]

Annex E: Serious acute and chronic toxicities due to ARV drugs that may require therapy modification: Clinical presentation, laboratory abnormalities, and implications for ART management[a]

Possible clinical manifestations (Most common ARV drug(s) associated with the toxicity)	Possible laboratory abnormalities[b]	Implications for antiretroviral drug treatment
Acute Serious Adverse Reactions		
Hypersensitivity Reaction(ABC or NVP)		
• BC: combination of acute onset of both respiratory and gastrointestinal symptoms after starting ABC, including fever, fatigue, myalgia, nausea, vomiting, diarrhea, abdominal pain, pharyngitis, cough, dyspnea; rash (usually mild) may or may not occur; progressive worsening of symptoms soon after receives ABC dose, usually occurs within 6-8 weeks • NVP: Systemic symptoms of fever, myalgia, arthralgia, hepatitis, with or without rash	• Elevated transaminases • Elevated bilirubin	• Discontinue all ARV until symptoms resolve • If possible, monitor transaminases, bilirubin • If receiving NVP,NVP should NOT be re administered to the patient in future • Once symptoms resolve, either to restart ART with change to alternative ARV (if on NVP regimen, this is required);or • to restart current ART regimen with close observation; if symptoms recur, substitute an alternative ARV[c]
Acute Pancreatitis (NRTI class, particularlyd 4T,ddI;morerarely3TC)		
• Severe nausea and vomiting • Severe abdominal pain • May have accompanying lactic acidosis (see below)	• Elevated transaminases • Elevated eosinophil count	• Immediately discontinue all ARVs until symptoms resolve • NVP or ABC should NOT be re administered to the patient in future • Once symptoms resolve, restart ART with substitution of an alternative ARV for ABC or NVP[c]
Lactic Acidosis(NRTI class,particularlyd4T)		
• Generalised fatigue and weakness • Gastrointestinal features (nausea, vomiting, diarrhea, abdominal pain, hepatomegaly, anorexia, poor weight gain and/or sudden unexplained weight loss) • May have hepatitis or pancreatitis (see above) • Respiratory features (tachypnea and dyspnea) • Neurological symptoms (inc. motor weakness).	• Increased anion gap • Lactic acidosis • Elevated aminotransferase • Elevated CPK • Elevated 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)[c]

Annex E: Serious acute and chronic toxicities due to ARV drugs that may require therapy modification: Clinical presentation, laboratory abnormalities, and implications for ART management[a]

Possible clinical manifestations (Most common ARV drug(s) associated with the toxicity)	Possible laboratory abnormalities[b]	Implications for antiretroviral drug treatment
Acute Serious Adverse Reactions		
Severe Rash/Stevens Johnson Syndrome(NNRTI class, particularly NVP, less common EFV)		
• Rash usually occurs during first 68 weeks of treatment • Mild to moderate rash: erythematous, maculopapular, confluent, most often on the body and arms, with no systemic symptoms • Severe rash: extensive rash with moist desquamation, angioedema, or serum sickness-like reaction; or a rash with constitutional findings such as fever, oral lesions, blistering, facial edema, conjunctivitis • Life-threatening Stevens Johnson Syndrome or toxic epidermal necrolysis	• Elevated aminotransferase	• If mild or moderate rash, can continue ART without interruption but close observation • For severe or life-threatening rash, discontinue all ARVs until symptoms resolve • NVP should NOT be re administered 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)[c]
Severe, Life-Threatening Anemia (AZT)		
• Severe pallor, tachycardia • Significant fatigue • Congestive heart failure	• Low haemoglobin	• If refractory to symptomatic treatment (e.g., transfusion),discontinue AZT only and substitute an alternative NRTI[c]
Severe neutropaenia (AZT)		
• Sepsis/infection	• Low neutrophil count	• If refractory to symptomatic treatment (e.g., transfusion),discontinue AZT only and substitute an alternative NRTI[c]

Annex E: Serious acute and chronic toxicities due to ARV drugs that may require therapy modification: Clinical presentation, laboratory abnormalities, and implications for ART management[a]

Possible clinical manifestations (Most common ARV drug(s) associated with the toxicity)	Possible laboratory abnormalities[b]	Implications for antiretroviral drug treatment
Chronic Late Serious Adverse Reactions		
Lipodystrophy/Metabolic Syndrome (d4T; PIs)		
• Fat loss and/or fat accumulation 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 a. Insulin resistance, including diabetes mellitus b. Potential risk for later coronary artery disease	• Hypertriglyceridaemia; • Hyper-cholesterolaemia • Low HDL levels • Hyperglycemia	• 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;morerarely3TC)		
• Pain, tingling, numbness of hands or feet; refusal to walk • Distal sensory loss • Mild muscle weakness and areflexia can occur	• None	• Stop suspect NRTI only and substitute a different NRTI that is not associated with neurotoxicity[c] • Symptoms may take several weeks to resolve

Notes:

a) Alternative explanations for the toxicity must be excluded before it is concluded it is secondary to the ARV drug. Note: This table does not describe detailed clinical toxicity management, only management of the ART regimen.

b) All laboratory abnormalities may not be observed.

c) See Table 7 (Section IX) for recommended antiretroviral drugs substitutions.

ARV - antiretroviral drug; ART-antiretroviral therapy; CPK -creatinine phosphate kinase; LDH -lactate dehydrogenase; HDL -high-density lipoprotein; NRTI- nucleoside analogue reverse transcriptase inhibitor; NNRTI non-nucleoside reverse transcriptase inhibitor; PI- protease inhibitor

Annex F: Summary of Formulations and dosages of anti-retroviral drugs for infants and children

This Annex contains information for anti-retroviral drugs for which there are paediatric indications, formulations, or sufficient information from authoritative sources to provide guidance on the proper doses. These take into consideration situations that are unique to resource-constrained settings including the potential for lack of refrigeration and need to administer tablets or capsules to small children. For simplification, recommended doses are provided in ranges based on the weight of the child. Where recommendations for dosing are by body-surface-area (BSA), approximations of weight/height for age, through use of clinical growth charts of children from the United States were used to calculate estimated BSAs. Though weight and height can both be measured, it may be impractical to expect providers in many settings to accurately estimate BSA.

The primary source for information for these monographs is the package insert (product labeling) from the brand name product made by the innovator (brand name) company for each drug. This information was supplemented with information from other authoritative publications and expert consultation. Additionally, since information concerning drug dosing may be updated, providers are cautioned to consider the most recent guidelines and product labeling.

There are multi-source (often referred to as "generic") antiretroviral drugs available from several companies. Though the information contained in these monographs is expected to be useful for multi-source ("generic") products as well, strengths of tablets, capsules, and concentration of liquid formulations may vary from the information contained here. Additionally, there are some products that are fixed-dose combination tablets that have quantities of drugs that are not appropriate for small children. Providers should consider the quality of the multi-source products and consult the WHO "Access to HIV/AIDS Drugs and Diagnostics of Acceptable Quality Procurement, Quality and Sourcing Project" for guidance. The list of WHO-prequalified manufacturers is continuously updated and is available at: *http://www.who.int/medicines*

Annex G: Severity grading of selected clinical and laboratory toxicities most commonly seen with recommended antiretroviral drugs for children

Parameter	Mild	Moderate	Severe	Severe, Potentially life-threatening
General guidance to estimating severity grade				
Characterisation of symptoms and general guidance on management	Symptoms causing no or minimal interference with usual social & functional activities:[a] No therapy needed, monitor	Symptoms causing greater than minimal interference with usual social & functional activities:[a] May require minimal intervention and monitoring	Symptoms causing inability to perform usual social & functional activities requires medical care and possible hospitalisation	Symptoms causing inability to perform basic self-care functions: b Requires medical or operative intervention to prevent permanent impairment, persistent disability, or death
Haematology[c] Standard International Units are listed in italics				
Absolute neutrophil count	750 - <1,000/mm^3 0.75 x10^9 - <1x10^9/L	500 - 749/mm^3 0.5 x109 - 0.74^{9}x10^9/L	250 - 500/mm^3 0.25 x10^9 - 0.5x10^9/L	<250/mm^3 <0.250 x 10^9/L
Hemoglobin (child >60 days of age)	8.5- 10.0 g/dL 1.32- 1.55 mmol/L	7.5-<8.5g/dL 1.16 - <1.32mmol/L	6.5-<7.5g/dL 1.01- <1.16 mmol/L	< 6.5g/dL < 1.01mmol/L Or severe clinical symptoms due to anemia (e.g., cardiac failure) refractory to supportive therapy
Platelets	100,000-<125,000/mm^3 100x10^9 - 125x10^9/L	50,000-<100,000/mm^3 50x10^9 œ <100x10^9/L	25,000-<50,000/mm^3 25x10^9 -<50x10^9/L	<25,000/mm^3 < 25 x 10^9/L or bleeding
Gastrointestinal[c]				
Laboratory				
ALT (SGPT)	1.25- 2.5xULN	2.6 - 5.0 x ULN	5.1 -10.0 x ULN	>10.0 x ULN
AST (SGOT)	1.25-2.5xULN	2.6 - 5.0 x ULN	5.1 -10.0 x ULN	>10.0 x ULN
Bilirubin (>2weeks of age)	1.1 - 1.5xULN	1.6 - 2.5xULN	2.6 - 5.0 x ULN	>5.0 x ULN
Lipase	1.1 - 1.5xULN	1.6 - 3.0 x ULN	3.1 - 5.0 x ULN	>5.0 x ULN
Pancreatic amylase	1.1 -1.5xULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	>5.0 x ULN

Annex G: Severity grading of selected clinical and laboratory toxicities most commonly seen with recommended antiretroviral drugs for children

Parameter	Mild	Moderate	Severe	Severe, Potentially life-threatening
Clinical				
Diarrhea ≥1 year of age	Transient or intermittent episodes of unformed stools OR increase of ≤3 stools over baseline per day	Persistent episodes of unformed to watery stools OR increase of 4œ 6 stools over baseline per day	Grossly bloody diarrhea OR increase of ?7 stools per day OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
< 1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR hypotensive shock
Nausea	Transient (< 24hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24œ 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR aggressive rehydration indicated (e.g., IV fluids)	Persistent nausea with no or minimal oral intake resulting in dehydration with aggressive rehydration indicated
Pancreatitis	N/A	Symptomatic AND hospitalization not indicated (other than emergency treatment) 5.65 - < 8.49 mmol/L	Symptomatic AND hospitalization not indicated (other than emergency treatment) 8.49 - 13.56 mmol/L	Life-threatening consequences (e.g., circulatory failure, haemorrhage, sepsis) > 13.56 mmol/L
Neuromuscular weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR respiratory muscle weakness impairing ventilation

Annex G: Severity grading of selected clinical and laboratory toxicities most commonly seen with recommended antiretroviral drugs for children

Parameter	Mild	Moderate	Severe	Severe, Potentially life-threatening
Clinical (continued)				
Neurosensory alteration (including painful neuropathy)	Asymptomatic with sensory alteration on exam OR minimal paraesthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or par aesthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or par aesthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paraesthesia causing inability to perform basic self-care functionsC

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; December 2004.

a. Usual social and functional activities in young children include those that are appropriate to their age and culture (e.g. social interactions, play activities, learning tasks).

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

c. Values are provided for children in general except where age groups are specifically noted

Parameter	Mild	Moderate	Severe	Severe, Potentially life-threatening
Other laboratory parameters - Standard international units are listed in italics				
Cholesterol (fasting, paediatric <18 years old)	170 -< 200 mg/dL 4.40- 5.15 mmol/L	200 - 300 mg/dL 5.16 - 7.77mmol/L	>300 mg/dL > 7.77mmol/L	NA
Glucose, serum, high: No 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

Annex G: Severity grading of selected clinical and laboratory toxicities most commonly seen with recommended antiretroviral drugs for children

Parameter	Mild	Moderate	Severe	Severe, Potentially life-threatening
Other laboratory parameters - Standard international units are listed in italics				
Lactate	< 2.0 x ULN without acidosis	í 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences or related condition present	Increased lactate with pH < 7.3 with life-threatening consequences (e.g. neurological findings, coma) or related condition present
Triglycerides (fasting)	NA	500 - < 751 mg/dL 5.65 - <8.49mmo/l	751 - 1,200 mg/dL 8.49 - 13.56mmol/dl	>1,200 mg/dL >13.56 mmol/l
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. indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

Parameter	Mild	Moderate	Severe	Severe, Potentially life-threatening
Allergic/dermatologic				
Acute systemic allergic reaction	Localised urticaria (wheals) lasting a few hours	Localised urticaria with medical intervention indicated, OR mild angioedema	Generalised urticaria, OR angio edema with medical intervention indicated, OR symptomatic mild bronchospasm	Acute anaphylaxis OR life-threatening bronchospasm or laryngeal edema

Annex G: Severity grading of selected clinical and laboratory toxicities most commonly seen with recommended antiretroviral drugs for children

Parameter	Mild	Moderate	Severe	Severe, Potentially life-threatening
Allergic/dermatologic				
Cutaneous reaction rash	Localised 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 generalised bullous lesions OR Stevens-Johnson syndrome, OR ulceration of mucous membrane involving two or more distinct mucosal sites, OR Toxic Epidermal Necrolysis (TEN)

Parameter	Mild	Moderate	Severe	Severe, Potentially life-threatening
Neurologic				
Alteration in personality, behaviour or in mood	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities 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 & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Onset of confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Onset of delirium, obtundation, or coma

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. **Notes:**

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

b. Usual social and functional activities in young children include those that are age and culturally appropriate (e.g. social interactions, play activities, learning tasks, etc) c. Activities that are age and culturally appropriate (e.g. feeding self with culturally appropriate eating implement, walking or using hands). ULN upper limit of normal

Annex H: Sexual maturity rating (Tanner Staging) in adolesents

Stage	Female				M ale				
	Age range (year)	Breast growth	Pubic hair growth	Other changes	Age range (year)	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	n/a
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	10.5-16.5	Further enlargement	Significant enlargement, especially in diameter	Increase in amount; curling	n/a
IV	10 - 17	Separation of contour; areola and nipple form secondary mound above breast tissue	Adult in the type but not 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	Axillary hair and some facial hair develop
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

Annex I: Recommended tiered laboratory capabilities for ART monitoring in resource-limited settings

Diagnosis& monitoring laboratory tests		Primary care level	District level	Regional/ Referral level
HIV Antibody testing[a]		✓	✓	✓
HIV virological diagnostic testing[b]		-	+	✓
Haemoglobin[c]		+	✓	✓
WBC and differential		-	✓	✓
CD4 (absolute count and %)		-	✓	✓
Pregnancy Testing[d]		+	✓	✓
ALT		-	✓	✓
Full chemistry (including but not restricted to: liver enzymes, renal function, glucose, lipids, amylase and serum electrolytes)		-	-	✓
Diagnostic tests for treatable co infections and major HIV/AIDS-related opportunistic diseases	Basic microscopy for TB and malaria (sputum smear for TB and blood film for malaria diagnosis)[e]	+	✓	✓
	Full cerebral spinal fluid (CSF) aspirate examination (microscopy, India ink, Gram stain, Ziehl-Neelsen). Syphilis and other STI diagnostic tests.	-	✓	✓
	Diagnostic tests for hepatitis B, hepatitis C serology, bacterial microbiology and cultures and diagnostic tests and procedures for PCP, Cryptococcus, toxoplasmosis and other major OIs)	-	+	✓
HIV viral load measurement[f]		-	-	+

Key: ✓ Essential test
+ Desirable, but not essential test
- Not essential test

ALT alanine transaminase; CSF-cerebrum spinal fluid; WBC -white blood count; PCP Pneumocystis pneumonia

Notes:

a. Rapid tests are recommended at primary level and conventional methodologies can be used at district and regional/central levels.

b. Virological testing for establishing HIV diagnosis in infants and children less than 18 months of age; can be performed using dried blood spots (DBS).

c. Should be available if AZT is being considered for use.

d. Should be available if EFV is being considered for use.

e. Referral if microscopy is not available.

f. Viral load measurement is currently not recommended for decision-making on initiation or regular monitoring of ART in resource-limited settings. Technology for assessment of viral load can also be used to diagnose HIV infection although it is not yet standardised for this purpose.

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