2006

Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access

Recommendations for a public health approach

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Abbreviations

3TC lamivudine
Ab antibody
ABC abacavir
ACTG AIDS clinical trials group
AFB acid-fast bacilli
AIDS acquired immunodeficiency syndrome
ALT alanine aminotransferase
a.m. ante meridiem (denotes morning)
ART antiretroviral therapy
ARV antiretroviral (drug)
AST aspartate aminotransferase
AUC area under curve
AZT zidovudine (also known as ZDV)
BAL bronchoalveolar lavage
b.d. twice daily
BSA body surface area
CD4+ T-lymphocyte bearing CD4 receptor
CHAP Children with HIV Antibody Prophylaxis (clinical trial)
CMV cytomegalovirus
CNS central nervous system
CPK creatinine phosphokinase
CPT co-trimoxazole preventive therapy
CRAG cryptococcal antigen
CSF cerebrospinal fluid
CT computerized tomography
CTX co-trimoxazole
CXR chest X-ray
d4T stavudine
DART Development of Antiretroviral Therapy (in Africa)
DBS dried blood spot
ddI didanosine
DNA deoxyribonucleic acid
DOT directly observed therapy
EFV efavirenz
EIA enzyme immunoassay
EMEA European Medicines Agency
ELISA enzyme-linked immunosorbent assay
FBC full blood count
FDA Food and Drug Administration
FDC fixed-dose combination
FTC emtricitabine
GI gastrointestinal
HDL high-density lipoprotein
Hgb haemoglobin
hgc hard gel capsule
HIV human immunodeficiency virus
HIVDR HIV drug resistance
HIVNET HIV Network for Prevention Trials
HIVResNet Global HIV Drug Resistance Network
HPPMCS HIV Paediatric Prognostic Markers Collaborative Study
HSV herpes simplex virus
ICD immune complex dissociated
IDV indinavir

IMCI integrated management of childhood illness

INH isoniazid

IRIS immune reconstitution inflammatory syndrome

LDH lactic dehydrogenase

LDS lipodystrophy

LGE lineal gingival erythema

LIP lymphocytic interstitial pneumonia

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 hairy leukoplakia

PACTG Paediatric 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

p.m. post meridiem (denotes afternoon)

PML progressive multifocal leukoencephalopathy

PMTCT prevention of mother-to-child transmission (of HIV)

/r low-dose ritonavir

RDA recommended daily allowance

RNA ribonucleic acid

RT reverse transcriptase

RTI reverse transcriptase inhibitor

RTV ritonavir

RTV-PI ritonavir-boosted protease inhibitor

SD standard deviation

SJS Stevens-Johnson syndrome

SQV saquinavir

STI structured treatment interruption

TB tuberculosis

TDF tenofovir disoproxil fumarate

TEN toxic epidermal necrolysis

TLC total lymphocyte count

TRG Technical Reference Group

ULN upper limit of normal

Up24 Ag ultrasensitive p24 antigen

URTI upper respiratory tract infection

WBC white blood cell count

WHO World Health Organization

1. INTRODUCTION

The most efficient and cost-effective way to tackle paediatric HIV globally is to reduce mother-to-child transmission (MTCT). However, every day there are nearly 1500 new infections in children under 15 years of age, more than 90% of them occurring in the developing world and most being associated with MTCT (1). HIV-infected infants frequently present with clinical symptoms in the first year of life, and by one year of age an estimated one-third of infected infants will have died, and about half by 2 years of age (2, 3). There is thus a critical need to provide antiretroviral therapy (ART) for infants and children who become infected despite the efforts being made to prevent such infections.

In countries where it has been successfully introduced, ART has substantially changed the face of HIV infection. 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 countries hardest hit by the epidemic, unprecedented efforts made since the introduction of the '3 by 5' targets and global commitments to rapidly scale up 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, a lack of affordable simple diagnostic testing technologies, a lack of human capacity, insufficient advocacy and understanding that ART is efficacious in children, limited experience with simplified standardized treatment guidelines, and a lack of affordable practicable paediatric antiretroviral (ARV) formulations. Consequently, far too few children have been started on ART in resource-limited settings. Moreover, the need to treat an increasing number of HIV-infected children highlights the primary importance of preventing the transmission of the virus from mother to child in the first place.

WHO guidelines for the use of ART in children were considered within the guidelines for adults published in 2004 (4). Revised, stand-alone comprehensive guidelines based on a public health approach have been developed in order to support and facilitate the management and scale-up of ART in infants and children.

The present guidelines are part of WHO's commitment to achieve universal access to ART by 2010. Related publications include the revised treatment guidelines for adults (i.e. the 2006 revision), revised guidelines on ARV drugs for treating pregnant women and preventing HIV infection in infants, guidelines on the use of co-trimoxazole preventive therapy (CPT),[(i)] and revised WHO clinical staging for adults and children (5).

(i) These three documents are currently in preparation and are expected to be published by WHO in 2006.

II. Objectives of the Guidelines

These stand-alone treatment guidelines serve as a framework for selecting the most potent and feasible first-line and second-line ARV regimens as components of expanded national responses for the care of HIV-infected infants and children. Recommendations are provided on:

- 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;
- clinical and laboratory monitoring of ART;
- substitution of ARVs for toxicities.

The guidelines consider ART in different situations, e.g. where infants and children are coinfected with HIV and TB or have been exposed to ARVs either for the prevention of MTCT (PMTCT) or because of breastfeeding from an HIV-infected mother on ART. They address the importance of nutrition in the HIV-infected child and of severe malnutrition in relation to the provision of ART. Adherence to therapy and viral resistance to ARVs are both discussed with reference to infants and children. A section on ART in adolescents briefly outlines key issues related to treatment in this age group.

WHO strongly recommends that Paediatic formulations including fixed dose combinations (FDC) of ARVs be made available by the Pharmaceutical Industry. Consultation between partners including the Pharmaceutical Industry and medecines regulatory authorities will be pursued in a separate process. This guideline does not therefore cover the specific needs for ARV drug development.

WHO recognizes the need to strengthen health systems, including human resources capacity and monitoring capabilities, with a view to maximizing 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 counts for infants and young children is important for assisting in decision-making on initiation and optimizing the 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 treatment advisory boards, national AIDS programme managers and other senior policy-makers who are involved in the planning of national and international HIV care strategies for children in resource-limited countries.

The major limitation in developing these guidelines is the lack of appropriate ARV formulations for use in children, and in certain situations the only available option may be to use ARV products intented for adult use.

III. Development of the Guidelines

Since the original guidance on ART for infants and children became available in 2004 there have been advances in the diagnosis and treatment of HIV and data have emerged on efficacy, resistance, drug-drug interactions and the long-term toxicities of ART based on use in resource-limited settings. At a consultation of the Technical Reference Group on Paediatric HIV Care and Treatment (TRG) in Geneva on 20–21 June 2005, experts reviewed and assessed scientific evidence and experiences in the scaling up of paediatric ART and HIV care. This consultation provided the basis for the present recommendations. In giving their advice the experts 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 according to national and international guidelines should begin as soon as is practicable.
- To support implementation in resource-limited settings, ARV regimens should be standardized and simplified. The recommendations in these guidelines are harmonized with the WHO guidelines on treatment in adults, ARVs for treating pregnant women and preventing MTCT of HIV to 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 on regimens that both offer a durable response and preserve future treatment options.
- The recommendations should be based on evidence from randomized controlled trials, high-quality scientific studies for non-treatment related options, or observational cohort data, or, if insufficient evidence is available, on expert opinion, and they should be identified as such. The strength of the recommendations has been indicated as a guide to the degree to which they should be considered by country programmes (Table 1).

- Cost-effectiveness was not explicitly considered as part of these recommendations, although the realities with respect to the availability of human resources, health system infrastructures and socioeconomic contexts were taken into account.
- Revisions to existing recommendations should not disrupt the scale-up efforts already under way in countries. Adaptations in accordance with prevailing local situations may be necessary in order to facilitate implementation.

Following the production of draft guidelines by the designated writing committee, the document was sent to institutional and organizational partners worldwide and made available on the WHO website for public consultation during the period 3–12 November 2005. At a consultation of the writing committee in Geneva on 17–18 November 2005, all comments were validated and addressed, as appropriate, in the final document, which has been reviewed again by the TRG (a list of TRG members is provided in Annex A).

Table 1. Grading of recommendations and levels of evidence

Strength of recommendation	Level of evidence to guide recommendation
A. Recommended – should be followed B. Consider – applicable in most situations C. Optional	I. At least one randomized controlled trial with clinical, laboratory or programmatic endpoints II. At least one high quality study or several adequate studies with clinical, laboratory or programmatic endpoints III. Observational cohort data, one or more case controlled or analytic studies adequately conducted IV. Expert opinion based on evaluation of other evidence

Source: Adapted from references (6) and (7), and:

WHO Evidence Network, http://www.euro.who.int/HEN/Syntheses/hepatitisC/20050408_5

Evidence-based medicine, http: //www.ebm-guidelines. com/ebmg/itk.kati

IV. ESTABLISHING DIAGNOSIS OF HIV INFECTION

This section summarizes WHO recommendations for establishing the presence of HIV infection[(i)] in order to ensure that infants and children can access HIV care and treatment and to aid clinical management. The definitive diagnosis of HIV infection in children at any age requires diagnostic testing that confirms the presence of the human immunodeficiency virus. Antibody testing identifies HIV antibody. However, as maternal HIV antibody transferred passively during pregnancy can persist for as long as 18 months in children born to HIV-infected mothers (8) the interpretation of positive HIV antibody test results is difficult in children below this age. In order to diagnose HIV infection definitively in children aged under 18 months, 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 HIV DNA (9);
- assays to detect HIV RNA (10-13);
- assays to detect p24 antigen (14-16).

The technology for virological tests is often considered too costly and complex for roll-out in low-resource settings. Real-time PCR detects HIV-RNA and HIV-DNA and several automated platforms are commercially available. It has become cheaper and easier to standardize than with previous methods for PCR, providing several advantages in the early diagnosis of HIV infection in children and the monitoring of the effectiveness of ART (17). Ultrasensitive p24 (Up24Ag) assays are also promising alternatives for use in resource-constrained settings (18). The evaluation of such technologies merits further research and urgent standardization. Regardless of the testing technology that will be introduced on a wider scale, the reliability of laboratories should be continuously ensured with standard quality assessments.

Blood may be difficult to collect from young infants and must be sent immediately to the laboratory. More recently, the use of dried blood spots (DBSs) for both HIV-DNA or HIV-RNA testing and Up24 Ag assay has proved robust and reliable (19-26). DBSs do not require venepuncture but can be obtained by using blood

(i) Technical recommendations on diagnosis and case definitions for HIV infection in infants and children are published separately and are being updated in 2006.

from a finger-stick or heel-stick. They carry a smaller biohazard risk than liquid samples, are stable at room temperature for prolonged periods and are easier to transport, thus facilitating centralized laboratory testing (19). The use of DBSs should be more widely implemented in order to improve access to virological testing in a range of resource-limited settings.

National programmes in charge of PMTCT and the provision of ART should strive to ensure that diagnostic protocols are in place for systematic testing of HIV-exposed infants and children, and of symptomatic children where HIV is suspected, including the 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 in infant diagnosis. It needs to be emphasized that children under 18 months of age who are known or suspected to have been exposed to HIV should be closely monitored and should benefit early in life from interventions such as CPT, even where virological testing is not available for the definitive diagnosis of HIV infection.

While HIV antibody testing cannot be used to diagnose HIV infection definitively in infants under 18 months of age, it can be useful for identifying potentially uninfected infants as early as 9 to 12 months of age if they are not breastfed or ceased breastfeeding six weeks or more before the antibody test, as most uninfected HIV-exposed infants have lost maternal antibody by the age of 12 months.

In children aged 18 months or more, HIV antibody tests, including rapid antibody tests (either rapid HIV tests or laboratory based HIV antibody enzyme immunoassays [EIAs] or a combination of both), can be reliably used to diagnose HIV infection definitively in the same manner as they are used in adults.(i)

Additional investment by governments to improve access to earlier HIV diagnosis for infants could 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 the quality of life. In addition, early diagnosis offers other benefits that extend beyond economic savings (27).

Children may or may not have a living parent or identified legal guardian and issues of consent, competency to consent, disclosure, confidentiality and counselling have to be considered. National policies need to be clear in their recommendations on how to provide HIV testing services to infants and children, and programmes should ensure tools and resources provide clear specific guidance

(i) The precise algorithms or combination of tests required to diagnose HIV infection for diagnostic and surveillance purposes are further explained in reference 25.

on informed consent, counselling and disclosure for HIV testing in children.[i] If HIV infection is diagnosed in a young child or infant the mother herself is usually HIV-infected and partners and other siblings may also be infected. Appropriate counselling and support should therefore be provided to families when testing for HIV in children.

Children aged under 18 months

Definitive laboratory diagnosis of HIV infection in children aged under 18 months can only be made by conducting virological testing. For purposes of clinical management including iniation of ART, where access to these virological tests is limited, WHO advises that the first virological testing should be conducted at or around 6 weeks following birth (28-30). Although earlier virological testing, during the first 48 hours of life of an HIV-exposed infant, can identify 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 (30). It is considered more programmatically efficient to perform initial virological testing from the age of 6 weeks. A positive virological test at any age, however, is considered diagnostic of HIV infection. Preferably, a repeat test on a separate specimen should be done to confirm an initial positive test. It is recognized, however, that in severely resource-constrained settings, repeat virological testing on either the same specimen or a separate one to confirm diagnosis may not be feasible or affordable.

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 on the basis of one positive virological test, HIV antibody testing should preferably be performed after 18 months of age in order to confirm HIV infection (Fig. 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. Consequently, a negative virological test in an infant who is continuing to breastfeed does not rule out HIV infection. On the basis of expert opinion, WHO advises that virological assays to detect HIV infection can be conducted at least six weeks or more after the complete cessation of breastfeeding. If a child is 9–18 months of age when breastfeeding is discontinued, HIV antibody testing can be performed prior to

(i) The WHO online toolkit on HIV testing and counselling includes a section of resources on HIV testing and counselling in children and is available at: http://who.arvkit.net/tc/en/index.jsp

virological testing because HIV antibody testing is less expensive and often easier to perform than virological testing. Only infants and children who still have HIV antibody (i.e. those who have either acquired HIV infection or have persisting maternal antibodies) are likely to be HIV-infected and therefore need further virological testing for definitive diagnosis of infection (Fig. 1).[(i)]

HIV-exposed symptomatic infants and children

Where virological testing is not routinely available, any child under 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 in a symptomatic infant or child indicate HIV infection.

HIV-exposed asymptomatic infants and children

By the age of 12 months most uninfected HIV-exposed children have lost maternal antibody, and testing HIV antibody-positive at this age can be considered indicative of HIV infection (i.e. 94.5% seroreversion at the age of 12 months) (31-33). This should be confirmed by repeat antibody testing after the age of 18 months.

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

When HIV DNA assays are used for diagnosis, the use of ARV drugs in the mother or infant for PMTCT should not affect the test result. 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, and so HIV DNA testing can be conducted in infants who have received ARV for MTCT prevention. There are theoretical concerns about the sensitivity of HIV RNA or Up24 antigen assays. However experts based on currently available data recommend that the RNA or Up24Ag can be used at any time from 6 weeks of age (12,13,26).

Diagnosing infection when the mother is on ART

Theoretical concerns also relate to whether maternal ART during breastfeeding affects HIV RNA or p24 detection in infants in the light of the relatively high ART levels found in the infants of breastfeeding mothers (34), DNA detection

(i) The precise time taken by children to develop HIV antibody following postpartum acquisition of HIV infection is not known.

is unaffected by maternal ART. Experts recommend that all the above methods of virological testing can be used from 6 weeks of age even if the mother is breastfeeding and on ART.

Children aged 18 months and more

Definitive HIV diagnosis in children aged 18 months and more (with known or unknown HIV exposure) can be made with antibody tests, including rapid antibody tests following standard testing algorithms used for adults (Fig. 1). The confirmation of a positive antibody test result should follow standard national testing algorithms, and at a minimum should involve duplicate testing by means of a different HIV antibody test (35, 36). The use of rapid antibody tests for diagnosis has the advantage that the results become available at the time of the clinic visit.

Presumptive clinical diagnosis of HIV infection

No single clinical diagnostic algorithm has proved highly sensitive or specific for the diagnosis of HIV infection. Clinical algorithms are rarely more than 70% sensitive for the accurate diagnosis of infection (37) and they vary considerably with age, in particular they are less reliable in children aged under 12 months (38). HIV antibody testing, especially rapid testing, and increased access to early virological testing must be made available to help clinicians implement improved diagnostic algorithms. However, there are situations where the use of a clinical algorithm may be required to initiate appropriate life-saving treatment of a seriously ill child under the age of 18 months. Currently, insufficient data are available to make firm recommendations on the use of clinical algorithms combined with the measurement of CD4 or other parameters for establishing HIV infection. It should be emphasized that WHO clinical staging of HIV disease can only be conducted where HIV infection has been established.

Children aged under 18 months

For infants and children aged under 18 months where access to virological testing is not yet available but where there are symptoms 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 (see Section V).

WHO encourages researchers and national programmes to validate approaches to presumptive clinical diagnosis in children under 18 months of age, including studies to determine if % CD4+ or CD4/CD8 ratio combined with clinical signs

and symptoms improves the early diagnosis of HIV infection. WHO urges national programmes to increase access to diagnostic testing for HIV infection for all children born to HIV-infected women. The development of tests applicable to resource-limited settings so as to allow early diagnosis of HIV infection in infants is critical to the implementation of recommendations for the initiation of appropriate care, including ART, in children aged under 18 months.

Children aged 18 months and more

For children aged 18 months and older with signs and symptoms suggestive of HIV, WHO strongly recommends the use of antibody testing following national protocols in order to diagnose HIV infection (Table 2 & Fig. 1). Presumptive clinical diagnosis of severe HIV disease is therefore not indicated because standard HIV antibody testing is diagnostic of HIV infection in this age group. Some clinical conditions are very unusual without HIV infection (i.e. *Pneumocystis* pneumonia, oesophageal candidiasis, lymphoid interstitial pneumonitis, Kaposi's sarcoma and cryptococcal meningitis), and the diagnosis of these conditions thus suggests HIV infection and indicates the need to perform HIV antibody testing.

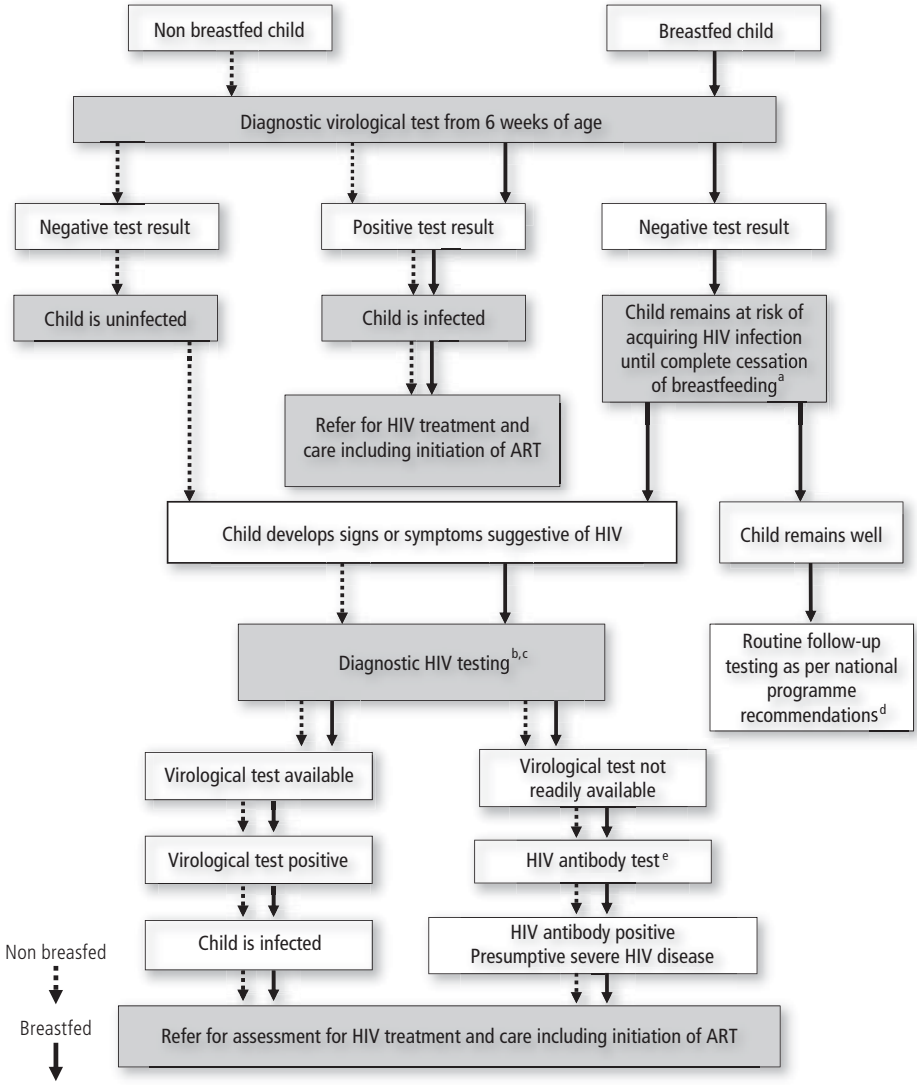
Table 2 summarizes the recommended methodologies for establishing the presence of HIV infection.

Table 2. Summary of recommendations on methods for establishing the presence of HIV infection in infants and children

Method of diagnosis	Recommendations for use	Strength of recommendation/ level of evidence
Virological methods	To diagnose infection in infants and children aged under 18 months; initial testing is recommended from 6 weeks of age	HIV DNA [A(I)] HIV RNA [A(I)] U p24 ag [CII]
HIV antibody testing	To diagnose HIV infection in mother or identify HIV exposure of infant	A(I)
	To diagnose HIV infection in children aged 18 months or more	A(I)
	To identify HIV-antibody positive children aged under 18 months and support a presumptive clinical diagnosis of severe HIV disease to allow initiation of ART	A(IV) [a]
	To exclude HIV infection where HIV antibody negative in children aged under 18 months who are HIV exposed and never breastfed	A(I)
	To exclude HIV infection where HIV antibody negative in children aged under 18 months who are HIV exposed and discontinued breastfeeding for more than 6 weeks	A (IV)

[a] Children aged under 18 months who have positive HIV antibody tests include those who are truly HIV-infected and those who have persisting maternal antibody but are uninfected. By the age of 12 months most uninfected children have lost maternal antibody and positive antibody testing at this time usually indicates HIV infection, although confirmatory testing at 18 months is recommended.

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 virological 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 initiating ART in infants and children relies on clinical and immunological assessment. In order to facilitate scale-up to universal access to ART, WHO emphasizes 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, and WHO encourages national programmes to increase access to CD4 measurement technologies. Decision-making about starting treatment is particularly important for children aged under 12 months as the probability of death in untreated HIV-infected children is high: mortality rates of up to 40% by the age of 1 year have been reported (2, 3, 39, 40).

The decision about when to start ART should also involve evaluation of the social environment of the child who may need therapy. This should include the identification of a clearly defined caregiver who understands the prognosis of HIV and the implications of ART (i.e. lifelong therapy, non-adherence, administration, toxicities and storage of drugs). Access to nutritional support (see Section XIII) and family support groups, preferably including the identification of a secondary (back-up) informed caregiver is advised. The status of disclosure to the child and among the family are also 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 harmonized with the adult classification system (Table 3).

Table 3. 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

[a] Annex B provides further details on staging events and criteria for recognizing them.

Clinical staging is for use where HIV infection has been confirmed (i.e. serological and/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 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 recognizing them.

A preliminary analysis of the revised WHO staging based on clinical signs at baseline and disease history in children enrolled in the Children with HIV Antibiotic Prophylaxis (CHAP) trial (41) showed that clinical stage without ART can predict mortality. However, this was dependent on the malnutrition criteria in the staging definitions (D. Gibb, unpublished observations, 2005). The clinical stage therefore 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. There is an urgent need for studies on the use of clinical criteria (i.e. clinical staging events on treatment) for when to switch the ARV regimen in the absence of viral load testing (see Section X).

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 in order to guide decision-making on the initiation of ART. The 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 the age of about 6 years; percentage CD4+ (i.e. %CD4+) values vary less with age. In considering the results of immunological parameters, age must therefore be taken into account as a variable. In children under 5 years of age the absolute CD4 count tends to vary within an individual child more than %CD4+. Currently, therefore, the measurement of %CD4+ is thought to be more valuable in children under 5 years of age. Absolute CD4 counts and, to a lesser extent, %CD4+ values, fluctuate within an individual and values can vary with intercurrent illness, physiological changes, timing of test or test variability. Serial measurements are therefore more informative than individual values and also reflect trends over time. Where possible, these assessments should compare 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 absolute CD4 counts and %CD4+, two values below threshold should, if possible, be obtained before the 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 stages 1 and 2) (5, 42-44). The results of CD4 measurement are also useful for monitoring 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 above) (Table 5) are derived from longitudinal data on HIV-infected infants and children, and, except in children aged under 1 year, correspond to a 12-month mortality risk of 5% or less (45). It should be noted that in infants under 6 months of age the %CD4+ or the 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 cells/mm^3). These data are based on studies in HIV-infected children in resource-rich countries. Studies aimed at validating these thresholds in infected children in resource-limited countries are urgently needed.(i) These thresholds also indicate the level at or below which ART is

(i) In the United States of America, where virological testing in the neonatal period is routinely performed, in view of the poor predictive value of CD4 values most experts tend to start all HIV-infected infants on ART.

indicated. Where %CD4+ is not available, absolute CD4 count thresholds may be used (i.e. <1500 cells/mm^3 for infants aged ≤11 months, <750 cells/mm^3 for children aged 12–35 months, or <350 cells/mm^3 for children aged 36–59 months). For children aged 5 years and above the same cut-off value as in adults, i.e. <200 cells/mm^3, can be used (Table 5). Asymptomatic HIV-infected children (i.e. those with clinical stage 1 and 2 disease) should be considered for ART when immunological values fall to near the described threshold values. A drop below threshold values should be avoided. It should be emphasized that severe HIV-related disease always requires ART, irrespective of whether defined clinically or immunologically. Advanced HIV disease also requires the initiation of ART, again whether defined clinically or immunologically (see Table 3 and Annex C). However, in children aged 12 months and above 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 12–35 months or >15% or >200 cells/mm^3 in children aged 5 years and above 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 serve as a guide as to whether ART is urgently required or can be delayed (Section XII). Annex C provides 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 (46). 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 aged 3–5 years, <2000/mm^3 for children aged 5–8 years) (Table 6) define similar mortality risks to those of the CD4 thresholds (47). As for the %CD4+ and the absolute CD4 count, the predictive value of TLC for mortality in very young children (i.e. under 6 months of age) is poor, as high mortality can occur even at high TLC values. In situations where CD4 measurements are not available, TLC may be used as an indication of the need to initiate ART in infants or children aged up to 8 years with WHO paediatric clinical stage 2 disease.

The figure in Annex D illustrates the 12-month mortality risk at selected thresholds for %CD4+, absolute CD4 count and TLC.

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

WHO paediatric stage	Availability of CD4 cell measurements	Age-specific treatment recommendation [A (II)]*	
		≤11 months	≥12 months
4[a]	CD4[b]	Treat all	
	No CD4		
3[a]		Treat all	Treat all, CD4-guided in those children with TB,[c] LIP, OHL, thrombocytopenia
	No CD4		Treat all[c]
2	CD4[b]	CD4-guided[d]	
	No CD4	TLC-guided[d]	
1	CD4[b]	CD4-guided[d]	
	No CD4[b]	Do not treat	

* Strength of recommendation/level of evidence.

[a] Stabilize any opportunistic infection before initiation of ART.

[b] Baseline CD4 is useful for monitoring 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 XII).

[d] Refer to Table 5 for CD4 and table 6 for TLC values.

TABLE 5. CD4 CRITERIA FOR SEVERE HIV IMMUNODEFICIENCY

Immunological marker[a]	Age-specific recommendation to initiate ART[b] [A (I)]*			
	≤11 months	12 months to 35 months	36 months to 59 months	≥5 years
%CD4+[c]	<25%	<20%	<15%	<15%
CD4 count[c]	<1500 cells/mm^3	<750 cells/mm^3	<350 cells/mm^3	<200 cells/mm^3

* Strength of recommendation/level of evidence.

[a] Immunological markers supplement clinical assessment and should therefore be used in combination with clinical staging. CD4 is preferably measured after stabilization 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 aged <5 years.

TABLE 6. TLC CRITERIA FOR 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]	Age-specific recommendation to initiate ART[b] [C (II)]*			
	≤11 months	12 months to 35 months	36 months to 59 months	5 to 8 years[c]
TLC	<4000 cells/mm^3	<3000 cells/mm^3	<2500 cells/mm^3	<2000 cells/mm^3

* 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 on which to base recommendations on the use of TLC for decision-making in children aged over 8 years.

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, WHO does not currently recommend its routine use in order to assist with decisions on when to start therapy in resource-limited settings. 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.

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, guided by expert opinion, has developed clinical criteria for diagnosing presumptively severe HIV disease in children under 18 months of age, in order to allow appropriate management of potentially HIV-infected children. 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 the initiation of ART. The use of a presumptive clinical diagnosis of infection in a child aged under 18 months for the initiation of ART should be accompanied by immediate efforts to establish the HIV diagnosis with the best nationally or locally available test for age but at the latest with HIV antibody testing at 18 months of age. Decisions on further treatment should be adjusted at that time in accordance with the results.

In infants and children who have been started on ART on the basis of a presumptive clinical diagnosis of severe HIV disease the therapy should be closely monitored. ART should be stopped in infants and children where HIV infection can be confidently ruled out and who are no longer exposed to HIV (i.e. through breastfeeding from an HIV-infected mother).

The initiation of ART on the basis of a presumptive clinical diagnosis of severe HIV disease is not recommended for use by clinical care providers who are not appropriately trained in HIV care or the administration of ART. The use of clinical criteria to make a presumptive diagnosis of HIV infection is not needed in children aged 18 months and above as antibody testing establishes their HIV infection status.

Box 1 lists the criteria for the presumptive clinical diagnosis and Box 2 summarizes the WHO recommendations for starting ART in infants and children.

Box 1. Clinical criteria for presumptive diagnosis of severe HIV disease in infants and children aged under 18 months 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 as being 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:
  - oral thrush;[b]
  - severe pneumonia;[b]
  - 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.

* Strength of recommendation/level of evidence

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

[b] As per IMCI definition:

- **Oral thrush:** Creamy white to yellow soft small plaques on red or normally coloured mucosa which can often be scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender.
- **Severe pneumonia:** Cough or difficult breathing in a child with chest indrawing, stridor or any of the IMCI general danger signs; i.e. lethargic or unconscious, not able to drink or breastfeed, vomiting, and presence or history of convulsions during current illness; responding to antibiotics.
- **Severe sepsis:** Fever or low body temperature in a young infant with any severe sign, e.g. fast breathing, chest indrawing, bulging fontanelle, lethargy, reduced movement, not feeding or sucking breast milk, convulsions.

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

Box 2. SUMMARY OF WHO RECOMMENDATIONS FOR ART INITIATION IN INFANTS AND CHILDREN

1. Infants and children with established HIV infection (as per Section IV) 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 over 12 months with tuberculosis, lymphocytic interstitial pneumonia, oral hairy leukoplakia or thrombocytopaenia, ART initiation may be delayed if CD4 is available and above threshold values[a] for initiating ART;
   - WHO paediatric clinical stage 2 disease *and* CD4 *or* TLC[b] value at or below threshold; [a]
   - WHO paediatric clinical stage 1 disease *and* CD4 value at or below threshold.[a]
2. If virological testing is not available to confirm HIV infection, HIV antibody-positive infants and children aged under 18 months should be considered for ART if they have clinically diagnosed presumed severe HIV disease.[c]

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

[b] Threshold values for TLC are provided in Table 6. TLC is useful for decision-making for of 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 in Box 1.

VI. What to start – recommended first-line ARV regimens in infants and children

Considerations for treatment using a public health approach

Countries are encouraged to use a public health approach to support and facilitate wider access to ART. Among the key tenets of this approach are standardization and simplification of ARV regimens. It is therefore suggested that countries select a limited number of first-line regimens and suitable second-line regimens, recognizing 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 in order to achieve the best possible suppression of viral replication and to arrest the progression of HIV disease. It is important to maximize the durability and efficacy of any first-line regimen by incorporating approaches to support adherence.

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

- ability to treat all ages;
- suitability of drug formulation, particularly for infants and young children and caregivers, including, where possible, licensing approval by national drug regulatory authorities for the product and the 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 caregivers, as appropriate);
- prevalent coexisting conditions (e.g. coinfections, malnutrition, malaria, TB, possibly hepatitis B and C);

- availability and cost-effectiveness;
- capacity of drug procurement and supply systems.

The choice of an appropriate ARV regimen may be further influenced by: access to a limited number of ARV drugs in forms suitable for the treatment of infants and young children (see special considerations below); limited health service infrastructures (including human resources); and the presence of varied HIV types (e.g. HIV-2).

Considerations for drug formulations and doses for children

Quality-assured[(i)] ARV drugs in fixed-dose combinations (FDCs),[(ii)] or blister packs[(iii)] are mostly used in adults and older children. It is to be hoped that they increasingly become available in the future for administration to younger children. Once-daily dosing has become available for some adult ARV combinations and further simplifies drug regimens. The advantages of FDCs and once-daily dosing include improved adherence which, in turn, limits the emergence of drug resistance and 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 under 14 kg.

Syrups and solutions remain necessary for treating infants and very young children who cannot swallow whole tablets or capsules but they have shortcomings, which may include limited availability, high cost, storage difficulties, reduced shelf-life, alcohol excipient and poor palatability. As children become older it is preferred to give solid formulations (parts of scored tablets or combination preparations; see WHO/UNICEF meeting report on paediatric ARV formulations at http://www.who.int/3by5/paediatric/en/index.html). For some ARVs,

(i) In the context of this document, quality-assured medicines assembled in fixed-dose combinations (FDCs) include individual products deemed to meet international standards for quality, safety and efficacy. For WHO's work on the prequalification of ARVs, see: http://www.who.int/3by5/amds/en/

(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 aluminium blister containing two or more pills, capsules or tablets.

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, and some solid formulations do not have all the drug components evenly distributed in the tablets, while others lack pharmacokinetic data to enable accurate dosing. National drug regulatory authorities should consider these factors when making decisions on licensing products for use in children.

While satisfactory virological and immunological benefits in children receiving an adult fixed-dose combination of stavudine/lamivudine/nevirapine (d4T/3TC/NVP) tablets in fractions were reported from Thailand (48) and Uganda (49), the use of tablets that require cutting up, particularly unscored tablets, can result in the underdosing or overdosing of children, and this may 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 suboptimal, may, however, be the only currently available option for the treatment of children as soon as feasible (usually when a weight of 10–12 kg is achieved), and may be considered when no alternatives are available. The use of tablet cutters is beneficial but it is preferable not to cut tablets to fractions below a half. Pharmacokinetic studies in Malawian children confirm that the use of single-drug liquid formulations is better than splitting adult FDCs for smaller children (50).

Dosing in children is usually based on either body surface area or weight (51). As these change with growth, drug doses must be adjusted in order to avoid the risk of underdosage. Standardization is important and it is desirable to provide health care workers with tables of simplified drug doses that can be administered. Such tables may vary between localities in accordance with the availability of ARV drugs and formulations in the countries concerned. WHO has developed prototype dosing tables based on weight, and tools to assist countries with the standardization and calculation of drug doses[(i)] (Annex E). Fixed-dose formulations for children became available in late 2005; they include d4T/3TC/NVP in different strengths, although they are not yet approved by stringent regulatory authorities.

FDC of standard first and second line ARV regimens are urgently needed for younger children.

(i) A web-based tool to assist in development of dosing tables for national programmes should be available on the WHO website from mid 2006.

Considerations for the choice of a first-line regimen

Studies of antiretroviral therapy in children demonstrate that similar improvements to those obtained in adults are seen in morbidity, mortality and surrogate markers with many different potent ARV regimens (39, 52-55). The preferred option when choosing a first-line regimen for infants and children is two nucleoside reverse transcriptase inhibitors (NRTIs) plus one non-nucleoside reverse transcriptase inhibitor (NNRTI) (Box 3). These drugs prevent HIV replication by inhibition of the action of reverse transcriptase, the enzyme that HIV uses to make a DNA copy of its RNA. The technical reference group based this decision on available evidence, clinical experience and programmatic feasibility for the wider introduction of ART to infants and children in resource-limited settings. NRTI/NNRTI-based regimens are efficacious and 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 [PIs]) for the second line. The disadvantages include different half-lives, the fact that a single mutation is associated with resistance to some drugs (e.g. lamivudine [3TC], NNRTIs), and, in respect of the NNRTIs, 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], zidovudine [AZT]) or a guanosine analogue NRTI (i.e. abacavir [ABC]), combined with a cytidine analogue NRTI, (i.e. lamivudine [3TC] or emtricitabine [FTC]) and an NNRTI (i.e. efavirenz [EFV] or nevirapine [NVP]). A caveat is that EFV is not currently recommended for use in children under 3 years of age because of a lack of appropriate dosing information, although these matters are under study. For such children, consequently, NVP is the recommended NNRTI. Additional concerns about NNRTIs as components of first-line regimens relate to their use in adolescents (see Section XIV); 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^3. The available data on infants and children indicate a very low incidence of severe hepatotoxicity for NVP without association with CD4 count (56).

Box 3. SUMMARY OF RECOMMENDED PREFERRED FIRST-LINE ARV REGIMENS FOR INFANTS AND CHILDREN

Regimen of 2 NRTI plus 1 NNRTI:[a]

[A (II)]*

AZT[b] + 3TC[c] + NVP[d]/EFV[e]
d4T[b] + 3TC[c] + NVP[d]/EFV[e]
ABC + 3TC[c] + NVP[d]/EFV[e]

* Strength of recommendation/level of evidence.

[a] The use of AZT, d4T, ABC with 3TC results in several possible dual nucleoside combinations (see following section on choice of NRTI).

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

[c] Where available, FTC can be used instead of 3TC in children over 3 months of age.

[d] NVP should be used with caution in postpubertal adolescent girls (considered as adults for treatment purposes) with baseline CD4 absolute cell counts >250/mm^3.

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

The use of a triple NRTI regimen (i.e. AZT/d4T + 3TC + ABC) can be considered as an option for simplifying initial therapy in special circumstances (Box 4). A concern is the somewhat lower virological potency of this regimen compared to a two-class triple drug combination in adult studies (57-60) and therefore its use is currently restricted to 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 XII). Another possible indication for the use of a triple NRTI regimen is the treatment of pregnant adolescent girls with CD4 absolute cell counts >250/mm^3. This regimen, especially where combined in a single pill, could also be considered in adolescents with anticipated or documented poor adherence (see Section XIV).

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

Regimen of triple NRTI:

[C (III)]*

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

* 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 in children over 3 months of age.

Choice of NRTIs

The drugs from the NRTI class recommended for children within the public health approach are described below.

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

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

The choice between d4T, AZT or ABC to be combined with 3TC should be made at the country level on the basis of local considerations but it is recommended that at least two of these NRTIs be available to allow the substitution of one drug for the other should there be toxicity.

Stavudine (d4T) is an 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 (62) and lactic acidosis. In addition, elevated hepatic transaminases and pancreatitis have been observed. d4T can also cause peripheral neuropathy, although these complications appear to be less common in children than in adults (63, 64). d4T liquid formulations require a cold chain and the capsule size starts at 15 mg only. While fewer

laboratory monitoring requirements may be a good reason to favour d4T over AZT as the chosen NRTI component, in particular during the rapid scale-up of programmes, the considerable risk of lipoatrophy in children treated with d4T-containing regimens remains. National programmes may therefore need to take into account the comparative short-term and long-term toxicities of first-line options (see Section VIII) and introduce measures for the close monitoring of drugs associated with an increased risk for toxicities. It is worth emphasizing that d4T and AZT should never be used together because of proven antagonism between them (65, 66) (Box 5).

Zidovudine (AZT) is generally well tolerated in children but has been associated with metabolic complications of therapy, although to a lesser extent than d4T. Initial drug-related side-effects are more frequent with AZT and the drug can cause severe anaemia and neutropenia; haemoglobin monitoring before and during treatment with AZT is thus useful. This is particularly important in areas with stable malaria or where malnutrition is common and anaemia is highly prevalent in young children. Large volumes of AZT liquid formulation 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, where neither drug should be restarted. As noted above, AZT should not be administered in combination with d4T.

Abacavir (ABC), has been included in these revised paediatric guidelines as an alternative NRTI in first-line therapy, representing a change from the 2003 guidelines that recommended reserving the use of ABC as part of second-line regimens. Clinical trial results in antiretroviral-naive persons demonstrating efficacy, availability of ABC in paediatric formulation, and the resulting potential to deliver family-based care of HIV-infected parents and children with ABC/3TC, offset concerns about introducing an additional first-line drug. Reports from a randomized, partly blind multicentre trial comparing dual NRTI regimens (PENTA-5) (67) have shown that ABC-containing dual NRTI regimens (ABC/3TC or ABC/AZT) are more effective than regimens containing AZT + 3TC 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 adults, with very little haematological toxicity. NRTI combinations containing ABC therefore provide a good NRTI backbone for use with NNRTIs or as part of a triple nucleoside regimen. Of all the NRTI drugs, ABC has the least effect on mitochondrial DNA (68) and would be the preferred substitute for d4T in children developing 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 about 3% of children who receive it (67). 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 consult their care provider immediately if signs or symptoms of a hypersensitivity reaction occur.

Tenofovir (TDF), is another drug that has been incorporated as an effective option for first-line regimens in adults. Because of concerns about the limited data on safety and toxicity (i.e. bone mineralization and potential renal toxicity) the use of TDF in children is not encouraged until further data become available. TDF is generally well tolerated (69), although there have been reports of renal insufficiency in adult patients receiving it (70-72). A study in 16 HIV-infected children (age range 6.4 to 17.9 years) on 12-month treatment comparing TDF and d4T reported that TDF did not impair bone mineral accrual while demonstrating a good immunological response to ART (73). However, a paediatric study in HIV-infected antiretroviral-experienced children (age range 8.3 to 16.2 years) demonstrated a decrease of more than 6% in bone mineral density in about 30% of those evaluated after 48 weeks of TDF therapy, thus potentially limiting the use of TDF among prepubertal children (74).

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

Box 5. Summarizes the NRTI drug combinations that should be avoided.

Box 5. NRTI DRUG COMBINATIONS TO BE AVOIDED[a]

- **d4T + AZT - both drugs work through common metabolic pathways [A(I)]***
- **d4T + ddI[b] - these drugs have overlapping toxicities [A(I)]***
- **TDF + 3TC + ABC[c]**
- **TDF + 3TC + ddI[d]**
- **TDF + ddI + NNRTI[e]**

} **these regimens are associated with a high incidence of early virologic failure [A(III)] ***

* Strength of recommendation/level of evidence

[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 (see Section XI).

[c] Data from three clinical trials in adults involving the combination of TDF + 3TC + ABC demonstrated high rates of virological failure and drug resistance. Given these concerns and the lack of clinical data, this NRTI backbone should not be used in treatment-naïve patients. Another report confirms that ABC and TDF select for the K65R mutation, which reduces susceptibility to both drugs (75).

[d] A pilot study using this regimen resulted in a high incidence of K65R mutation and virologic failure (76).

[e] Source: references (77-80).

Choice of NNRTIs

NNRTI-based regimens are now the most widely prescribed combinations for initial therapy. They are potent, i.e. they rapidly reduce the 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) have both demonstrated clinical efficacy when administered in appropriate combination regimens in children. However, differences in toxicity profile, the potential for interaction with other treatments, a lack of dosing information for EFV in young children, and cost are factors that need to be taken into consideration when choosing an NNRTI (81-88).

Efavirenz (EFV) is not currently recommended for use in infants and children under 3 years of age because there is no established dosing. EFV is primarily associated with toxicities related to the central nervous system (CNS), teratogenicity and rash. Rash is more frequent in children than 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 have revealed transient CNS disturbance in 26% to 36% of children receiving EFV (55, 88). EFV should be avoided in children with a history of severe psychiatric illness, where there is a potential for pregnancy (unless effective contraception can be assured) and during the first trimester of pregnancy. In these situations, NVP may be the better choice (see below). EFV may be considered as the NNRTI of choice in children with TB/HIV coinfection (see Section XII).

Nevirapine (NVP) should only be given in combination with other antiretrovirals, except when used for single-dose prophylaxis to reduce the risk of perinatal HIV transmission. NVP has a higher incidence of rash than other ARVs. NVP-related rash may be severe and life-threatening, including Stevens-Johnson syndrome, and, as noted 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. There are limited data on the use of NVP in children coinfected with HIV and hepatitis B. NVP is currently the only NNRTI syrup available for infants. It also exists as part of three-drug FDCs which could be used for older children when quality-assured formulations of proven bioequivalence are available.

NVP may be the preferred choice in adolescent girls when there is potential for pregnancy, or during the first trimester of pregnancy when EFV should be avoided because of its potential teratogenic effect. However, symptomatic NVP-

associated hepatotoxicity or serious rash, while uncommon, is more frequent in women than in men, and is more likely to be seen in antiretroviral-naive women with higher CD4 cell counts (>250 cells/mm^3). Thus, NVP should be used with caution in adolescent girls with CD4 counts between 250 and 350 cells/mm^3; if used in such adolescent girls, careful monitoring is needed during the first 12 weeks of therapy, preferably including liver enzyme monitoring.

Limited data indicate that both EFV and NVP may interact with estrogen-based contraceptive pills. Because exposure to EFV should be avoided in the first trimester of pregnancy it is recommended that sexually active adolescent girls receiving EFV consistently use barrier methods to prevent pregnancy in addition to or instead of oral contraceptives. Studies are in progress to evaluate interactions between medroxyprogesterone acetate and selected PI and NNRTI drugs.

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

Use of protease inhibitors (PIs) in initial therapy

It is recommended that the PI class of drugs be reserved for second-line therapy because the use of PIs in an initial treatment regimen compromises any subsequent second-line regimen. Until further data become available, this also holds true in situations where single-dose NVP has been used for PMTCT (see Section VII). Currently available PIs are described in more detail in Section XI.

VII. Considerations for ART in infants previously exposed to ARV drugs

ART in infants exposed to ARVs through interventions to prevent mother-to-child transmission

If a mother has received ARVs during pregnancy, either for prevention 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 prevention (i.e. the infant component of 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 prevention of MTCT, because a single point mutation is associated with resistance to each of these drugs (89, 90). 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 (89). 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 (i.e. South Africa NEVEREST study and Botswana) or are planned (i.e. multicountry PACTG 1060), as they are in mothers, to investigate whether single-dose NVP prophylaxis compromises subsequent ART with NNRTI-based regimens. WHO recognizes the urgency of such research. 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 ARVs due to maternal ART in breastfeeding 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(30, 81). 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. Because of the benefits of breastmilk, continued breastfeeding should be encouraged. In addition, it is possible that the ingestion of subtherapeutic 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 insufficient data to make recommendations.

Box 6 summarizes the recommendations on ART in infants with previous or continuing exposure to ARVs.

Box 6. Summary of recommendations on ART in infants and children exposed to ARV drugs [B (IV)]*

- Infants who were exposed to ARVs for prevention of mother-to-child transmission, either the maternal or infant component, and/or
- Breastfeeding infants who are exposed to antiretroviral drugs because of maternal ART

} should be considered eligible for the standard 2 NRTIs + 1 NNRTI first-line ARV regimen using the same doses and criteria as are outlined in Sections V and VI.

Research is urgently needed to identify the efficacy of ART in infants with previous or continuing exposure to ARVs.

* Strength of recommendations/ level of evidence.

VIII. ANTIRETROVIRAL DRUG TOXICITY

It is sometimes difficult to differentiate between complications of HIV disease and toxicity (also known as adverse events) secondary to ARV drugs used for the management of HIV infection or drug-drug interactions. Alternative explanations for toxicity must be excluded before concluding that it is secondary to the ARV drugs. Such explanations for an observed toxicity could include a concurrent infectious process (e.g. 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 ARV drugs (such as isoniazid-induced hepatitis in a child on tuberculosis treatment or co-trimoxazole-induced rash in a child receiving CPT). Adverse reactions that have a non-ARV drug etiology do not require the ARV drug to be changed. However, because of the risk of potentially life-threatening hepatotoxicity associated with NVP, hepatic dysfunction of any etiology requires careful consideration be given to the 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 (91). However, some toxicities are less common in children than in adults (e.g. NVP-related symptomatic hepatotoxicity is rare in children), while others are more 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 should be paid to pharmacovigilance and post-marketing surveillance in paediatric populations.

Drug-related adverse events may be acute, occurring soon after a drug has been administered; they may be subacute, occurring within 1 to 2 days of administration; or they may be late, occurring after prolonged drug administration. Such adverse events may vary in severity from mild to severe and life-threatening. Experience with ARV drugs has led to the recognition of several types of distinct adverse drug effects that may be most common with certain ARV drugs or drug classes, including:

- haematological adverse events associated with 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, 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 to a lesser degree with certain other NRTI drugs (abnormalities include fat maldistribution and body habitus changes, hyperlipidaemia; hyperglycaemia, insulin resistance, diabetes mellitus, osteopaenia, 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 can also be assessed by means of a limited number of laboratory tests, depending on the specific ARV combination regimen that is utilized and the health care setting. Routine laboratory monitoring, although desirable, is not required and cannot be carried out in many decentralized facilities.

The management of the patient and the decision about the potential need to stop drugs or to substitute[(i)] a new ARV drug for a drug associated with 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 7). Given the limited number of ARV drugs and drug combinations available in resource-limited settings, it is preferable to pursue drug substitutions where feasible so to avoid premature switching to completely new alternative regimens, and 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 the substitution of an ARV drug associated with toxicity by a drug in the same ARV class but with a different toxicity profile (e.g. peripheral neuropathy) or by a drug in a different class, but do not require discontinuation of all ART. *Severe life-threatening toxicity* requires discontinuation of all ARV drugs and the initiation of appropriate supportive therapy (such as intravenous fluids), depending on the toxicity, with substitution of another drug for the one associated with the toxicity once the patient is stabilized and the toxicity is resolved (see Annex F). NNRTI drugs have a much longer half-life than NRTIs, leading to a concern that

(i) Substitution is the exchange of one drug in a (first-line) regimen for another (first-line regimen) drug; this is different from switching a drug because of failure when all drugs of a regimen are changed to a different (second-line) regimen (see Sections IX and X).

stopping all drugs simultaneously results in exposure to drugs from the NNRTI class only. However, if a child has a life-threatening toxicity, all ARV drugs should be stopped simultaneously until the patient is stabilized.

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 for management to district or regional hospital centres or consultation with an HIV expert is recommended.

Regardless of their severity, adverse events may affect adherence to therapy. A proactive approach to managing toxicity is recommended. Discussing the potential side-effects of the ART regimen before the initiation of therapy and during the early stages of treatment with the child and her/his caregivers as well as support during minor and moderate adverse events, can increase the likelihood of adherence to therapy (see Section XVI). The child and the caregivers 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 the NVP-associated Stevens-Johnson syndrome, symptomatic hepatitis or the ABC-associated hypersensitivity reaction.

Box 7. 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 attributable to an ARV drug or to a non-ARV medication taken at the same time.
3. Consider other disease processes (e.g. viral hepatitis in a child on ARV drugs who develops jaundice) because not all problems that arise during treatment are caused by ARV drugs.
4. Manage the adverse event according to severity. In general:
   - ***Severe life-threatening reactions*** *(Annex F):* Immediately discontinue all ARV drugs, manage the medical event (i.e. symptomatic and supportive therapy) and reintroduce ARV drugs using a modified regimen (i.e. with an ARV substitution for the offending drug) when the patient is stabilized.[a]
   - ***Severe reactions:*** Substitute the offending drug without stopping ART.[a]
   - ***Moderate reactions:*** Consider continuation of ART as long as feasible. If the patient does not improve on symptomatic therapy, consider single-drug substitutions.[a] For a few moderate toxicities (e.g. peripheral neuropathy or lipodystrophy) single drug substitution needs to be considered earlier.
   - ***Mild reactions*** are bothersome but do not require changes in therapy.
5. Stress the maintenance of 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 stabilized.

[a] Refer to Table 7 for substitution options.

IX. SUBSTITUTING WITHIN A FIRST-LINE ANTIRETROVIRAL DRUG REGIMEN IN INFANTS AND CHILDREN BECAUSE OF DRUG TOXICITY

If toxicity is related to an identifiable drug in a regimen the offending drug can generally be replaced with another drug from the same class that does not have the same adverse effect, 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 resource-limited settings, drug substitutions should be limited to situations where toxicity is severe or life-threatening (see Annex F). For reasons of toxicity the substitution of drugs from the PI class 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 toxicities it may not be possible to identify an optimal substitute drug. For example, in respect of NVP-associated Stevens-Johnson syndrome, most clinicians would avoid substituting another NNRTI drug (efavirenz) because of 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	Most frequent significant toxicity for the ARV drug	Suggested first-line ARV drug substitution
ABC	Hypersensitivity reaction	AZT
AZT	Severe anaemia[a] or neutropenia[b]	d4T or ABC
	Lactic acidosis	ABC[d]
	Severe gastrointestinal intolerance[c]	d4T or ABC
d4T	Lactic acidosis	ABC[d]
	Peripheral neuropathy	AZT or ABC[f]
	Pancreatitis	
	Lipoatrophy/metabolic syndrome[e]	ABC
EFV	Persistent and severe central nervous system toxicity[g]	NVP
	Potential teratogenicity (adolescent girl in first trimester of pregnancy, or of childbearing potential and not receiving adequate contraception)	
NVP	Acute symptomatic hepatitis[h]	EFV[i]
	Hypersensitivity reaction	Preferred substitution of NVP to: ▪ a third NRTI (disadvantage: may be less potent) *or* ▪ PI (disadvantage: premature start of class usually reserved for second-line)[k]
	Severe or life-threatening rash (Stevens-Johnson syndrome)[j]	

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

[a] Exclude malaria in areas of stable malaria, severe anaemia is defined as Hb < 7.5 g/dl.

[b] Defined as neutrophil count < 500/mm^3.

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

[d] Reinitiation of ART should not include d4T or AZT if possible, therefore ABC is preferred.

[e] Substitution of d4T typically may not reverse lipoatrophy.

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

[g] e.g. persistent hallucinations or psychosis.

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

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

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

[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).

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(83-86). Genetic differences in drug metabolism may also be important (92, 93). It is recommended that programmes primarily use clinical criteria, supported, where possible, with CD4 criteria, in order to identify 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, adherence to therapy should have been assessed and considered to be optimal, and any intercurrent opportunistic infections should have been treated and resolved, and immune reconstitution inflammatory syndrome (IRIS) excluded. Additionally, before considering a change in treatment because of growth failure it should be ensured that the child is receiving adequate nutrition.

Clinical definition of treatment failure

The detection of new or recurrent clinical events classified within the WHO clinical staging may also reflect progression of disease when a child is on ART. Treatment failure should be considered when either new or recurrent stage 3 or 4 clinical events develop in a child on therapy (Table 8).

Immune reconstitution inflammatory syndrome

Clinical disease progression should be differentiated from the IRIS, an entity that has been observed in adults and less frequently in children starting ART, particularly those with very low CD4 values (97-102). Symptoms are similar to those seen in opportunistic infections. They usually occur within the first three months after the start of potent ART (103), concurrent with a rapid rise in CD4 values. It is also possible that immunological reconstitution may lead to the development of atypical presentations of some opportunistic infections.

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

TABLE 8. USING THE WHO PAEDIATRIC CLINICAL STAGING EVENTS TO GUIDE DECISION-MAKING ON SWITCHING TO SECOND-LINE THERAPY FOR TREATMENT FAILURE

New or recurrent event on ART[a]	Management options [b, c, d] [A (IV)]
No new events or PGL (T1)	▪ **Do not switch to new regimen** ▪ Maintain regular follow up
Stage 2 events (T2)	▪ **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
Stage 3 events (T3)	▪ **Treat and manage staging event and monitor response[e]** ▪ Check if on treatment 24 weeks or more ▪ Assess and offer adherence support ▪ Assess nutritional status and offer support ▪ Check CD4 [f] – where available ▪ Institute more frequent follow-up ▪ **Consider switching regimen**
Stage 4 events (T4)	▪ **Treat and manage staging event** ▪ Check if on treatment 24 weeks or more ▪ Assess and offer adherence support ▪ Assess nutritional status and offer support ▪ Check CD4 [f] – where available ▪ **Switch regimen**

* Strength of recommendation/ level of evidence.

a A clinical event refers to a new or recurrent condition as classified in the WHO clinical staging at the time of evaluating the infant or child on ART. Annex B provides more details about the clinical events.

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

c Differentiation of opportunistic infections from IRIS is important.

d 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.

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

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

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 characterized by a drop in the CD4 to values at or below their age-related CD4 threshold for the initiation of treatment after initial immune recovery following the initiation of ART. Thus recognition of treatment failure on the basis of immunological values relies on comparison with previous CD4 values. Switching a regimen should particularly be considered if CD4 values fall to below 15% (12–35 months of age), 10% (36–59 months of age), or 100 cells/mm^3 (≥5 years of age). Immunological criteria for recognizing treatment failure are supplemental to clinical criteria (Box 8 and Table 9).

Box 8. CD4 criteria to guide decision-making on switching to a second-line regimen[a,b,c]

[B (IV)]*

- Development of age-related severe immunodeficiency after initial immune recovery.[c]
- New progressive age-related severe immunodeficiency, confirmed with at least one subsequent CD4 measurement.[c]
- Rapid rate of decline to below threshold of age-related severe immunodeficiency.[c]

* Strength of recommendation/level of evidence.

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

b Preferably at least two CD4 measurements should be available.

c Age-related severe immunodeficiency values as defined in Table 5; switching should particularly be considered if %CD4+ values fall to <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 aged under 5 years and absolute CD4 counts 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 on switching ART

CD4 values supplement clinical findings when decisions are being made on switching therapy (Box 8 and Table 9). For children who develop new or recurrent clinical stage 3 conditions these values are useful in determining the need for switching ART. In such children, if the 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. no new clinical events or stage 1 or 2 events), 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 advisable. A regimen switch is not recommended in children with no new clinical events or events of clinical stage 1, 2 or 3 where CD4 values drop but remain above their age-related threshold (Box 8 and Table 9). New or recurrent clinical stage 4 conditions generally warrant a treatment regimen switch although this may be delayed if CD4 is above age related threshold for severe immunodeficiency. In children in whom regimen switch is delayed based on CD4, increased clinical and CD4 follow up is warranted.

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

Where CD4 values are not available a simplified approach is needed to guide decisions on the need to switch to a second-line regimen (Tables 8 and 9). A new or recurrent stage 4 event (T4) is usually a sufficient criterion to consider switching. In children developing a new or recurrent stage 3 event (T3), and where CD4 measurements are not available, switching the regimen may be considered. However, it is recommended that a child with pulmonary or lymph node TB or with severe recurrent bacterial pneumonia (all considered clinical stage 3 events) 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 a regimen should not be switched if CD4 measurements are not available.

Decision-making on switching ART using viral load measurement

WHO does not currently recommend the use of routine viral load in decision making on treatment failure. Where CD4 and clinical criteria for recognizing treatment failure are conflicting then viral load assessment can add useful information. In adults a viral load greater than 10,000 copies is proposed to reflect viral replication suggestive of treatment failure, thresholds for children are not yet defined and validation is urgently required. Levels of HIV-RNA greater than 100,000 copies in children are associated with greater risk of mortality and indicate a need to switch therapy (45, 104).

TABLE 9. DECISION-MAKING ON SWITCHING TO SECOND-LINE THERAPY FOR TREATMENT FAILURE BASED ON AVAILABILITY OF CD4 MEASUREMENT

New or recurrent clinical event on ART[a]	Availability of CD4 measurement[b]	Management options[c] [A (IV)]*
T1 or T2 event(s)	No CD4	■ **Do not switch regimen**
	CD4	■ Consider switching regimen only if two or more values below the age-related threshold for severe immunodeficiency[d] are available ■ Increase clinical and CD4 follow-up if CD4 approaches the age-related threshold for severe immunodeficiency[e]
T3 event(s)	No CD4	■ **Consider switching regimen[e,f]**
	CD4	■ Switching regimen is recommended if CD4 is below the age-related threshold for severe immunodeficiency[d] and particularly if the child initially had a good immune response to ART ■ Increase clinical and CD4 follow -up if CD4 approaches age related threshold for severe immunodeficiency
T4 event(s)	No CD4	■ **Recommend switching regimen**
	CD4	■ Switching is generally recommended but it may not be necessary where CD4 is above age related threshold for severe immunodeficiency

* Strength of recommendation/ level of evidence.

[a] Clinical events refer to new or recurrent events presenting while the child is on ART.

[b] Consideration of previous CD4 is useful.

[c] Any intercurrent infections should be treated according to national treatment guidelines and it is necessary to ensure that the child had at least 24 weeks of ART, adherence to therapy has been assessed and considered adequate before considering switching to a second-line regimen. Additionally, in considering changing treatment because of growth failure, it should be ensured that the child has adequate nutrition.

[d] 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 aged under 5 years and absolute CD4 counts after 5 years of age is preferred; if serial CD4 values are available the rate of decline should be taken into consideration.

[e] Some T3 conditions (i.e. pulmonary or lymph node tuberculosis and severe bacterial pneumonia) do not always indicate the need to switch regimens.

[f] Viral load determination may be useful to support recognition of treatment failure.

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

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, because change in TLC is a poor predictor of treatment success (105). Moreover, drug resistance testing will not become a routine part of clinical care in resource-limited settings in the foreseeable 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 less complex methods for monitoring CD4 and 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 and minimize the risk of cross-resistance, and it should be based on drugs expected to retain activity against the child's virus. 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 maintained in most resource-limited settings. This highlights the importance of choosing potent and effective first-line regimens and maximizing their durability and effectiveness by optimizing adherence.

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

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

Choice of NRTIs

NRTI cross-resistance, especially in the presence of long-standing virological failure allowing the accumulation of multiple drug resistance mutations, may compromise the potency of alternative dual NRTI components. Limited data currently make it necessary to make empirical alternative choices with a view to providing as much antiviral activity as possible. 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. In these guidelines, ABC + 3TC have been introduced as a nucleoside combination of the first-line regimen; in this case, AZT + ddI would be the choice for an alternative regimen. Didanosine has weak acid stability and is easily damaged by stomach acid, and the oral absorption of ddI is fairly low (40%) but rapid. The chewable tablets include an antacid buffering compound to neutralize stomach acid. The chewable tablets are large and fragile, and are reasonably foul-tasting, and the buffering compound tends to cause diarrhoea. An enteric-coated ddI formulation may be better tolerated than the buffered tablet form and may therefore be the preferred formulation for enhancing tolerability and promoting treatment adherence. Administration constraints for ddI in adults (i.e. administration one hour before or two hours after meals because of reduced bioavailability of ddI with food) may not apply in paediatric patients as the systemic exposure to ddI in children is similar in the presence or absence of food (51, 106-108). Box 5 lists the NRTI drug combinations to be avoided.

Choice of PIs

PIs prevent viral replication by inhibiting the activity of an enzyme called protease that is used by the HIV to generate proteins required in the assembly of new virus particles. The PIs in use for children include lopinavir, indinavir, saquinavir, ritonavir and nelfinavir; a range of new PIs are available to treat adults. Ritonovir is exceptional as it is the only ARV drug inhibiting a liver enzyme that normally metabolizes PIs. It is now rarely used for its own antiviral activity but remains widely used in low doses to enhance other protease inhibitors. Because of its mode of action it also interacts with numerous other medications and can cause a large number of side-effects on its own. The advantages of PI-based regimens include proven clinical efficacy and well-described toxicities. Because of the diminished potential of almost any second-line nucleoside component, a low-dose RTV-enhanced PI (PI/r) component, i.e. lopinavir (LPV)/r or saquinavir (SQV)/r, is generally preferable to nelfinavir (NFV) alone for second-line regimens (51, 109). However, the use of PIs other than LPV/r (which is available in coformulation) and NFV is more problematic in children because of a lack of suitable paediatric formulations for indinavir (IDV) and SQV and a lack of appropriate dosing information for RTV-boosted PIs other than LPV/r. SQV/r can be considered as an alternative in children weighing more than 25 kg (who can receive the adult dose) and who are able to swallow capsules. Other limitations related to the use of RTV-boosted PIs include the requirement for a cold chain and poor tolerability of RTV. In late 2005 a tablet formulation of LPV/r not requiring a cold chain became available. The tablets have not yet been studied in children; they cannot be split into smaller amounts but may be acceptable for use in older children for whom adult doses can be given. In these guidelines, LPV/r remains the preferred PI for use in children if there is a secure cold chain.

Data from small studies have shown that the use of NFV in children receiving SQV resulted in twofold to threefold increased SQV exposure (in PI-naive children) (110, 111) or fourfold to twentyfold increased SQV exposure compared with SQV only (51). In addition, the majority of children receiving SQV/NFV combinations achieved threshold SQV concentrations that appeared more likely to maintain a virological response for 48 weeks or more in comparison with children who received SQV as a single PI (110). Nevertheless, studies comparing SQV/r and SQV/NFV found a more pronounced reduction of viral load and increase in CD4 cells in children receiving SQV/r (112).

A regimen combining NFV with full-dose RTV has been assessed by the Paediatric AIDS Clinical Trials Group (PACTG) Protocol 403. The results suggest that therapy with NFV and RTV and ddI is more efficacious in NRTI-experienced children than a regimen containing NFV, NVP and d4T; the addition of RTV to NFV increased the NFV area under the curve (AUC) by about 20%, which is similar to observations in adults (113). However, 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 are insufficient to allow firm recommendations for practice.

NFV alone is considered as an alternative for the PI component if an 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 diarrhoea, high-dose requirements (i.e. infants aged under 1 year need at least 150 mg/kg/day in order to achieve NFV concentrations close to the minimum therapeutic doses required for older children and adults (114, 115), 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. Preliminary results for the new 625-mg tablets indicate reduced incidence of diarrhoea and better bioavailability but they are more difficult to crush(116). Recent trials have addressed the use of dual-boosted PIs: an open-label prospective study assessing the efficacy and safety of dual boosted SQV/LPV/RTV in NRTI-pretreated children (aged between 6.9 and 9.9 years) showed a good virological response and a significant immunological response, although elevated triglyceride and cholesterol levels were observed. LPV and SQV levels appeared to be higher in Thai children than in Caucasian children studied in previous trials (117). In highly pretreated adult patients, a regimen containing dual-boosted PIs, i.e. LPV/r plus SQV soft gel capsules (sgc)[(i)] was well tolerated and produced a good virological response except where PI resistance mutation was observed (118). However, because of the high likelihood of occurrence of adverse events associated with PIs, dual-boosted PIs are not included in these recommendations.

(i) The 200-mg soft gel formulation of SQV was discontinued in February 2006.

Several new PIs have become available for use in adults (e.g. tipranavir and atazanavir) but they are currently not licensed for use in children or there are insufficient data to guide their use in children. WHO urges manufacturers to ensure timely evaluation in children and early access if these drugs are proven to be effective 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 10).

NRTI/NNRTI/PI combination regimens have been studied in treatment-experienced children and have been well tolerated. In a study of 175 antiretroviral-experienced HIV-infected children with advanced HIV disease, four-drug regimens including two NRTIs, an NNRTI (NVP), and a PI (RTV or NFV) were well tolerated, and resulted in significant increases in CD4 cell counts, even in children who had only a partial virological response to therapy (119). Thus an NNRTI +/- alternative NRTIs plus an RTV-boosted PI can be considered if drug availability so 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 metabolize some PIs, dose adjustments may be needed and the use of an RTV-boosted PI is recommended to ensure adequate PI drug levels.

The clinical efficacy of continuing 3TC for a child in whom an initial first-line regimen including 3TC fails (i.e. standard regimen based on either two NRTIs plus one NNRTI or triple NRTI) has not been proven. In adults, data suggest that continuing 3TC therapy even in the presence of multidrug resistance (including the M184V mutation associated with 3TC resistance) may continue to provide additional antiviral activity, attributable to decreased viral replicative fitness and increasing thymidine analogue susceptibility (120).

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

PIs may have been used in a first-line regimen where the NNRTI has been substituted with a PI because of severe toxicity and because a triple NRTI regimen is not feasible. When such a first-line regimen fails it is not considered safe to reintroduce the NNRTI class.

Although not recommended by WHO, PIs may nevertheless have been used as initial therapy. 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 specialized and individualized HIV care is provided, and consideration of ARVs not included in the standard public sector formulary, would be appropriate. However, this option may not be open to all patients. Any subsequent regimen would have to be based on the limited available formulary, including NNRTIs and NRTIs. For these reasons, WHO does not recommend the premature use of the PI drug class in first-line regimens.

TABLE 10. RECOMMENDED SECOND-LINE REGIMENS IN INFANTS AND CHILDREN IN THE EVENT OF TREATMENT FAILURE OF FIRST-LINE REGIMENS

Recommended second-line regimen: boosted PI component + two RTI components

First-line regimen at failure	Preferred second-line regimen [A (II)]*		
	RTI components (NRTI/NNRTI)[a]		**PI component[b]**
2 NRTI + 1 NNRTI AZT- or d4T-containing	ddI[c] + ABC[d]	**plus**	LPV/r [f] *or* SQV/r [g] *or* NFV [h]
ABC-containing	ddI[c] + AZT		
Triple NRTI	ddI[c] + EFV[e] *or* NVP		

* Strength of recommendation/level of evidence.

a Continuation of 3TC in second-line regimens 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 recommend to introduce AZT after use of d4T or vica versa.

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

f LPV/r is available coformulated as solid and liquid.

g SQV/r should not be used in children or adolescents weighing less than 25 kg.

h Unboosted NFV may need to be used where no cold chain is 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. Considerations for infants and children coinfected 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 coinfection with TB and HIV in children have been reported from resource-limited countries (121), the prevalence of HIV in TB-infected children ranging from 10% to 60% (122-127). Isoniazid (INH) preventive therapy is recommended for HIV-infected children who live in areas of high TB prevalence or are household contacts of TB patients (128) following exclusion of active disease.

Considerations for the diagnosis of TB

Primary disease in children presents with a broader range of non-pulmonary and pulmonary manifestations. In addition, problems in obtaining sufficient sputum from infants and young children for smear microscopy and culture complicate the process of making a definite diagnosis of TB. In many cases, particularly in young children, diagnosis is presumptive and is based on a constellation of clinical signs and symptoms, known contact with a household member with TB disease, and the child's response to anti-TB therapy. The principles for the treatment of TB in HIV-infected children are the same as in HIV-uninfected children. While all HIV-exposed infants and children should benefit from CPT, this intervention is particularly important in children coinfected with TB and HIV (129). Studies in adults have indicated better survival rates in patients coinfected with HIV and TB who received co-trimoxazole prophylaxis than in patients receiving no prophylaxis (130).

Considerations for the choice of first-line ARV regimens in children receiving rifampicin-containing TB treatment

The co-management of TB and HIV, and the treatment of HIV infection, is complicated by drug interactions, particularly rifampicin and the NNRTI and PI

classes. These drugs have similar routes of metabolism and coadministration results in subtherapeutic antiretroviral drug levels. Overlapping toxicity profiles may result in an increased risk of toxicity. ART may need to be interupted and dose adjustments of ART may be needed when taken with TB drugs. The choice of ART regimen in TB/HIV coinfected children is also complicated by the limited options for paediatric drug formulations and/or dosing information (particularly for children under 3 years of age) for antiretroviral drugs.

The first-line treatment recommendation for children with TB and HIV coinfection is the triple NRTI regimen (i.e. d4T or AZT + 3TC + ABC). Alternatively, in children over 3 years of age a standard first-line regimen of two NRTIs + EFV (i.e. the NNRTI component) is suggested. In children under 3 years of age, the use of a standard first-line regimen of two NRTIs + NVP (i.e. as the NNRTI component) is recommended. In a study in HIV-infected adults a regimen of AZT/3TC/ABC had lower virological potency than an EFV-based regimen (79% versus 89% efficacy at 32 weeks) (59). However, because of concern about the potential for subtherapeutic dosing of NNRTIs with concomitant rifampicin a triple NRTI regimen is the preferred choice in this situation.

The appropriate dosing of NNRTI drugs when given with rifampicin has not been well established. The coadministration of EFV and rifampicin results in a decrease in the AUC of EFV by 22–26% (131). In adults, both standard (600 mg) and increased (800 mg) EFV doses have been used with rifampicin. However, there have been adequate virological and immunological response with standard 600-mg dosing (132), and higher doses are associated with a higher incidence of toxicity. Because of concerns related to teratogenicity, EFV should also be avoided in adolescent girls of childbearing potential (without adequate contraception) or who are in the first trimester of pregnancy. NVP levels are also reduced with concurrent rifampicin, with larger reductions in AUC of 31–37% (131, 133); the use of higher doses of nevirapine with rifampicin has not been evaluated. Additionally, NVP, like rifampicin and isoniazid, has potential hepatic toxicity. As with EFV, some clinical reports indicate adequate virological and immunological responses and acceptable toxicity with standard doses of NVP with concomitant rifampicin (134). However, because NVP levels are reduced more than EFV levels, a regimen of two NRTIs + 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 the exact NVP dose requirement in children receiving rifampicin.

Considerations for the timing of ART initiation following the initiation of rifampicin-containing TB treatment

In HIV-infected children with TB disease, the initiation of TB treatment is the priority. However, the optimal timing for the initiation of ART during TB treatment is not known. The decision on when to start ART after starting TB treatment involves a balance between the child's age, the 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 (extrapulmonary TB, excepting lymph node TB). However, the results of CD4 measurements, if available, are important in making decisions about the urgency of initiating ART. Because the degree of immunodeficiency in TB/HIV coinfected children is highly correlated with mortality (121), earlier initiation of ART is more critical in coinfected children with low CD4 values. Thus, in children with WHO paediatric clinical stage 4, regardless of immunological criteria, and in children with clinical stage 3 and concurrent severe or advanced immunodeficiency,(i) WHO recommends that ART should begin between two and eight weeks after the start of TB therapy, when the child has stabilized on this therapy. In children with clinical stage 3 who have either nonsignificant or mild immunodeficiency, the clinical response to TB therapy can guide the decision as to whether ART should be initiated urgently or can be delayed. A clinical response to TB treatment should be expected within the first few weeks of receiving anti-TB therapy. In a child with a good clinical response to TB therapy the initiation of ART may be delayed until after the completion of this therapy, provided that the response is closely monitored and the need for ART is reassessed after the TB therapy has been completed. If an appropriate clinical response is not observed it may be necessary to begin ART earlier rather than later (e.g. before the two-month induction phase of TB therapy is completed). The potential for IRIS (see below) should be considered in all children starting ART, particularly in those with low CD4 values.

In situations where CD4 measurements are not available, children with paediatric clinical stage 3 should begin to receive ART with the same urgency as children with paediatric clinical stage 4, except for those with lymph node TB (Table 11).

(i) Advanced immunodeficiency can be assumed to be up to 4% above the 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).

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

ART should continue in children already on a first-line ARV regimen who are subsequently diagnosed with TB. However, the ARV regimen should be reviewed and may need adjustment in order to ensure optimal treatment of both TB and HIV and to decrease the potential for toxicities and drug-drug interactions. In children receiving a standard first-line regimen of two NRTIs + one NNRTI and where TB has occurred because of primary infection or as part of IRIS (see below), a substitution of NNRTI to a triple NRTI first-line regimen can be considered. Alternatively, the children could remain on their standard regimen of two NRTIs + one NNRTI, which is more optimal in children receiving EFV-based regimens rather than NVP-based regimens. In children and adolescents for whom EFV is not recommended and who are taking NVP, standard doses should 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, if available, should be checked. Where TB is being considered as a sign of treatment failure of the first-line regimen, switching to a second-line regimen can be considered if the children have received an adequate trial of ART (i.e. more than 24 weeks), have initially responded to it, and have not responded to anti-TB treatment. Because the concurrent use of rifampicin and any PI is not recommended, consultation is suggested for the 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 because of the decrease in PI drug levels. The use of SQV with higher-dose (i.e. full-dose) RTV boosting has been suggested, but, because of significant hepatocellular toxicity observed in adults receiving this combination with rifampicin, concomitant administration of rifampicin with RTV-boosted SQV as part of ART 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). However, the presence of a cold chain should be ensured. The use of other boosted PI

combinations is discouraged until further data become available. NFV should not be administered with rifampicin (135, 136). The construction of other salvage regimens in this situation may need to be considered. Reassessment and referral for the construction of a salvage regimen, as appropriate, are indicated.

Tables 11 and 12 summarize the WHO recommendations for ART in HIV-infected children diagnosed with TB. Research is urgently needed to evaluate the pharmacokinetics and clinical outcomes of administration of NNRTI and PIs with rifampicin in children so that evidence-based recommendations can be made.

IRIS IN THE CONTEXT OF COTHERAPY

IRIS has been observed in patients receiving anti-TB therapy who were initiated on ART. This syndrome has been primarily reported in adults (but also in children) and is characterized by a worsening of disease after initial clinical improvement, with new onset of systemic symptoms, especially fever, a worsening of pulmonary infiltrates, the development of peripheral and mediastinal adenopathy, and expanding CNS lesions in patients with tuberculomas. These reactions may occur during the first three months of ART, are generally self-limiting and last 10–40 days, although some reactions may be severe and require a short course of treatment with a glucocorticoid (102) (see also Section X).

TABLE 11. RECOMMENDATIONS FOR THE TIMING OF ART FOLLOWING THE INITIATION OF TB TREATMENT WITH A RIFAMPICIN-CONTAINING REGIMEN IN HIV-INFECTED INFANTS AND CHILDREN

Clinical stage of child with TB (as an event indicating need for ART)	**Timing of ART following initiation of TB treatment (rifampicin-containing regimen)** [a]	**Recommended ARV regimen** [c] [B (IV)]*
WHO paediatric clinical stage 4 [b]	▪ **Start ART soon after TB treatment** (between 2 and 8 weeks following start of TB treatment)	<u>In children <3 years</u>:[d] ▪ Triple NRTI first-line regimen (d4T or AZT + 3TC + ABC) *or* ▪ Standard first-line regimen of two NRTIs + NVP[c] <u>In children >3 years:</u>[d] ▪ Triple NRTI first-line regimen (d4T or AZT + 3TC + ABC) *or* ▪ Standard first-line regimen of two NRTIs + EFV[e] 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 of 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 may be reasonable to delay initiation of ART	
	Where CD4 is available: ▪ **Evaluate the possibility of delaying 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 two NRTIs + NNRTI first-line regimen (Table 4) is recommended

	– Severe and advanced immunodeficiency:[f] initiate ART soon after TB treatment (between 2 and 8 weeks following start of TB treatment) – Mild or no immunodeficiency:[g] Initiation of ART may be delayed until after the completion of TB therapy; closely monitor response to TB therapy and reassess need for ART after TB therapy; if no improvement, consider starting ART	

* Strength of recommendation / level of evidence.

[a] Administration of CPT is important in children with TB/HIV coinfection.

[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] Because of lack of data the ranking of preferred or alternative ARV regimens is not possible.

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

[f] Severe immunodeficiency as per Table 5; advanced immunodeficiency is assumed to be up to 5% above the 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 nonsignificant immunodeficiency is assumed at age specific CD4 levels above those defining advanced immunodeficiency (see above and Annex C).

TABLE 12. RECOMMENDATIONS FOR CO-MANAGEMENT OF TB AND HIV IN INFANTS AND CHILDREN DIAGNOSED WITH TB WHILE RECEIVING FIRST-LINE OR SECOND-LINE ARV REGIMENS

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

* Strength of recommendation / level of evidence

[a] Administration of co-trimoxazole preventive therapy (CPT) is important in children with TB/HIV coinfection.

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

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

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

XIII. Considerations for nutrition in HIV-infected infants and children

Malnutrition is a common condition in HIV-infected children and is major contributor to mortality in both HIV-uninfected and HIV-infected children. In HIV-infected children, wasting (i.e. low weight for height/length) has been associated with reduced length of survival (137), while weight loss has 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 (138-140).

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.(i) In HIV-infected children, severe growth problems (i.e. growth failure and severe malnutrition/wasting criteria for clinical stage 3 and 4 disease, respectively) not attributable to inadequate nutritional intake may point to the need for ART to be initiated. Growth is also useful in the evaluation of the 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.

Following is a brief summary of key nutritional interventions relevant to the care of HIV-infected infants and children before or during ART. For more details, reference should be made to existing manuals and guidelines on the clinical or nutritional management of HIV-infected children (141-148).

Nutritional assessment and support

In view of the close interrelationship between HIV infection, nutritional status and growth, WHO recommends that early nutritional intervention (i.e. nutritional assessment and support) should be an integral part of the care plan of HIV-infected children.

(i) In children the three most commonly used anthropometric indices to assess their growth status are weight-for-height, height-for-age and weight-for-age, further details are available at http://www.who.int/nutgrowthdb/about/introduction/en/index4.html

Nutritional assessment, i.e. the systematic evaluation of current nutritional status, diet and nutrition-related symptoms, is critical in the early identification of malnutrition and poor growth as well as in the monitoring of HIV disease progression and treatment efficacy for children on ART. As for all infants, HIV-infected infants should be measured monthly, ideally with the use of standardized growth curves. Thereafter, children should be weighed at each review and full nutritional assessments should be made every three months unless the child in question requires particular attention because of growth problems or special nutritional requirements.

A proactive approach to nutritional support in HIV-infected children is important because of the increased energy needs associated with the infection. In asymptomatic HIV-infected children, resting energy expenditure is increased by about 10%, while increases in energy needs of between 50% and 100% have been reported in HIV-infected children experiencing growth failure. Increased utilization and excretion of nutrients in HIV infection can lead to micronutrient deficiencies (149). Nutritional support should thus include early efforts to continue breastfeeding where possible, ensure adequate nutrient intake on the basis of locally available and affordable foods and a daily intake of micronutrients equivalent to one recommended daily allowance (RDA) (146, 147, 150). It is recommended to increase the energy intake of HIV-infected infants and children by 10% of the RDA for their age and sex if they are asymptomatic and by 20–30% of the RDA if they are symptomatic or recovering from acute infections (148). These requirements are considered minimal and more may be needed in children with nutritional deficiencies (151). Increased protein requirement exceeding that required in a balanced diet to satisfy the total energy requirements (12 to 15% of the total energy intake) is not needed (148).

Current evidence is inconclusive about the effects of micronutrient supplementation on the transmission and progression of HIV infection. However, evidence from randomized clinical trials in HIV-infected children confirms results from studies in HIV-uninfected individuals indicating that supplementation with large doses of vitamin A reduces overall morbidity and diarrhoeal morbidity as well as all-cause mortality (150, 152, 153). Vitamin A supplements should be given in accordance with the WHO recommended high-dose prevention schedule for children at high risk[(i)] of vitamin A deficiency (144). The counselling of mothers about breastfeeding and of all children and their caregivers about food and water hygiene are further core elements of nutritional support.

(i) Children at high risk of vitamin A deficiency include, among others, those with severe infections or severe protein-energy malnutrition.

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. The 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[i] the evaluation of the need to start or switch ART, family education about locally available food choices and referral to food programmes, preferably with support for the whole family. In addition the selection of specific palatable high-energy foods for children with conditions that interfere with normal ingestion or digestion (e.g. sore throat or mouth, oral thrush, diarrhoea) may both alleviate symptoms and ensure sufficient energy intake.

ART IN SEVERELY MALNOURISHED INFANTS AND CHILDREN

Severe wasting[ii] is a common clinical presentation of HIV infection in children. All children with severe malnutrition are at risk for a number of life-threatening problems and urgently require therapeutic feeding. The phase of malnutrition treatment at which to start ART is not known. Expert opinion therefore suggests that HIV-infected children with severe malnutrition according to international (146, 147) or national guidelines be stabilized before decisions are made on the initiation of ART. The initial treatment of severe malnutrition lasts until the children have stabilized on this treatment and their appetites have returned. In HIV-uninfected children this initial phase should not take longer than 10 days, whereas 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 and any underlying infections or conditions, the children's clinical condition should be re-evaluated. The initiation of ART may be considered on the basis of the criteria listed in Section V. In respect of HIV-infected children who are slow to improve on malnutrition treatment, a decision may be taken (either for inpatients or outpatients) 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 emphasized that, where malnutrition is endemic, HIV-infected children may become severely malnourished because of a lack of an adequately balanced diet, and that with restoration of the nutritional status the initiation of ART may no longer be appropriate. This may be a particularly important consideration for children presumptively diagnosed with severe HIV

[i] Available at http://www.who.int/child-adolescent-health/publications/pubIMCI.htm

[ii] 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 146).

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

In children who rapidly gain weight because of adequate nutrition and ART, dosages of ARVs should be frequently reviewed (see Annex E). The recurrence of severe malnutrition that is not caused by a lack of food in children receiving ART may indicate treatment failure and the need to switch therapy (see Section X).

There are no published studies on the effectiveness, pharmacokinetics and safety of ARVs in severely malnourished children. Further research on these matters is urgently needed.

XIV. CONSIDERATIONS FOR ART IN ADOLESCENTS

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

There are distinct groups of HIV-infected adolescents who may require ART. Adolescents who have been infected around birth and those who become infected during adolescence. Adolescents with perinatal infection who began ART during early childhood because of rapid progression of HIV disease have some years of contact with health services and are likely to have experienced various ARV treatments; their parents are often aware of their HIV status. In respect of these adolescents, challenges may relate mainly to: the disclosure of HIV status to them if this has not been done by their parents; developmental delays; the transition from paediatric to adult care, including the choice of appropriate ARV regimens; and adherence.

HIV-infected adolescents (i.e. those infected around birth, as infants or young children) often face considerable physical challenges. They may experience delayed growth and development, often resulting in late puberty and, in girls, delayed or irregular menstrual cycles (154). Stunting and/or wasting caused by progressing HIV illness, frequently exacerbated by malnutrition, may further complicate decision-making on whether to follow ARV treatment guidelines for adults or children.

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 started on the paediatric schedule and should be monitored with particular care because they are at the time of hormonal changes associated with the growth spurt. Adolescents in Tanner stage IV or V are considered to be adults and the same recommendations and special considerations apply as for adults.[(i)] However, in choosing an appropriate

[(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.

ARV regimen and dose it is necessary to go beyond considering maturity. Simplification of treatment regimens and anticipated long-term adherence are further important criteria. Other considerations relate to the use of EFV and NVP in adolescent girls. EFV should not be used in adolescent girls who are at risk of pregnancy (i.e. are sexually active and not using adequate contraception) or 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 is more likely to be seen in antiretroviral-naive females with higher absolute CD4 cell counts (>250 cells/mm^3). NVP should therefore be used with caution in adolescent girls with absolute CD4 counts between 250 and 350 cells/mm^3; if used in such adolescent girls, careful monitoring is needed during the first 12 weeks of therapy, preferably including liver enzyme monitoring. In situations where both EFV and NVP should not be included in first-line regimens for adolescent girls the use of a triple NRTI regimen may be indicated.

Adherence to long-term therapy is particularly difficult among adolescents. In addition to providing routine adherence assessment and support (see Section XVI), health care providers may want to consider issues that are particularly relevant to adolescents and impair optimal adherence to ART, possibly including the adolescents' perception of being immortal, their desire for independence, lack of disclosure of HIV status, and stigma. The parents of adolescents who have become infected as infants or young children may find it hard to share the diagnosis of HIV with their children because of fear of stigma or blame from their own children. However, without this knowledge it is impossible for adolescents to progress completely through the transition process into adult care. Sharing this diagnosis with peers is difficult for adolescents who are aware of their HIV status. 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 whom they want to know about their condition; and 4) have a support system so that they know where to obtain help and advice when necessary. Simple ARV regimens will maximize adherence.

XV. Clinical and laboratory monitoring

Clinical and laboratory assessments are required at baseline (i.e. at entry into HIV care), during the care of patients who are not yet eligible for ART, and for starting and maintaining ART. In resource-limited settings, WHO recommends that primarily clinical parameters be used for monitoring ART. However, it is highly desirable to develop a laboratory monitoring protocol on a country basis 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 in order to determine the clinical stage of HIV disease and, where available, CD4 testing to determine, eligibility for ART and other interventions such as CPT. Further objectives are evaluation for the presence of active opportunistic infections and referral of infected infants or children to a chronic care setting within the public health system. The baseline assessment should also serve as a means to provide counselling and support for children and/or caregivers concerning secondary prevention and disclosure of HIV diagnosis to others, as well as to identify particular needs.

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

- clinical staging of HIV disease (Annex B);
- identification of concomitant medical conditions (e.g. TB, pregnancy in adolescent girls);
- detailing of concomitant medications, including co-trimoxazole and traditional or herbal therapies;
- weight, height, head circumference and other measures of growth;
- developmental status;
- nutritional status, including assessment of quality and quantity of intake;

- for those eligible for ART, assessment of children's and caregiver's preparedness 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; Section IV);
- measurement of CD4, where available;
- haemoglobin measurement: in infants and children initiated on AZT-containing first-line regimens;
- white blood cell count (WBC);
- pregnancy test for sexually active adolescent girls;
- screening for TB and malaria (and diagnostic testing where clinically indicated), and for other major treatable HIV coinfections and HIV-related opportunistic diseases as clinically indicated (Table 13).

TLC should **only** be used at baseline assessment for ART in resource-limited settings if CD4 cell measurements are unavailable. There is a reasonable correlation between TLC and CD4 levels in symptomatic patients (46, 155-157) and association of TLC with risk of mortality in paediatric studies (46, 47).

Routine monitoring of children who are not yet eligible for ART

The clinical evaluation of infants and children who are not yet eligible for ART should be performed every three to six months and should include the same parameters as are used in baseline evaluations. Together with the results of CD4 measurement they are useful for updating the WHO paediatric clinical and immunological stage at each visit, and for determining whether the infants or children in question have become eligible for treatment. Clinical evaluation and CD4 measurements should 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 is indicated.

Routine monitoring of children on ART

Once a child is on ART, in addition to the parameters used before ART (except for confirmation of HIV infection status), *clinical assessment* should cover the child's and caregiver's understanding of the therapy as well as anticipated support and adherence to the therapy. Observation of the child's responses to therapy should also include symptoms of potential drug toxicities or treatment failure. Particularly important signs of infants' and children's responses 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 depends on the response to ART but should be at a minimum be at weeks 2, 4, 8 and 12 after starting ART and then every 2-3 months once the child has stabilized on therapy. In infants and children who were started on ART on the basis of a presumptive clinical diagnosis of severe HIV disease, HIV infection status should be confirmed as soon as possible.

Laboratory assessment of CD4 is desirable every six months or more frequently if clinically indicated (Table 13). The TLC is not suitable for the monitoring of therapy because a change in its value does not reliably predict treatment success (105). In infants and children initiated on AZT-containing first-line regimens the measurement of haemoglobin should be performed during the first few months of treatment (at weeks 4, 8 and 12 after initiation of ART) or in a symptom-directed approach. Tests of liver function (i.e. liver enzymes) are recommended during the first few months of treatment in infants and children receiving nevirapine or who have coinfection 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 in accordance with the specific drugs used, but laboratory monitoring of adverse events should largely be directed by clinical symptoms (Annexes F and G). It should be noted that an inability to perform laboratory monitoring should not prevent children from receiving ART.

TABLE 13. LABORATORY PARAMETERS FOR MONITORING INFANTS AND CHILDREN AT BASELINE, BEFORE AND DURING ART

Diagnosis and monitoring laboratory tests	Baseline (at entry into care)	At initiation of first-line or second-line ARV regimen	Every six months	As required or symptom-directed
HIV diagnostic testing: virological and Ab testing	✓	-	-	-
Haemoglobin[a]	✓	✓	-	✓
WBC and differential[b]	✓	✓	-	✓
%CD4 or absolute CD4 cell count[c]	✓	✓	✓	✓
Pregnancy testing in adolescent girls	✓	✓ [d]	-	✓
Full chemistry (including, but not restricted to, ALT,[e] liver enzymes, renal function, glucose, lipids, amylase, lipase and serum electrolytes)[f]	-	-	-	✓
HIV viral load measurement[g]	-	-	-	✓

[a] Haemoglobin monitoring at weeks 4, 8 and 12 after initiation of ART is recommended by some experts if AZT is used.

[b] Monitoring at weeks 4, 8 and 12 after initiation of ART is optional.

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

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

[e] The predictive value of pre-emptive liver enzyme monitoring is considered very low by some experts. WHO recommends 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 children on nevirapine-based regimens, or for adolescent girls with CD4 values over 250 cells/mm^3 and for infants and children coinfected with hepatitis B or hepatitis C virus or other hepatic disease.

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

[g] At present, viral load measurement is not recommended for decision-making on the initiation or regular monitoring of ART in resource-limited settings. Tests for assessment of HIV RNA viral load can also be used to diagnose HIV infection (17), and to assess discordant clinical and CD4 findings in children suspected of failing ART.

Laboratory capability for routine monitoring

Although protocols for monitoring the safety and efficacy of ART are important, WHO recognizes the restricted infrastructure for the different tests at different levels in the health system. WHO has therefore tiered its laboratory monitoring recommendations to primary health care centres (level 1), district hospitals (level 2) and regional referral centres (level 3) in order to facilitate HIV care and treatment in a variety of locations (Annex I). Standard quality assessment of laboratories at all levels is important for ensuring reliability.

XVI. Adherence to ART

Adherence is related to the clinical and virological responses to therapy in infants and children (158-160). Studies of drug adherence in adult patients in Western countries have suggested that higher levels of drug adherence are associated with improved virological and clinical outcomes and that rates exceeding 90% are desirable in order to maximize the benefits of ART (161, 162). It is therefore critical to focus on maximizing adherence in order to ensure the durability of effect of ARV regimens and to minimize the emergence of drug resistance. Experience has demonstrated that it can be particularly difficult to adhere to daily medication regimens, especially over long periods. Numerous approaches to supporting and improving adherence have been investigated and have begun to be explored in Western countries. As ART becomes increasingly available to children in low-resource settings, attention to adherence will be just as important. Furthermore, various programmatic issues cause barriers to optimal adherence to treatment and may have to be addressed.

Adherence in children is a special challenge because of factors relating to children, caregivers, medications and the interrelationships of these factors. 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, the successful treatment of a child requires the commitment and involvement of a responsible caregiver. This may be particularly complicated if the family unit is disrupted as a consequence of adverse health or economic conditions. Mothers of HIV-infected children are frequently HIV-infected themselves and the care of the children may be less than optimal because of the mothers' compromised health. It is preferable that a secondary (back-up) informed caregiver be involved in the care of an HIV-infected child. In addition, caregivers are often concerned with the disclosure of HIV status to other family members, friends or schools, thus restricting the child's options for seeking support. Finally, an understanding of how the developmental stage of the child influences the extent to which he or she will cooperate with the regular administration of medicine helps to guide planning and support for the process.

Efforts to support and maximize adherence should begin before the initiation of treatment (163). The development of an adherence plan and the education of the child 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. If medication is mixed with food the consumption of all food is important in order to ensure administration of the full required dose. Especially for young children the employment of additional methods may be necessary, including the tasting of medications, practising the measurement of liquids, and training in pill swallowing. When choosing regimens, policy-makers and programmers should consider ways to minimize the number of pills and/or the volumes of liquids as well as the frequency of dosing, avoidance of food restrictions, the feasibility of using FDCs 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 a regimen, particularly for some ART combinations with a higher risk of 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 the persistence of subtherapeutic NNRTI drug levels and may lead to the premature development of NNRTI drug resistant virus. Emphasizing the need to consistently take the ARV drugs is therefore particularly important with an NNRTI/NRTI-based first-line regimen. An uninterrupted ARV supply in both facilities and at the household level is clearly essential.

The continuous assessment and support of adherence are vital components of a proactive approach to ART. The assessment of adherence should be a concern of every health care provider participating in the care of children. It should be performed whenever there is a visit to a health centre in order to identify children in need of the greatest support for adherence. The measurement of adherence may, however, be difficult, particularly in children. Quantitative methods are generally employed (asking children or caregivers how many doses of medication have been missed during the past 3, 7 or 30 days) but the responses may not reflect true adherence as children and caregivers learn the social desirability of reporting complete adherence. 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 between children and caregivers, as well as by the limited availability of information when the caregivers bringing children to clinics are not responsible for supervising ART administration (164). Reviews of pharmacy records as well as pill counts can provide valuable information about adherence. Viral load measurements can be used to assess adherence to medication but are unlikely to be widely available in low-resource settings at present and are an expensive way to monitor adherence.

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

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

XVII. Strategies in the event of failure of second-line regimens

Multidrug resistance in children who have received multiple antiretroviral regimens is an increasing problem in Western countries. Limited data are available on which to base recommendations about treatment options. Various strategies that balance benefits for children might be explored to maintain CD4,[(i)] reduce adverse events and enhance the prevention of opportunistic infections. If children have end-stage HIV disease and no further suitable ARVs are available, stopping ART and keeping them comfortable with symptom-based care may have to be considered.

Considerations for the use of ARV salvage regimens

A number of treatment approaches have been considered in clinical trial settings, although largely in adults and where virological monitoring is possible. These include the addition or substitution of new drugs (such as enfurvirtide/T20), mega-HAART (combining of five or more drugs, including two or more protease inhibitors), strategic recycling of drugs, structured treatment interruptions (STIs) and the continuation of current therapy until additional drugs become available. The analysis of 13 HIV cohorts involving adult patients who had three-class virological failure indicates that achieving and maintaining an absolute CD4 count above 200 cells/mm^3 becomes the primary aim. Treatment regimens that achieve suppression of viral load below 10 000 copies per ml or at least 1.5 $\log_{10}$ below the off-treatment value may not be associated with CD4 cell-count decline (165). 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 attributable to the presence of multiple resistance mutations. Studies in adults suggest therapeutic benefit from NRTI treatment in the presence of drug resistant HIV (119, 120, 166-170). Decisions about therapy in such situations are complex and require, at least, consultation with an HIV specialist.

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

Considerations for palliative care and stopping ART

The prevention of opportunistic infections, the relief of symptoms and the management of pain need to continue, even when the option to stop ART may have to be considered. Symptoms and pain are a major cause of discomfort 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 [(i)] is a particular challenge in resource-limited settings because there is paucity of experience and of 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 of 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 that may not be appropriate for their needs. Few resource-limited settings have inpatient facilities for terminal care, and home-based care is usually preferred. Families must be involved in decisions about the best place for care and the preferred place of death if children have end-stage HIV disease.

(i) Adapted from reference 171.

XVIII. Drug resistance

Considerations on drug resistance in infants and children

Infants and children acquire resistant virus or develop resistance because of ARV exposure for prophylaxis or treatment. In perinatal acquisition the infant acquires resistant virus from the mother in utero, intrapartum or postpartum during breastfeeding. The transmission of a resistant virus can occur: 1) from an ARV-naive mother infected with HIV already resistant to ARV; 2) from a mother exposed to ARVs before becoming pregnant; or 3) from a mother who has been exposed to ARVs during pregnancy either for her own health or for prophylaxis of MTCT. Issues related to the development of viral resistance attributable to PMTCT and ART in infants are discussed in Section VII.

Treatment-related development of resistance in children is, as in adults, frequently related to the use of suboptimal suppressive regimens or subtherapeutic drug levels because of either insufficient adherence or pharmacokinetic problems (172) and represents one of the main reasons for treatment failure (173). Children may develop viral resistance as a result of ART, the infant ARV prophylaxis of MTCT intervention, or possibly due to exposure to subtherapeutic levels of ARVs during breastfeeding (i.e. from mothers receiving ART).

Considerations for minimizing the emergence of drug resistance

The emergence of HIV drug resistance (HIVDR) is of increasing concern in countries where ART is widely used and represents a potential impediment to the achievement of long-term success in the rapid scale-up of ART in resource-limited settings. Minimizing the emergence and transmission of HIVDR is therefore essential in order to ensure the efficacy of the limited number of antiretroviral drugs available in many countries. The optimization of adherence is vital for minimizing resistance, alongside standardized protocols for ARV use in prophylaxis and treatment. Specific problems that should be considered in treating children include the need to switch formulations as children cross thresholds of weight or age, and unavailability of a range of suitable paediatric

ARV dose formulations. In the event of discontinuation of ARVs for toxicity it may be necessary to accommodate staggered stopping of individual drug components.

Countries are encouraged to implement strategies for minimizing the development and spread of HIVDR by choosing appropriate drug combinations, ensuring reliable ARV drug quality and supply, and providing culturally appropriate support for adherence. Furthermore, the surveillance and monitoring of HIVDR at country level are recommended as part of the overall monitoring of the effectiveness of antiretroviral programmes. These studies are an important public health tool for informing national, regional and global ARV scale-up programmes about trends in drug resistance patterns with a view to enabling timely policy development so as to minimize the impact of such resistance.

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

Because of the particularities in the transmission of resistant virus in infants and children, however, countries should consider the implementation of surveillance and monitoring protocols that are being developed by WHO specifically for the paediatric population. The study population for HIVDR surveillance should include pregnant women and newly-infected infants (i.e. infants that may have perinatally-acquired resistant virus), and should thus identify the transmission of resistant virus. Monitoring studies on the emergence of resistance during ART should include cohorts of infants and children starting ART, on ART and experiencing treatment failure, at sentinel sites.

As for adults, WHO does not recommend drug resistance testing for individual infant and child management in settings where other basic laboratory measurements, such as CD4 and HIV viral load, are not yet available. The WHO/HIVResNet strategy for HIVDR in the paediatric population is being developed under the coordination of WHO in collaboration with HIVResNet.

(i) To be published by WHO in 2006.

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ANNEX B, PART A: WHO CLINICAL STAGING OF HIV FOR INFANTS AND CHILDREN WITH ESTABLISHED HIV INFECTION

(Diagnosis of HIV infection according to recommendations in section IV. All clinical events or conditions referred to are described in Annex B, Part B.)

Clinical stage 1
Asymptomatic
Persistent generalized lymphadenopathy
Clinical stage 2 [(i)]
Unexplained persistent hepatosplenomegaly
Papular pruritic eruptions
Extensive wart virus infection
Extensive molluscum contagiosum
Recurrent oral ulcerations
Unexplained persistent parotid enlargement
Lineal gingival erythema
Herpes zoster
Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis)
Fungal nail infections
Clinical stage 3 [(i)]
Unexplained moderate malnutrition not adequately responding to standard therapy
Unexplained persistent diarrhoea (14 days or more)
Unexplained persistent fever (above 37.5 °C, intermittent or constant, for longer than one month)
Persistent oral candidiasis (after first 6 weeks of life)
Oral hairy leukoplakia
Acute necrotizing ulcerative gingivitis/periodontitis
Lymph node TB
Pulmonary TB
Severe recurrent bacterial pneumonia
Symptomatic lymphoid interstitial pneumonitis
Chronic HIV-associated lung disease including bronchiectasis
Unexplained anaemia (<8.0 g/dl), neutropenia (<0.5 x $10^9/L^3$) or chronic thrombocytopenia (<50 x $10^9/ L^3$)

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

(i) Unexplained refers to where the condition is not explained by other causes.

(ii) Some additional specific conditions can be included in regional clasifications (e.g. Penicilliosis in Asia, HIV associated rectovaginal fistula in Africa).

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

(Diagnosis of HIV infection according to recommendations in Section IV.)

Clinical event	Clinical diagnosis	Definitive diagnosis
Stage 1		
Asymptomatic	No HIV-related symptoms reported and no clinical signs on examination.	Not applicable
Persistent generalized lymphadenopathy (PGL)	Persistent swollen or enlarged lymph nodes >1 cm at two or more non-contiguous sites (excluding 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

Clinical event	Clinical diagnosis	Definitive diagnosis
Extensive wart virus infection	Characteristic warty skin lesions; small fleshy grainy bumps, often rough, flat on sole of feet (plantar warts); facial, more than 5% of body area or disfiguring.	Clinical diagnosis
Extensive molluscum contagiosum infection	Characteristic skin lesions: small flesh-coloured, pearly or pink, dome-shaped or umbilicated growths, may be inflamed or red; facial, more than 5% of body area or disfiguring. Giant molluscum may indicate advanced immunodeficiency.	Clinical diagnosis
Recurrent oral ulcerations (two or more in six months)	Aphthous ulceration, typically with a halo of inflammation and yellow-grey pseudomembrane.	Clinical diagnosis
Unexplained parotid enlargement	Asymptomatic bilateral swelling that may spontaneously resolve and recur, in absence of other known cause; usually painless.	Clinical diagnosis
Herpes zoster	Painful rash with fluid-filled blisters, dermatomal distribution, may be haemorrhagic on erythematous background, and may become large and confluent. Does not cross the midline.	Clinical diagnosis
Recurrent upper respiratory tract infection (URTI)	Current event with at least one episode in past six months. Symptom complex: fever with unilateral face pain and nasal discharge (sinusitis) or painful swollen eardrum (otitis media), sore throat with productive cough (bronchitis), sore throat (pharyngitis) and barking croup-like cough (LTB), persistent or recurrent ear discharge.	Clinical diagnosis
Stage 3		
Unexplained moderate malnutrition	Weight loss: low weight-for-age, up to -2 standard deviations (SDs), not explained by poor or inadequate feeding and/or other infections, and not adequately responding to standard management.	Documented loss of body weight of -2 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.

Clinical event	Clinical diagnosis	Definitive diagnosis
Unexplained persistent fever (intermittent or constant for longer than one month)	Reports of fever or night sweats for longer than one month, either intermittent or constant, with reported lack of response to antibiotics or antimalarials. No other obvious foci of disease reported or found on examination. Malaria must be excluded in malarious areas.	Documented fever of >37.5 °C with negative blood culture, negative malaria slide and normal or unchanged CXR, and no other obvious foci of disease.
Oral candidiasis (after first 6 weeks of life)	Persistent or recurring creamy white soft small plaques which can be scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender (erythematous form).	Microscopy or culture.
Oral hairy leukoplakia	Fine small linear patches on lateral borders of tongue, generally bilaterally, which do not scrape off.	Clinical diagnosis
Lymph node TB	Nonacute, painless "cold" enlargement of lymph nodes, usually matted, localized in one region. May have draining sinuses. Response to standard anti-TB treatment in one month.	Histology or fine needle aspirate for Ziehl Neelsen stain. Culture.
Pulmonary TB (History of contact with adult with smear positive PTB)	Nonspecific symptoms, e.g. chronic cough, fever, night sweats, anorexia and weight loss. In older children, productive cough and haemoptysis as well.	Isolation of M. Tuberculosis on sputum culture, +/- Abnormal CXR.
Severe recurrent bacterial pneumonia	Cough with fast breathing, chest in-drawing, nasal flaring, wheezing, and grunting. Crackles or consolidation on auscultation. Responds to course of antibiotics. Current episode plus one or more in previous six months.	Isolation of bacteria from appropriate clinical specimens (induced sputum, BAL, lung aspirate).
Acute necrotizing ulcerative gingivitis or stomatitis, or acute necrotizing ulcerative periodontitis	Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odour, and rapid loss of bone and/or soft tissue.	Clinical diagnosis

Clinical event	Clinical diagnosis	Definitive diagnosis
Symptomatic LIP	No presumptive clinical diagnosis.	CXR: bilateral reticulonodular interstitial pulmonary infiltrates present for more than two months with no response to antibiotic treatment and no other pathogen found. Oxygen saturation persistently <90%. May present with cor pulmonale and may have increased exercise-induced fatigue. Characteristic histology.
Chronic HIV-associated lung disease (including bronchiectasis)	History of cough productive of copious amounts of purulent sputum (bronchiectasis only), with or without clubbing, halitosis, and crepitations and/or wheezes on auscultation.	CXR; may show honeycomb appearance (small cysts) and/or persistent areas of opacification and/or widespread lung destruction, with fibrosis and loss of volume.
Unexplained anaemia (<8g/dl), or neutropenia (<0.5 x 10^9/L) or chronic thrombocytopenia (<50 X 10^9/L/)	No presumptive clinical diagnosis.	Laboratory testing, not explained by other non-HIV conditions, or not responding to standard therapy with haematinics, antimalarials or anthelminthics as outlined in IMCI.
Stage 4		
Unexplained severe wasting, stunting or severe malnutrition not adequately responding to standard therapy	Persistent weight loss not explained by poor or inadequate feeding or other infections and not adequately responding in two weeks to standard therapy. Characterized by: visible severe wasting of muscles, with or without oedema of both feet, and/or weight-for-height of -3 SDs, as defined by WHO IMCI guidelines.	Documented weight loss of >-3 SD +/- oedema.
Pneumocystis pneumonia (PCP)	Dry cough, progressive difficulty in breathing, cyanosis, tachypnoea and fever; chest indrawing or stridor. (Severe or very severe pneumonia as in IMCI.) Usually of rapid onset especially in infants under 6 months of age. Response to high-dose co-trimoxazole +/- prednisolone.	CXR, typical bilateral perihilar diffuse infiltrates; microscopy of induced sputum or BAL or NPA.

Clinical event	Clinical diagnosis	Definitive diagnosis
Recurrent severe bacterial infection, e.g. empyema, pyomyositis, bone or joint infection, meningitis but excluding pneumonia	Fever accompanied by specific symptoms or signs that localize infection. Responds to antibiotics. Current episode plus one or more in previous six months.	Culture of appropriate clinical specimen.
Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration or visceral at any site)	Severe and progressive painful orolabial, genital, or anorectal lesions caused by HSV infection present for more than one month.	Culture and/or histology.
Oesophageal *Candida* (or *Candida* of trachea, bronchi or lungs).	Chest pain and dysphagia (difficulty in swallowing), odynophagia (pain on swallowing food and fluids) or retrosternal pain worse on swallowing (food and fluids) responds to specific treatment. In young children, suspect particularly if oral *Candida* observed and food refusal occurs and/or difficulties/crying when feeding.	Macroscopic appearance at endoscopy, microscopy of specimen from tissue or macroscopic appearance at bronchoscopy or histology.
Extrapulmonary/ disseminated TB	Systemic illness usually with prolonged fever, night sweats, weight loss. Clinical features of organs involved, e.g. sterile pyuria, pericarditis, ascites, pleural effusion, meningitis, arthritis, orchitis.	Positive microscopy showing AFB or culture of Mycobacterium tuberculosis from blood or other relevant specimen except sputum or BAL. Biopsy and histology.
Kaposi sarcoma	Typical appearance in skin or oropharynx of persistent, initially flat, patches with a pink or blood-bruise colour, skin lesions that usually develop into nodules.	Macroscopic appearence or by histology.
CMV retinitis or CMV infection affecting another organ, with onset at age over 1 month.	Retinitis only: may be diagnosed by experienced clinicians: typical eye lesions on fundoscopic examination; discrete patches of retinal whitening with distinct borders, spreading centrifugally, often following blood vessels, associated with retinal vasculitis, haemorrhage and necrosis.	Histology or CMV demonstrated in CSF by culture or DNA-PCR.
CNS toxoplasmosis with onset at age over 1 month.	Fever, headache, focal neurological signs, convulsions. Usually responds within 10 days to specific therapy.	Positive serum toxoplasma antibody AND of available single/ multiple intracranial mass lesions on neuro imaging (CT or MRI).

Clinical event	Clinical diagnosis	Definitive diagnosis
Extrapulmonary cryptococcosis including meningitis	Meningitis: usually subacute, fever with increasing severe headache, meningism, confusion, behavioural changes that responds to cryptococcal therapy.	Isolation of Cryptococcus *neoformans* from extrapulmonary site or positive cryptococcal antigen test (CRAG) on CSF or blood.
HIV encephalopathy	At least one of the following, progressing over at least two months in the absence of another illness: - failure to attain, or loss of, developmental milestones, loss of intellectual ability; *or* - progressive impaired brain growth demonstrated by stagnation of head circumference; *or* - acquired symmetric motor deficit accompanied by two or more of the following: paresis, pathological reflexes, ataxia, gait disturbances.	Neuro imaging demonstrating atrophy and basal ganglia calcification, exclusion of other causes.
Disseminated mycosis (coccidiomycosis, histoplasmosis, penicilliosis)	No presumptive clinical diagnosis.	Histology: usually granuloma formation. Isolation: antigen detection from affected tissue; culture or microscopy from clinical specimen or blood culture.
Disseminated mycobacteriosis other than TB	No presumptive clinical diagnosis.	Nonspecific clinical symptoms including progressive weight loss, fever, anaemia, night sweats, fatigue or diarrhoea; plus culture of atypical mycobacteria species from stool, blood, body fluid or other body tissue, excluding lung.
Chronic cryptosporidiosis (with diarrhoea)	No presumptive clinical diagnosis.	Cysts identified on modified ZN stain.
Chronic Isospora	No presumptive clinical diagnosis.	Identification of isospora.
Cerebral or B cell non-Hodgkin lymphoma	No presumptive clinical diagnosis.	CNS imaging: at least one lesion with mass effect; histology of relevant specimen.

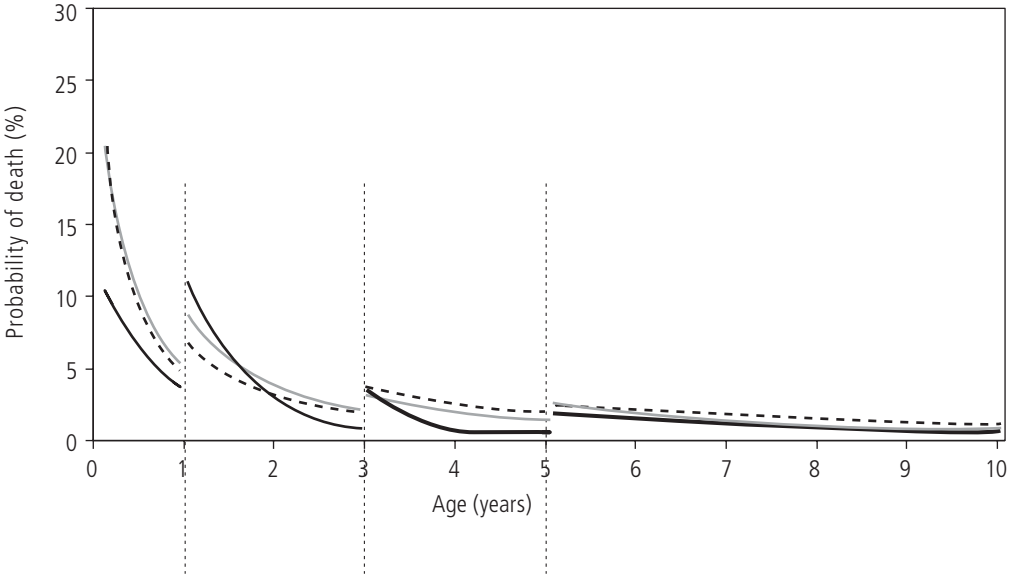
Clinical event	Clinical diagnosis	Definitive diagnosis
Progressive multifocal leukoencephalopathy (PML)	No presumptive clinical diagnosis.	Progressive neurological disorder together with white matter lesions on neuroimaging or positive polyomavirus JC (JCV) PCR on CSF.
Symptomatic HIV associated nephropathy	No presumptive clinical diagnosis	Renal biospy
Symptomatic HIV associated cardiomyopathy	No presumptive clinical diagnosis	Cardiomegaly and evidence of poor left ventricular function confirmed by echocardiography.

ANNEX C: WHO CLASSIFICATION OF HIV-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	25–29	20–24	15–19	200–349
Severe	<25	<20	<15	<200 *or* <15%

Source: Based on WHO global and regional consultations and data from references (45, 174).

ANNEX D: 12-MONTH MORTALITY RISK AT SELECTED THRESHOLDS FOR %CD4+, ABSOLUTE CD4 COUNT AND TOTAL LYMPHOCYTE COUNT BY AGE



%CD4+<25 (<1 yr), <20% (1 to <3 yrs), <15% (3 to 5 yrs), <15% (≥5 yrs)

CD4<150 (<1 yr), <750 (1 to <3 yrs), 350 (3 to <5 yrs), 200 (≥5 yrs)

TLC<4000 (<1 yr), <3000 (1 to <3 yrs), 2500 (3 to <5 yrs), 2000 (≥5 yrs)

Note: CD4 is denoted as % CD4+ and absolute count in cell/mm^3, TLC values are in cells/mm^3.

Source: reference (47).

Annex E: Prescribing information and weight based dosing of available ARV formulations for infants and children

WHO strongly encourages the development of formulations appropriate for paediatric use, particularly solid formulations in doses that can be used by paediatric patients under 14 kg.

This Annex contains information on ARV drugs for which there are paediatric indications, formulations or sufficient information and evidence to provide guidance on prescribing and doses. Situations that are frequently encountered in resource-limited settings, including the potential for lack of refrigeration and the lack of syrup or liquid forms for small children are taken into consideration. For simplification, doses are provided in ranges based on children's weights: although weight and height can both be measured it may be impractical to expect providers in many settings to calculate body surface area (BSA) accurately.

The work to develop simplified guidance on ARVs for use in children was undertaken by WHO as a result of recommendations made at a technical consultation held in November 2004. Further details of the meeting are available at: http://www.who.int/3by5/paediatric/en/index.html. Details of the members of the working group who assisted WHO are available in Annex A.

The primary source of information for the guidance provided is the package insert (product labelling) from the brand name product made by the innovator (brand name) company for each drug. This information was supplemented with data from other authoritative publications and expert consultation. Since information on drug dosing may be updated, providers are cautioned to consider the most recent guidelines and product labelling. Not all currently available ARV drugs are included. A web-based tool to assist in reviewing and adapting to country-specific simplified dosing guidance will be available online later in 2006.

Multisource, i.e. generic, antiretroviral drugs are available from several companies, however the strengths of tablets and capsules and the concentrations of liquid formulations may vary from the information given here. Additionally, some products are fixed-dose combination tablets containing quantities of drugs that are not appropriate for small children. Providers should consider the quality of multisource products and should consult the WHO document *Access to HIV/AIDS*

drugs and diagnostics of acceptable quality for guidance, which is available and updated at http://www.who.int/hiv/amds/selection/en/index.html.

WHO operates a voluntary prequalification system that was set up in 2001. This service facilitates access to medicines that meet unified standards of quality, safety and efficacy for HIV/AIDS, malaria and tuberculosis. Manufacturers (including manufacturers of multisource [generic] products) wishing their medicines to be included in the prequalified products list are invited to apply. Each manufacturer must present extensive information on the product (or products) submitted to allow qualified assessment teams to evaluate quality, safety and efficacy. The manufacturer must also open its manufacturing sites to an inspection team which assesses working procedures for compliance with WHO good manufacturing practices. Alternatively, the inspections carried out by stringent regulatory bodies are recognized and their work is not duplicated by WHO. A list of WHO-prequalified products is continuously updated and is available at http://mednet3.who.int/prequal/.

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

Part A. General principles

Details on individual drugs are available from the various manufacturers or the U.S. treatment guidelines (http://www.aidsinfo.nih.gov) or European treatment guidelines (http://ctu.mrc.ac.uk/penta/guidelin.pdf). Common and important toxicities of the antiretrovirals are provided in the main text of this document.

The WHO Dosing guidance provided here includes weight based tables calculated by estimation of body surface area (BSA). Suggested dosing is provided for one kilogram weight bands up to 10-14 kg, recognizing that these may be collapsed or simplified further. The target dose for the simplified tables for each antiretroviral drug is shown in the part 1 introduction component of the table. However, in some cases the dosing in a particular weight band may be somewhat above or below that recommended by the manufacturer. Decisions about dosing were based upon manufacturer's information, the antiretroviral drug formulation choices, available data from clinical studies, and expert paediatric pharmacology consultation, and were directed towards what could be considered the "optimal" dose for a particular weight band, *given the limitations imposed by currently available drug formulations*. Optimal dosing is given for all single ARV drugs and wherever possible combination solid FDCs. *This will be regularly reviewed and updated as further data or newer formulations become available.*

It is recommended that national treatment advisory panels and/or expert groups review and consider these principles and the prescribing information given current national policies, practice and drug regulatory requirements with a view to their suitability for national adaptation and adoption.

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

- It is preferable to use one formulation or fixed combination of any given drug(s).
- Oral syringes or other standardized devices of various sizes should be made available to support accurate dosing of liquid formulations.
- Large volumes of liquid or syrup formulations should be avoided where possible.
- In general, children should be switched to available solid formulations as soon as possible or as soon as they are tolerated.
- If liquid or syrup formulations are difficult to use for reasons of storage, volumes required, palatability or excipient nature solid dosage formulations are preferable.
- If solid formulations of first-line and second-line drugs developed for children are not available, acceptable or suitable, solid formulations currently used for adults can be used.
- Many tablets, but not all, may be divided in half but generally not further for drug safety reasons. Scored tablets are more easily split. Some tablets cannot be split and WHO recommends that where possible tablet splitting is conducted in the dispensing pharmacy using appropriate tablet cutters.
- Some adult FDCs may result in underdosing of individual components in children. Underdosing of FDCs should be avoided, particularly with drugs where there are concerns about rapid emergence of resistance (e.g. NNRTI drugs). In order to deliver induction dosing of nevirapine (NVP) during the first two weeks of therapy, triple drug fixed-dose combinations should not be used but rather the individual components of the regimen should be prescribed.
- Different dosing between a.m. and p.m. should be avoided where possible. However, in order to keep all regimens to no more than twice daily, there are instances where different quantities of solid dosage forms can be administered a.m. as opposed to p.m.

- The doses in the tables are presented in weight bands, accepting that some deviation from target dosing will occur.
- Children have to be weighed at each clinic visit, and dose changes are required as children grow and/or gain weight.
- When capsules are opened or tablets dissolved or crushed and added to food or liquid, it is important that the entire volume/amount of vehicle be taken to ensure administration of the full dose.

Weight-based doses were determined by using body surface area values calculated from median heights-for-weight from international growth charts using the formula:

BSA = square root [[weight (kg) x height (cm)]/3600].

From this work it is clear that formulations, particularly fixed dose combination formulations in solid forms for treating smaller children (under 10 -14 kg) are urgently needed to allow scale up of treatment for younger infants and children. WHO will make available additional guidance on required formulations, dosing information, and required phamacovigilance activities.

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

PART B. DRUG FORMULATIONS AND DOSAGES

1. NRTIs

Lamivudine (3TC)
Formulations
Oral solution: 10 mg/ml Tablet: 150 mg
Age (weight), dose and dose frequency
Target dose: 4 mg/kg/dose twice daily to a maximum of 150 mg twice daily Dose at <30 days: 2 mg/kg/dose twice daily Dose at ≥30 days: 4 mg/kg/dose twice daily Dose at >50 kg: 150 mg twice daily Note: Once-daily dosing is not yet approved for children but encouraging pharmacokinetic data are now available (175).
Other comments
General: ▪ Well tolerated ▪ No food restrictions ▪ Also active against hepatitis B Oral solution: ▪ Store solution at room temperature (i.e. 25 °C; use within one month of opening) Tablets: ▪ Store at 25 °C (permitted range:15 °C to 30 °C) ▪ Can be crushed and contents mixed with a small amount of water or food and immediately taken Pharmacokinetic data: ▪ Available for all ages

Lamivudine: Recommended dosing based on weight bands				
Weight range (kg)		**Formulation**	**Dose (ml, tablets)**	
Bottom	**Top**	**Target dose** 4 mg/kg/dose twice daily to a maximum 150mg/dose twice daily	**a.m.**	**p.m.**
5	5.9	10 mg/ml solution	3 ml	3 ml
6	6.9	10 mg/ml solution	3 ml	3 ml
7	7.9	10 mg/ml solution	4 ml	4 ml
8	8.9	10 mg/ml solution	4 ml	4 ml
9	9.9	10 mg/ml solution	4 ml	4 ml
10	10.9	10 mg/ml solution	5 ml	5 ml
11	11.9	10 mg/ml solution	5 ml	5 ml
12	13.9	10 mg/ml solution	6 ml	6 ml
		or 150 mg tablets	0.5	0.5
14	16.9	150 mg tablets	0.5	0.5
17	19.9	150 mg tablets	0.5	0.5
20	24.9	150 mg tablets	1	0.5
25	29.9	150 mg tablets	1	1
30	34.9	150 mg tablets	1	1

Stavudine (d4T)
Formulations
Oral solution: 1 mg/ml Capsules: 15 mg, 20 mg, 30 mg, 40 mg
Age (weight), dose and dose frequency
Target dose: 1 mg/kg/dose Dose at <30 kg: 1 mg/kg/dose twice daily Dose at >30kg: 30 mg/dose twice daily Adults >60 kg: currently 40 mg twice daily recommended;(using 30 mg dosing leads to delay or reduction of toxicity, although limited data on efficacy are available).
Other comments
General: ▪ Well tolerated ▪ **Do not use stavudine with zidovudine (AZT) due to an antagonistic effect** Oral solution: ▪ Palatable and well tolerated but requires refrigeration after reconstitution ▪ Powder for oral solution should be protected from excessive moisture and stored in tightly closed containers at 25 °C (permitted range: 15 °C to 30 °C) ▪ After constitution, needs refrigeration and storage in original container; discard any unused portion after 30 days ▪ Must be well shaken prior to each use Capsules: ▪ Can be opened and mixed with small amount of food or water (stable in solution for 24 hours if kept refrigerated) Pharmacokinetic data: ▪ Available for all ages

Stavudine: Recommended dosing based on weight bands				
Weight range (kg)		**Formulation**	**Dose (ml or capsules)**	
Bottom	**Top**	**Target dose** 1 mg/kg /dose twice daily up to 30 mg/dose twice daily	**p.m.**	**p.m.**
5	5.9	1 mg/ml syrup	6 ml	6 ml
6	6.9	20 mg capsules	0.5	0.5
		or 1 mg/ml syrup	7 ml	7 ml
7	7.9	20 mg capsules	0.5	0.5
		or 1 mg/ml syrup	8 ml	8 ml
8	8.9	20 mg capsules	0.5	0.5
		or 1 mg/ml syrup	9 ml	9 ml
9	9.9	20 mg capsules	0.5	0.5
		or 1 mg/ml syrup	10 ml	10 ml
10	10.9	15 mg capsules	1	1
11	11.9	15 mg capsules	1	1
12	13.9	15 mg capsules	1	1
14	16.9	20 mg capsules	1	1
17	19.9	20 mg capsules	1	1
20	24.9	20 mg capsules	1	1
25	29.9	30 mg capsules	1	1
30	34.9	30 mg capsules	1	1

'Stavudine 20 mg capsule can be dissolved in a measured quantity of water and half the quantity administered to provide dose shown in table'

Zidovudine (AZT [or ZDV])

Formulations

Syrup: 10 mg/ml

Capsules: 100 mg and 250 mg

Tablet: 300 mg

Age (weight), dose and dose frequency

Target dose for infants >6 weeks old:

Oral 180–240mg/m^2 per dose given twice daily (total daily dose of 360–480 mg/m^2)

Maximum dose 300 mg/dose given twice daily

Adult dose 250-300 mg/dose given twice daily

MTCT prevention dose:

Target dose in infants: *Oral:* 4 mg/kg every 12 hours starting within 12 hours after birth and continuing up to 1–6 weeks of age, depending on national recommendations

Intravenous: 1.5 mg/kg infused over 30 minutes, every 6 hours until oral dosing is possible.

Notes:

- For children with suspected nervous system involvement dose of 240mg/m^2 per dose given twice daily may be more beneficial.

Other comments

General:

- **Do not use stavudine with zidovudine (AZT) due to an antagonistic effect**
- No food restrictions
- Use with caution in children with anaemia due to potential for bone marrow suppression

Syrup (oral solution):

- Preferred in children <8 kg since accurate dosing with capsules is not practical in smaller children
- Is stable at room temperature but needs storage in glass jars and is light-sensitive

Capsules:

- May be opened and dispersed in water or on to a small amount of food and immediately ingested
- Storage at 15 °C to 25 °C

Tablets:

- Storage at 15 °C to 25 °C
- 300-mg tablets are often not scored; may be cut in half with a tablet splitter in a pharmacy.
- Tablets may be crushed and combined with a small amount of food or water and immediately ingested

Pharmacokinetic data:

- Available for all ages

Zidovudine: Recommended dosing based on weight bands; Range of tablets, capsules and syrup available					
Weight range (kg)		**Target dose** 180–240mg/m^2/dose twice daily		**Dose (ml or capsules or tablets)**	
Bottom	**Top**	**Formulation**		**a.m.**	**p.m.**
5	5.9	10 mg/ml syrup		6 ml	6 ml
6	6.9	10 mg/ml syrup		7 ml	7 ml
7	7.9	10 mg/ml syrup		8 ml	8 ml
8	8.9	10 mg/ml syrup		9 ml	9 ml
		or	100 mg capsules	1	1
9	9.9	10 mg/ml syrup		10 ml	10 ml
		or	100 mg capsules	1	1
10	10.9	10 mg/ml syrup		10 ml	10 ml
		or	100 mg capsules	1	1
11	11.9	10 mg/ml syrup		10 ml	10 ml
		or	100 mg capsules	1	1
12	13.9	10 mg/ml syrup		11 ml	11 ml
		or	100 mg capsules	1	1
14	16.9	100 mg capsules		2	1
		or	300 mg tablets	0.5	0.5
17	19.9	100 mg capsules		2	1
		or	300 mg tablets	0.5	0.5
20	24.9	100 mg capsules		2	2
		or	300 mg tablets	0.5	0.5
25	29.9	100 mg capsules		2	2
		or	300 mg tablets	1	0.5
30	34.9	100 mg capsules		3	3
		or	300 mg tablets	1	1

Zidovudine: recommended dosing based on weight bands; 100-mg capsules and syrup available					
Weight range (kg)		**Target dose** 180–240mg/m^2/dose twice daily		**Dose (ml or capsules)**	
Bottom	**Top**	**Formulation**		**a.m.**	**p.m.**
5	5.9	10 mg/ml syrup		6 ml	6 ml
6	6.9	10 mg/ml syrup		7 ml	7 ml
7	7.9	10 mg/ml syrup		8 ml	8 ml
8	8.9	10 mg/ml syrup		9 ml	9 ml
		or	100 mg capsules	1	1
9	9.9	10 mg/ml syrup		10 ml	10 ml
		or	100 mg capsules	1	1
10	10.9	10 mg/ml syrup		10 ml	10 ml
		or	100 mg capsules	1	1
11	11.9	10 mg/ml syrup		10 ml	10 ml
		or	100 mg capsules	1	1
12	13.9	100 mg capsules		1	1
14	16.9	100 mg capsules		2	1
17	19.9	100 mg capsules		2	1
20	24.9	100 mg capsules		2	2
25	29.9	100 mg capsules		2	2
30	34.9	100 mg capsules		3	3

Zidovudine: Recommended dosing based on weight bands; 300-mg tablets and syrup available				
Weight range (kg)		**Target dose** 180–240mg/m^2/dose twice daily	**Dose (ml or tablets)**	
Bottom	**Top**	**Formulation**	**a.m.**	**p.m.**
5	5.9	10 mg/ml syrup	6 ml	6 ml
6	6.9	10 mg/ml syrup	7 ml	7 ml
7	7.9	10 mg/ml syrup	8 ml	8 ml
8	8.9	10 mg/ml syrup	9 ml	9 ml
9	9.9	10 mg/ml syrup	10 ml	10 ml
10	10.9	10 mg/ml syrup	10 ml	10 ml
11	11.9	10 mg/ml syrup	10 ml	10 ml
12	13.9	10 mg/ml syrup	11 ml	11 ml
14	16.9	300 mg tablets	0.5	0.5
17	19.9	300 mg tablets	0.5	0.5
20	24.9	300 mg tablets	0.5	0.5
25	29.9	300 mg tablets	1	0.5
30	34.9	300 mg tablets	1	1

Abacavir (ABC)
Formulations
Oral solution: 20 mg/ml Tablet: 300 mg
Age (weight), dose and dose frequency
Target dose <16 years or <37.5 kg: 8 mg/kg/dose twice daily Maximum dose >16 years or ≥37.5 kg: 300 mg/dose twice daily Once-daily dosing is not yet approved for children but encouraging pharmacokinetic data are now available (175).
Other comments
General: ▪ **Parents must be warned about potential hypersensitivity reaction** ▪ **ABC should be stopped permanently if hypersensitivity reaction occurs** ▪ No food restrictions Tablets: ▪ Can be crushed and contents mixed with small amount water or food and immediately ingested ▪ Storage at room temperature of 20 °C to 25 °C Oral solution: ▪ Storage at room temperature of 20 °C to 25 °C; may be refrigerated Pharmacokinetic data: ▪ Available for children over the age of 3 months (see comment above)

Abacavir: Recommended dosing based on weight bands					
Weight range (kg)		**Target dosing** <16 years or <37.5 kg: 8 mg/kg/dose given twice daily Maximum dose >16 years or ≥37.5 kg: 300 mg/dose given twice daily		**Dose (ml or tablets)**	
Bottom	**Top**	**Formulation**		**a.m.**	**a.m.**
5	5.9	20 mg/ml syrup		2 ml	2 ml
6	6.9	20 mg/ml syrup		3 ml	3 ml
7	7.9	20 mg/ml syrup		4 ml	4 ml
8	8.9	20 mg/ml syrup		4 ml	4 ml
9	9.9	20 mg/ml syrup		4 ml	4 ml
10	10.9	20 mg/ml syrup		5 ml	5 ml
11	11.9	20 mg/ml syrup		5 ml	5 ml
		or	300 mg tablet	0.5	0.5
12	13.9	20 mg/ml syrup		6 ml	6 ml
		or	300 mg tablet	0.5	0.5
14	16.9	300 mg tablet		0.5	0.5
17	19.9	300 mg tablet		0.5	0.5
20	24.9	300 mg tablet		1	0.5
25	29.9	300 mg tablet		1	1
30	34.9	300 mg tablet		1	1

Didanosine (ddI [dideoxyinosine])

Formulations

Oral solution from paediatric powder/water:	10 mg/ml (in many countries must be made up with additional antacid)
Chewable tablets:	25 mg, 50 mg, 100 mg, 150 mg, 200 mg
Enteric-coated beadlets in capsules:	125 mg, 200 mg, 250 mg, 400 mg (designed for once daily dosing preferred but still not widely available)

Age (weight), dose and dose frequency

Dose <3 months:	50 mg/m^2/dose twice daily
Dose at 3 months to <13 years:	90–120 mg/m^2/dose twice daily
Maximum dose, ≥13 years or >60 kg:	200 mg/dose twice daily or 400 mg once daily

Once-daily dosing for chewable tablets is authorized in United Kingdom for children over the age of 6 years.

Other comments

General:

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

Oral suspension:

- Is not easy to use and should be avoided if possible
- Should be kept refrigerated; stable for 30 days; must be well shaken

Tablets:

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

Enteric-coated beadlets in capsules:

- Can be opened and sprinkled on a small amount of food

Pharmacokinetic data:

- Are available for all ages

Didanosine: Recommended dosing based on weight bands Once-daily EC capsules			
Weight range (kg)		**Target dose** Maximum dose: >13 years or >60 kg: 400 mg once daily	**Dose (capsules)**
Bottom	**Top**	**Formulation**	**a.m. or p.m.**
10	10.9	125 mg EC capsule	1
11	11.9	125 mg EC capsule	1
12	13.9	125 mg EC capsule	1
14	16.9	200 mg EC capsule	1
17	19.9	200 mg EC capsule	1
20	24.9	250 mg EC capsule	1
25	29.9	250 mg EC capsule	1
30	34.9	250 mg EC capsule	1

Didanosine: Recommended twice-daily dosing based on weight bands					
Weight range (kg)		**Target dosing** <3 months: 50 mg/m^2/dose twice daily 3 months to <13 years: 90–120 mg/m^2/dose twice daily Maximum dose: ≥13 years or >60 kg: 200 mg/dose twice daily or 400 mg once daily		**Dose (ml or tablets)**	
Bottom	**Top**	**Formulation**		**a.m.**	**p.m.**
5	5.9	10 mg/ml suspension		4 ml	4 ml
		or	25 mg chew tablet	2	2
6	6.9	10 mg/ml suspension		5 ml	5 ml
		or	25 mg chew tablet	2	2
7	7.9	10 mg/ml suspension		6 ml	6 ml
		or	25 mg chew tablet	2	2
8	8.9	10 mg/ml suspension		6 ml	6 ml
		or	25 mg chew tablet	2	2
9	9.9	10 mg/ml suspension		6 ml	6 ml
		or	25 mg chew tablet	2	2
10	10.9	10 mg/ml suspension		6 ml	6 ml
		or	25 mg chew tablet	3	2
11	11.9	10 mg/ml suspension		7 ml	7 ml
		or	25 mg chew tablet	3	3
12	13.9	10 mg/ml suspension		7 ml	7 ml
		or	25 mg chew tablet	3	3
14	16.9	10 mg/ml suspension		8 ml	8 ml
		or	25 mg chew tablet	4	3
17	19.9	10 mg/ml suspension		9 ml	9 ml
		or	25 mg chew tablet	4	4
20	24.9	25 mg chew tablet		5	5
25	29.9	25 mg chew tablet		5	5
30	34.9	25 mg chew tablet		5	5

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

2. NNRTIs

Efavirenz (EFV)
Formulations
Syrup: 30 mg/ml (Note: syrup has lower bioavailability and ratio of 1.3 syrup to solid formulation is suggested to achieve an equivalent dose) Capsules: 50 mg, 100 mg, 200 mg Tablets: 600 mg
Age (weight), dose and dose frequency
Target dosing: 19.5 mg/kg/day (syrup) or 15 mg/kg/day (capsule/tablet) Weight greater than 40 kg, 600 mg once daily
Other comments
General: ▪ Storage at 25 °C (permitted range: 15 °C to 30 °C) ▪ Insufficient data on dosing for children <3 years old ▪ EFV can be given with food but if taken with food, especially high-fat meals, absorption is increased by an average of 50% ▪ EFV is best given at bedtime in order to reduce CNS side-effects, especially during first two weeks Capsules: ▪ May be opened and added to a small amount of food or liquid; they have a very peppery taste but can be mixed with sweet foods to disguise the taste Pharmacokinetic data: ▪ Available for children over 3 years of age ▪ Insufficient data on dosing for children <3 years old

B. Efavirenz: Recommended once-daily dosing based on weight bands			
Weight range (kg)		**Target dose** 15 mg/kg/day (capsule/tablet) Weight >40 kg: 600 mg once daily	**Dose (capsules, tablets)** **Once daily, 3 years and above**
Bottom	**Top**	**Formulation**	
10	10.9	200 mg capsule	1
11	11.9	200 mg capsule	1
12	13.9	200 mg capsule	1
14	16.9	mg capsule	200 mg + 50 mg
17	19.9	mg capsule	200 mg + 50 mg
20	24.9	mg capsule	200 mg + 100 mg
25	29.9	mg capsule	200 mg + 100 mg + 50 mg
30	34.9	200 mg capsule	2
35	39.9	200 mg capsule	2
>40		600 tablet	1

Nevirapine (NVP)

Formulations

Oral suspension: 10 mg/ml
Tablet: 200 mg

Age (weight), dose and dose frequency

Target dose for maintenance: 160–200 mg/m^2 to maximum dose of 200 mg taken twice daily

Special considerations on dosing:

a) Induction dose: once daily for first 14 days; it is generally half the daily maintenance dose given once daily except where the maintenance dose is divided unequally between a.m. and p.m.

b) Maintenance dose: target dose is 160–200 mg/m^2/dose given twice daily adjusted for more aggressive dosing in younger ages.

c) For children 14–24.9 kg the suggested dose is 1 tablet a.m. and ½ tablet p.m. Due to the prolonged half-life of nevirapine the fluctuation in drug exposure associated with this dosing schedule is acceptable.

d) If a mild rash occurs during the first 14 days of induction dosing, continue once daily dosing and only escalate dose once the rash has subsided and the dose is well tolerated. If a severe rash occurs (especially if accompanied by fever, blistering or mucosal ulcerations), discontinue drug.

Dosing for MTCT prevention: 2 mg/kg/dose within 72 hours of birth once only

If the maternal dose of nevirapine was given less than 2 hours before delivery, then administer 2 mg/kg/dose to the infant immediately after birth and repeat within 24–72 hours of first dose.

If the infant weight is not available, administer 0.6 ml oral suspension.

Other comments

General:

- Parents must be warned about a potential severe, life-threatening rash during the 14-day lead-in period. The once-daily induction dose is used to reduce the frequency of rash.
- NVP should be permanently discontinued and not restarted in children who develop severe rash
- Drug interactions: avoid nevirapine if rifampicin is coadministered (see Section XVII)
- Can be given without regard to food
- Storage at 25 °C (permitted range 15 °C to 30 °C)

Oral suspension:

- Must be well shaken

Tablets:

- Are scored and can be divided into two equal parts to give a 100-mg dose; can be crushed and combined with a small amount of water or food and immediately administered

Pharmacokinetic data:

- Available for all ages

Nevirapine: Recommended induction dosing based on weight bands				
Weight range (kg)		**Target dose** Half of daily maintenance dosing (160–200 mg/m^2/dose to max 200 mg.)		**Dose (ml or tablets)**
Bottom	**Top**	**Formulation**		**Once daily**
5	5.9	10 mg/ml syrup		6 ml
6	6.9	10 mg/ml syrup		7 ml
7	7.9	10 mg/ml syrup		8 ml
8	8.9	10 mg/ml syrup		9 ml
9	9.9	10 mg/ml syrup		9 ml
		or	200 mg tablets	0.5
10	10.9	10 mg/ml syrup		10 ml
		or	200 mg tablets	0.5
11	11.9	10 mg/ml syrup		10 ml
		or	200 mg tablets	0.5
12	13.9	10 mg/ml syrup		11 ml
		or	200 mg tablets	0.5
14	16.9	200 mg tablets		0.5
17	19.9	200 mg tablets		1
20	24.9	200 mg tablets		1
25	29.9	200 mg tablets		1
30	34.9	200 mg tablets		1

Nevirapine: Recommended <u>maintenance</u> dosing based on weight bands				
Weight range (kg)		**Target dosing** 160–200 mg/m^2 to max 200 mg per dose twice daily	**Dose (ml or tablets)**	
Bottom	**Top**	**Formulation**	**a.m.**	**p.m.**
5	5.9	10 mg/ml syrup	6 ml	6 ml
6	6.9	10 mg/ml syrup	7 ml	7 ml
7	7.9	10 mg/ml syrup	8 ml	8 ml
8	8.9	10 mg/ml syrup	9 ml	9 ml
9	9.9	10 mg/ml syrup	9 ml	9 ml
		or 200 mg tablets	0.5	0.5
10	10.9	10 mg/ml syrup	10 ml	10 ml
		or 200 mg tablets	0.5	0.5
11	11.9	10 mg/ml syrup	10 ml	10 ml
		or 200 mg tablets	0.5	0.5
12	13.9	10 mg/ml syrup	11 ml	11 ml
		or 200 mg tablets	0.5	0.5
14	16.9	200 mg tablets	1	0.5
17	19.9	200 mg tablets	1	0.5
20	24.9	200 mg tablets	1	0.5
25	29.9	200 mg tablets	1	1
30	34.9	200 mg tablets	1	1

3. PROTEASE INHIBITORS

Saquinavir (SQV)
Formulations
Capsules: Hard gel capsules(hgc) : 200 mg Tablets: 500 mg
Age (weight), dose and dose frequency
▪ hgc studies reported using 33 mg/kg three times a day
Other comments
General: ▪ Should not be taken as sole protease inhibitor ▪ Should be taken with food as absorption is improved; it is suggested that it be taken within two hours after a meal Storage: ▪ hgc do not need refrigeration Pharmacokinetic data: ▪ Safety and effectiveness not yet well established in younger children ▪ Not licensed for use in children under 16 years of age or less than 25 kg

Nelfinavir (NFV)	
Formulations	
Powder for oral suspension:	50 mg per 1.25 ml scoop (200 mg per level teaspoon of 5 ml)
Tablet:	250 mg, 625 mg
Age (weight), dose and dose frequency	
<10 kg: dose listed is targeted to achieve a dose of ~75 mg/kg/dose twice daily ≥10 kg to 19.9 kg: dose listed is targeted to achieve a dose of ~60 mg/kg/dose twice daily ≥20 kg: maximum recommended dose of 1250 mg/dose twice daily	
Other comments	
General: ▪ Powder and tablets can be stored at room temperature ▪ Must be taken with food to improve absorption ▪ Drug interactions (less than ritonavir-containing protease inhibitors) ▪ Because of difficulties with powder the use of crushed tablets is preferred (even for infants) if the appropriate dose can be given Tablets: ▪ May be halved, or crushed and dispersed in water or on to a small amount of food and immediately ingested Pharmacokinetic data: ▪ Available for all ages ▪ However, there is extensive pharmacokinetic variability in infants, with a requirement for very high doses in infants <1 year of age.	

Nelfinavir: Recommended dosing based on weight bands				
Weight range (kg)		**Target dosing** <10 kg: ~75 mg/kg/dose twice daily >10 kg to 19.9 kg: ~60 mg/kg/dose twice daily >20 kg: max dose of 1250 mg twice daily	**Dose (ml or capsules)**	
Bottom	**Top**	**Formulation**	**a.m.**	**p.m.**
5	5.9	250 mg tablets	2	2
6	6.9	250 mg tablets	2	2
7	7.9	250 mg tablets	3	2
8	8.9	250 mg tablets	3	3
9	9.9	250 mg tablets	3	3
10	10.9	250 mg tablets	3	3
11	11.9	250 mg tablets	3	3
12	13.9	250 mg tablets	4	4
14	16.9	250 mg tablets	4	4
17	19.9	250 mg tablets	5	5
		or 625 mg tablets	2	2
20	24.9	250 mg tablets	5	5
		or 625 mg tablets	2	2
25	29.9	250 mg tablets	5	5
		or 625 mg tablets	2	2
30	34.9	250 mg tablets	5	5
		or 625 mg tablets	2	2
35	39.9	250 mg tablets	5	5
		or 625 mg tablets	2	2

Lopinavir/ritonavir (LPV/r) [coformulation]

Formulations

Oral solution: 80 mg/ml lopinavir plus 20 mg/ml ritonavir
Capsules: 133.3 mg lopinavir plus 33.3 mg ritonavir
Tablets: 200 mg lopinavir + 50 mg ritonavir

Age (weight), dose and dose frequency

Lopinavir target doses:

- 5–7.9 kg: 16 mg/kg/dose twice daily
- 8–9.9 kg: 14 mg/kg/dose twice daily
- 10–13.9 kg: 12 mg/kg/dose twice daily
- 14–39.9 kg: 10 mg/kg/dose twice daily

Ritonavir target doses:

- 7–15 kg: 3 mg/kg/dose twice daily
- 15–40 kg: 2.5 mg/kg/dose twice daily

Maximum dose: 400 mg lopinavir + 100 mg ritonavir taken twice daily

Other comments

General:

- Should be taken with food
- Preferably, oral solution and capsules should be refrigerated; however, can be stored at room temperature up to 25°C for two months; at >25°C drug degrades more rapidly
- There are many drug-to-drug interactions because RTV inhibits cytochrome P450

Oral solutions:

- Low volume but bitter taste

Capsules:

- Large
- **Should not be crushed or opened; must be swallowed whole**

Tablets :

- Do not have food restrictions although bioavailability is increased when administered with food
- Cannot be split

Pharmacokinetic data:

- Available for 6 months of age or older

Lopinavir/ritonavir: Recommended dosing based on weight bands						
Weight range (kg)		**Target dosing** See table over for lopinavir and ritonavir target doses			**Dose (ml or tablets)**	
Bottom	**Top**		**Formulation**		**a.m.**	**p.m.**
5	5.9		80 mg lopinavir/20 mg ritonavir per	ml solution	1 ml	1 ml
6	6.9		80 mg lopinavir/20 mg ritonavir per	ml solution	1.5 ml	1.5 ml
7	7.9		80 mg lopinavir/20 mg ritonavir per	ml solution	1.5 ml	1.5 ml
		or	133 mg lopinavir/33 mg ritonavir per	capsule	1	1
8	8.9		80 mg lopinavir/20 mg ritonavir per	ml solution	2 ml	2 ml
		or	133 mg lopinavir/33 mg ritonavir per	capsule	1	1
9	9.9		80 mg lopinavir/20 mg ritonavir per	ml solution	2 ml	2 ml
		or	133 mg lopinavir/33 mg ritonavir per	capsule	1	1
10	10.9		80 mg lopinavir/20 mg ritonavir per	ml solution	2 ml	2 ml
		or	133 mg lopinavir/33 mg ritonavir per	capsule	1	1
11	11.9		80 mg lopinavir/20 mg ritonavir per	ml solution	2 ml	2 ml
		or	133 mg lopinavir/33 mg ritonavir per	capsule	1	1
12	13.9		80 mg lopinavir/20 mg ritonavir per	ml solution	2 ml	2 ml
		or	133 mg lopinavir/33 mg ritonavir per	capsule	2	1
		or	200 mg lopinavir/50 mg ritonavir per	tablet	1	1
14	16.9		80 mg lopinavir/20 mg ritonavir per	ml solution	2 ml	2 ml
		or	133 mg lopinavir /33 mg ritonavir per	capsule	2	1
		or	200 mg lopinavir/50 mg ritonavir per	tablet	1	1
17	19.9		80 mg lopinavir/20 mg ritonavir per	ml solution	2.5 ml	2.5 ml
		or	133 mg lopinavir/33 mg ritonavir per	capsule	2	1
		or	200 mg lopinavir/50 mg ritonavir per	tablet	1	1
20	24.9		80 mg lopinavir/20 mg ritonavir per	ml solution	3 ml	3 ml
		or	133 mg lopinavir/33 mg ritonavir per	capsule	2	2
		or	200 mg lopinavir/50 mg ritonavir per	tablet	1	1

Weight range (kg)		Target dosing See table over for lopinavir and ritonavir target doses			Dose (ml or tablets)	
Bottom	**Top**	**Formulation**			**a.m.**	**p.m.**
25	29.9	80 mg lopinavir/20 mg ritonavir per		ml solution	3.5 ml	3.5 ml
		or 133 mg lopinavir/33 mg ritonavir per		capsule	2	2
		or 200 mg lopinavir/50 mg ritonavir per		tablet	2	1
30	34.9	80 mg lopinavir/20 mg ritonavir per		ml solution	4 ml	4 ml
		or 133 mg lopinavir/33 mg ritonavir per		capsule	3	3
		or 200 mg lopinavir/50 mg ritonavir per		tablet	2	2
35	39.9	80 mg lopinavir/20 mg ritonavir per		ml solution	5 ml	5 ml
		or 133 mg lopinavir/33 mg ritonavir per		capsule	3	3
		or 200 mg lopinavir/50 mg ritonavir per		tablet	2	2

Ritonavir (RTV)

Formulations

Soft gelatin capsules: 100mg

Liquid: 600 mg ritonavir per 7.5 ml (80 mg/ml)

Co- formulated with Lopinavir

Age (weight), dose and dose frequency

Target dose treatment :

<2 years: not established

≥2 to 16 years: 400 mg/m^2 twice daily by mouth up to maximum 600 mg twice daily

- Started at 250 mg/m^2 and increased at intervals of 2 to 3 days by 50 mg/m^2 twice daily to reduce side-effects

As a booster for Lopinavir:

Ritonavir target doses:

7–15 kg: 3 mg/kg twice daily

15–40 kg: 2.5 mg/kg twice daily

Other comments

General:

- Adverse event profile seen during clinical trials and postmarketing similar to that for adults
- Liquid must be kept at 20°C to 25°C and in original bottle
- Liquid is foul-tasting and excipient contains 43% alcohol
- Soft gel capsules contain 12% alcohol excipient
- Should be taken with food
- Liquid may be taken alone or mixed with milk or food but should not be mixed with other fluids, including water
- Many drug-to-drug interactions because RTV inhibits cytochrome P450

Pharmacokinetic data:

- Available for infants and children

4. Fixed-dose combinations

WHO encourages the use of fixed-dose combinations when formulations of assured quality and proven bioequivalence are available and offer operational advantages. Not all the FDCs in this table have been evaluated for prequalification by WHO.

Fixed-dose combinations of standard first-line ARV drugs that are suitable for children are urgently required to facilitate treatment of HIV in children. Further details and a current list of prequalified drugs are available at: http://mednet3.who.int/prequal/

FDCs of standard first and second line regimens for treating children under 10-14 kg are urgently required.

Zidovudine (AZT) plus lamivudine (3TC)
Formulations
Oral solution: not available Tablet: AZT (300 mg) plus 3TC (150 mg)
Age (weight), dose and dose frequency
Target dose. Zidovudine - 180-240mg/m^2/dose twice daily Lamivudine - 4mg/kg/dose twice daily Maximum dose: 1 tablet/dose twice daily
Other comments
General: ▪ See comments under individual drug components Tablets: ▪ Storage between 2°C and 30°C ▪ No food restrictions ▪ Can be crushed and contents mixed with a small amount of water or food and immediately taken Pharmacokinetic data: ▪ Available for adolescents and adults

B. AZT plus 3TC: Recommended dosing based on weight bands					
Weight range (kg)		**Target dosing as for individual components**		**Dose**	
Bottom	**Top**	**Formulation** 300 mg AZT/150 mg 3TC tablets		**a.m.**	**p.m.**
14	16.9	300/150	tablet	0.5	0.5
17	19.9	300/150	tablet	0.5	0.5
20	24.9	300/150	tablet	1	0.5
25	29.9	300/150	tablet	1	0.5
30	34.9	300/150	tablet	1	1

Stavudine (d4T) plus lamivudine (3TC)
Formulations
Oral solution: stavudine 10 mg + lamivudine 40 mg/5 ml Tablets: d4T (30 mg) plus 3TC (150 mg) *or* d4T (40 mg) plus 3TC (150 mg)
Age (weight), dose and dose frequency
Target dose: Stavudine- 1mg/kg/dose twice daily Lamivudine - 4mg/kg/dose twice daily Maximum dose: 1 tablet/dose twice daily
Other comments
General: ▪ See comments under individual drug components (Section 1 of annex E 'NRTIs') Tablets: ▪ Preferably, should not be split unless scored Pharmacokinetic data: ▪ Available for adolescents and adults

d4T plus 3TC: Recommended dosing based on weight bands					
Weight range (kg)		**Target dosing as for individual components**		**Dose (tablets)**	
Bottom	**Top**	**Formulation** 30 mg d4T/150 mg 3TC		**a.m.**	**p.m.**
10	10.9	30/150	mg tablets	0.5	0.5
11	11.9	30/150	mg tablets	0.5	0.5
12	13.9	30/150	mg tablets	0.5	0.5
14	16.9	30/150	mg tablets	1	0.5
17	19.9	30/150	mg tablets	1	0.5
20	24.9	30/150	mg tablets	1	0.5
25	29.9	30/150	mg tablets	1	1
30	34.9	30/150	mg tablets	1	1

Zidovudine (AZT) plus lamivudine (3TC) plus abacavir (ABC)
Formulations
Oral solution: not available Tablet: AZT (300 mg) plus 3TC (150 mg) plus ABC (300 mg)
Age (weight), dose and dose frequency
Target dose: Zidovudine - 180-240mg/m^2/dose twice daily Lamivudine - 4mg/kg/dose twice daily Abacavir - 8mg/kg/dose twice daily Maximum dose: 1 tablet/dose twice daily
Other comments
General: ▪ See comments under individual drug components ▪ Parents must be warned about potential hypersensitivity reaction ▪ ABC should be stopped permanently if hypersensitivity reaction occurs Pharmacokinetic data: ▪ Available only for adults and adolescents

AZT plus 3TC plus ABC: Recommended dosing based on weight bands				
Weight range (kg)		**Target dosing as for individual drugs**	**Dose (tablets)**	
Bottom	**Top**	**Formulation** 300 mg AZT/150 mg 3TC/300 mg ABC	**a.m.**	**p.m.**
14	16.9	300/150/300 mg tablets	0.5	0.5
17	19.9	300/150/300 mg tablets	0.5	0.5
20	24.9	300/150/300 mg tablets	1	0.5
25	29.9	300/150/300 mg tablets	1	0.5
30	34.9	300/150/300 mg tablets	1	1

Stavudine (d4T) plus lamivudine (3TC) plus nevirapine (NVP)
Formulations
Tablet: d4T (30 mg) plus 3TC (150 mg) plus NVP (200 mg); *or* d4T (40 mg) plus 3TC (150 mg) plus NVP (200 mg) As of June 2006 not yet WHO prequalified: Tablet: 6 mg stavudine/30 mg lamivudine/50 mg nevirapine (baby) Tablet: 12 mg stavudine/60 mg lamivudine/100 mg nevirapine (junior) Suspension: stavudine 10 mg / 5 ml + lamivudine 40 mg + nevirapine 70 mg
Age (weight), dose and dose frequency
Maximum dose: one 30-mg d4T-based tablet twice daily
Other comments
General: ▪ Contains a fixed dose of NVP, therefore cannot be used for nevirapine induction as nevirapine dose escalation required (see NVP dosing recommendations) ▪ See comments under individual drug components Tablets: ▪ Preferably, should not be split unless scored Pharmacokinetic data: ▪ Available for adults and adolescents. ▪ Limited data on use of FDCs in children

d4T plus 3TC plus NVP: Recommended dosing based on weight bands			
Weight range (kg)		**Formulation** 30 mg d4T/ 200 mg NVP/ 150 mg 3TC Target dosing as for individual drugs Dose (tablets)	
Bottom	**Top**	**a.m.**	**p.m.**
10	10.9	0.5	0.5
11	11.9	0.5	0.5
12	13.9	0.5	0.5
14	16.9	1	0.5
17	19.9	1	0.5
20	24.9	1	0.5
25	29.9	1	1
30	34.9	1	1

ANNEX F: SERIOUS ACUTE AND CHRONIC TOXICITIES CAUSED BY ARV DRUGS, POSSIBLY REQUIRING THERAPY MODIFICATION: CLINICAL PRESENTATION, LABORATORY ABNORMALITIES AND IMPLICATIONS FOR ART MANAGEMENT

(Alternative explanations for toxicity must be excluded before concluding that it is secondary to the ARV drug. This table describes management of the ART regimen but does not indicate detailed clinical toxicity management.)

Possible clinical manifestations (Most common ARV drug or drugs associated with the toxicity)	**Possible laboratory abnormalities[a]**	**Implications for antiretroviral drug treatment**
Acute serious adverse reactions		
Acute symptomatic hepatitis (NNRTI class, particularly NVP, more rarely EFV; NRTIs or PI class)		
▪ Jaundice ▪ Liver enlargement ▪ Gastrointestinal symptoms ▪ Fatigue, anorexia ▪ May have hypersensitivity component (rash, fever, systemic symptoms), usually occurs within 6–8 weeks ▪ May have accompanying lactic acidosis (see below) if secondary to NRTI drug	▪ Elevated transaminases ▪ Elevated bilirubin	▪ Discontinue all ARV until symptoms resolve ▪ If possible, monitor transaminases, bilirubin ▪ If receiving NVP, it should NOT be readministered to the patient in future ▪ Once symptoms resolve, either: – restart ART with change to alternative ARV (if on NVP regimen, this is required); or – restart current ART regimen with close observation; if symptoms recur, substitute an alternative ARV[b]

Acute pancreatitis (NRTI class, particularly d4T, ddI; more rarely 3TC)		
▪ Severe nausea and vomiting ▪ Severe abdominal pain ▪ May have accompanying lactic acidosis (see below)	▪ Elevated pancreatic amylase ▪ Elevated lipase	▪ Discontinue all ARVs until symptoms resolve ▪ If possible, monitor serum pancreatic amylase, lipase ▪ Once symptoms resolve, restart ART with substitution of an alternative NRTI, preferably one without pancreatic toxicity[b]
Hypersensitivity reaction (ABC or NVP)		
▪ *ABC:* Combination of acute onset of both respiratory and gastrointestinal symptoms after starting ABC, including fever, fatigue, myalgia, nausea, vomiting, diarrhoea, abdominal pain, pharyngitis, cough, dyspnoea; rash (usually mild) may or may not occur; progressive worsening of symptoms soon after receiving ABC dose, usually occurs within 6–8 weeks ▪ *NVP:* Systemic symptoms of fever, myalgia, arthralgia, hepatitis, with or without rash	▪ Elevated transaminases ▪ Elevated eosinophil count	▪ Immediately discontinue all ARVs until symptoms resolve ▪ NVP or ABC should NOT be readministered to the patient in future ▪ Once symptoms resolve, restart ART with substitution of an alternative ARV for ABC or NVP[b]

[a] All laboratory abnormalities may not be observed.

[b] See Table 7 (Section IX) for recommended antiretroviral drug substitutions.

Possible clinical manifestations (Most common ARV drug or drugs associated with the toxicity)	Possible laboratory abnormalities[a]	Implications for antiretroviral drug treatment
Lactic acidosis (NRTI class, particularly d4T)		
▪ Generalized fatigue and weakness ▪ Gastrointestinal features (nausea, vomiting, diarrhoea, abdominal pain, hepatomegaly, anorexia, poor weight gain and/or sudden unexplained weight loss) ▪ May have hepatitis or pancreatitis (see above) ▪ Respiratory features (tachypnoea and dyspnoea) ▪ Neurological symptoms (including motor weakness)	▪ Increased anion gap ▪ Lactic acidosis ▪ 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)[b]
Severe rash/Stevens-Johnson syndrome (NNRTI class, particularly NVP, less common EFV)		
▪ Rash usually occurs during first 6–8 weeks of treatment ▪ *Mild to moderate rash:* erythematous, maculopapular, confluent, most often on the body and arms, with no systemic symptoms	▪ Elevated aminotransferases	▪ If mild or moderate rash, ART can continue without interruption staying at induction dose until rash settles but with close observation, and only increase to maintenance dose once tolerated ▪ For severe or life-threatening rash, discontinue all ARVs until symptoms resolve ▪ NVP should NOT be readministered to the patient in the future

▪ *Severe rash:* extensive rash with moist desquamation, angio-oedema, or serum sickness-like reaction; or rash with constitutional findings such as fever, oral lesions, blistering, facial oedema, conjunctivitis ▪ Life-threatening Stevens-Johnson syndrome or toxic epidermal necrolysis		▪ Once symptoms resolve, restart ART with substitution of an alternative ARV for NVP (note: most experts would not change to another NNRTI drug if patient had severe or life-threatening Stevens-Johnson syndrome with NVP)[b]
Severe life-threatening anaemia (AZT)		
▪ Severe pallor, tachycardia ▪ Significant fatigue ▪ Congestive heart failure	▪ Low haemoglobin	▪ If refractory to symptomatic treatment (e.g. transfusion), discontinue AZT only and substitute an alternative NRTI[b]
Severe neutropenia (AZT)		
▪ Sepsis/infection	▪ Low neutrophil count	▪ If refractory to symptomatic treatment (e.g. transfusion), discontinue AZT only and substitute an alternative NRTI[b]

[a] All laboratory abnormalities may not be observed.

[b] See Table 7 (Section IX) for recommended antiretroviral drug substitutions.

Possible clinical manifestations (Most common ARV drug or drugs associated with the toxicity)	Possible laboratory abnormalities[a]	Implications for antiretroviral drug treatment
Chronic late serious adverse reactions		
Lipodystrophy/metabolic syndrome (d4T; PIs)		
▪ Fat accumulation and/or fat loss in distinct regions of the body: – increased fat around the abdomen, buffalo hump, breast hypertrophy – fat loss from limbs, buttocks and face occurs to a variable extent ▪ Insulin resistance, including diabetes mellitus ▪ Potential risk for later coronary artery disease	▪ Hyper- triglyceridaemia ▪ Hyper- cholesterolaemia ▪ Low HDL levels ▪ Hyperglycaemia	▪ Substitution of ABC or AZT for d4T may prevent progression of lipoatrophy ▪ Substitution of an NNRTI for a PI may decrease serum lipid abnormalities
Severe peripheral neuropathy (d4T, ddI; more rarely 3TC)		
▪ Pain, tingling, numbness of hands or feet; refusal to walk ▪ Distal sensory loss ▪ Mild muscle weakness and areflexia may occur	▪ None	▪ Stop suspect NRTI only and substitute a different NRTI that is not associated with neurotoxicity[b] ▪ Symptoms may take several weeks to resolve

[a] All laboratory abnormalities may not be observed.

[b] See Table 7 (Section IX) for recommended antiretroviral drug substitutions.

ANNEX G: SEVERITY GRADING OF SELECTED CLINICAL AND LABORATORY TOXICITIES MOST COMMONLY SEEN WITH RECOMMENDED ANTIRETROVIRAL DRUGS FOR CHILDREN

Parameter	Mild	Moderate	Severe	Severe and potentially life-threatening
General guidance on estimating severity grade				
Characterization of symptoms and general guidance on management	Symptoms causing no or minimal interference with usual social and functional activities:[a] No therapy needed, monitor	Symptoms causing greater than minimal interference with usual social and functional activities: may require minimal intervention and monitoring	Symptoms causing inability to perform usual social and functional activities: requires medical care and possible hospitalization	Symptoms causing inability to perform basic self-care functions:[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–<1000/mm^3 *0.75 x 10^9–<1 x 10^9/l*	500–749/mm^3 *0.5 x 10^9–0.749 x 10^9/l*	250–500/mm^3 *0.25 x 10^9–0.5 x 10^9/l*	<250/mm^3 *<0.250 x 10^9/l*
Haemoglobin (child >60 days of age)	8.5–10.0 g/dl *1.32–1.55 mmol/l*	7.5–<8.5 g/dl *1.16–<1.32 mmol/l*	6.5–<7.5 g/dl *1.01–<1.16 mmol/l*	<6.5 g/dl *<1.01 mmol/l* Or severe clinical symptoms attributable to anaemia (e.g. cardiac failure), refractory to supportive therapy
Platelets	100 000–<125 000/mm^3 *100 x 10^9–125 x 10^9/l*	50 000–<100 000/mm^3 *50 x 10^9–<100 x 10^9/l*	25 000–<50 000/mm^3 *25 x 10^9–<50 x 10^9/l*	<25 000/mm^3 *<25 x 10^9/l*or bleeding

Gastrointestinal[c]				
Laboratory				
ALT (SGPT)	1.25–2.5 x ULN	2.6–5.0 x ULN	5.1–10.0 x ULN	>10.0 x ULN
AST (SGOT)	1.25–2.5 x ULN	2.6–5.0 x ULN	5.1–10.0 x ULN	>10.0 x ULN
Bilirubin (>2 weeks of age)	1.1–1.5 x ULN	1.6–2.5 x ULN	2.6–5.0 x ULN	>5.0 x ULN
Lipase	1.1–1.5 x ULN	1.6–3.0 x ULN	3.1–5.0 x ULN	>5.0 x ULN
Pancreatic amylase	1.1–1.5 x ULN	1.6–2.0 x ULN	2.1–5.0 x ULN	>5.0 x ULN

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

[a] 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 and potentially life-threatening
Clinical				
Diarrhoea ≥1 year of age	Transient or intermittent episodes of unformed stools OR increase of ≤3 stools over baseline per day	Persistent episodes of unformed to watery stools OR increase of 4–6 stools over baseline per day	Grossly bloody diarrhoea OR increase of ≥7 stools per day OR intravenous fluid replacement indicated	Life-threatening consequences (e.g. hypotensive shock)
<1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR hypotensive shock
Nausea	Transient (<24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24–48 hours	Persistent nausea resulting in minimal oral intake for >48 hours OR aggressive rehydration indicated (e.g. intravenous fluids)	Persistent nausea with no or minimal oral intake resulting in dehydration with aggressive rehydration indicated
Pancreatitis	Not applicable	Symptomatic AND hospitalization not indicated (other than emergency treatment)	Symptomatic AND hospitalization not indicated (other than emergency treatment)	Life-threatening consequences (e.g. circulatory failure, haemorrhage, sepsis)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR aggressive rehydration indicated (e.g. intravenous fluids)	Life-threatening consequences (e.g. hypotensive shock)

Allergic/dermatological				
Acute systemic allergic reaction	Localized urticaria (weals) lasting a few hours	Localized urticaria with medical intervention indicated OR mild angio-oedema	Generalized urticaria OR angio-oedema with medical intervention indicated OR symptomatic mild bronchospasm	Acute anaphylaxis OR life-threatening bronchospasm or laryngeal oedema
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR ulceration of mucous membrane involving two or more distinct mucosal sites OR toxic epidermal necrolysis (TEN)

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

[a] 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 and potentially life-threatening
Neurological				
Alteration in personality, behaviour or mood[b]	Alteration causing no or minimal interference with usual social and functional activities[b]	Alteration causing greater than minimal interference with usual social and functional activities[b]	Alteration causing inability to perform usual social and functional activities [b] AND intervention indicated	Behaviour potentially harmful to self or others OR life-threatening consequences
Altered mental status	Changes causing no or minimal interference with usual social and functional activities[b]	Mild lethargy or somnolence causing greater than minimal interference with usual social and functional activities[b]	Onset of confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social and functional activities[b]	Onset of delirium, obtundation or coma
Neuromuscular weakness (including myopathy and neuropathy)	Asymptomatic with decreased strength on examination OR minimal muscle weakness causing no or minimal interference with usual social and functional activities[b]	Muscle weakness causing greater than minimal interference with usual social and functional activities[b]	Muscle weakness causing inability to perform usual social and functional activities[b]	Disabling muscle weakness causing inability to perform basic self-care functions OR respiratory muscle weakness impairing ventilation
Neurosensory alteration (including painful neuropathy)	Asymptomatic with sensory alteration on examination OR minimal paraesthesia causing no or minimal interference with usual social and functional activities	Sensory alteration or paraesthesia causing greater than minimal interference with usual social and functional activities	Sensory alteration or paraesthesia causing inability to perform usual social and functional activities	Disabling sensory alteration or paraesthesia causing inability to perform basic self-care functions[c]

Other laboratory parameters ***Standard international units are listed in italics***				
Cholesterol (fasting, paediatric <18 years old)	170–<200 mg/dl *4.40–5.15 mmol/l*	200–300 mg/dl *5.16–7.77 mmol/l*	>300 mg/dl *>7.77 mmol/l*	Not applicable
Glucose, serum, high: non-fasting	116–<161 mg/dl *6.44–<8.89 mmol/l*	161–<251 mg/dl *8.89–<13.89 mmol/l*	251–500 mg/dl *13.89–27.75 mmol/l*	>500 mg/dl *>27.75 mmol/l*
Glucose, serum, high: fasting	110–<126 mg/dl *6.11–<6.95 mmol/l*	126–<251 mg/dl *6.95–<13.89 mmol/l*	251–500 mg/dl *13.89–27.75 mmol/l*	>500 mg/dl *>27.75 mmol/l*
Lactate	<2.0 x ULN without acidosis	≥2.0 x ULN without acidosis	Increased lactate with pH <7.3 without life-threatening consequences or related condition present	Increased lactate with pH <7.3 with life-threatening consequences (e.g. neurological findings, coma) or related condition present
Triglycerides (fasting)	Not applicable	500–<751 mg/dl *5.65–<8.49 mmol/l*	751–1200 mg/dl *8.49–13.56 mmol/l*	>1200 mg/dl *>13.56 mmol/l*

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

ANNEX H: SEXUAL MATURITY RATING (TANNER STAGING) IN ADOLESCENTS

Stage	Female				Male				
	Age range (years)	Breast growth	Pubic hair growth	Other changes	Age range (years)	Testes growth	Penis growth	Pubic hair growth	Other changes
I	0–15	Pre-adolescent	None	Pre-adolescent	0–15	Pre-adolescent testes (≤2.5 cm)	Pre-adolescent	None	Pre-adolescent
II	8–15	Breast budding (thelarche); areolar hyperplasia with small amount of breast tissue	Long downy pubic hair near the labia, often appearing with breast budding or several weeks or months later	Peak growth velocity often occurs soon after stage II	10–15	Enlargement of testes; pigmentation of scrotal sac	Minimal or no enlargement	Long downy hair, often appearing several months after testicular growth; variable pattern noted with pubarche	Not applicable
III	10–15	Further enlargement of breast tissue and areola, with no separation of their contours	Increase in amount and pigmentation of hair	Menarche occurs in 2% of girls late in stage III	10.5–16.5	Further enlargement	Significant enlargement, especially in diameter	Increase in amount; curling	Not applicable

IV	10–17	Separation of contours; areola and nipple form secondary mound above breast tissue	Adult in type but not in distribution	Menarche occurs in most girls in stage IV, 1–3 years after thelarche	Variable: 12–17	Further enlargement	Further enlargement, especially in diameter	Adult in type but not in distribution	Development of axillary hair and some facial hair
V	12.5–18	Large breast with single contour	Adult in distribution	Menarche occurs in 10% of girls in stage V.	13–18	Adult in size	Adult in size	Adult in distribution (medial aspects of thighs; linea alba)	Body hair continues to grow and muscles continue to increase in size for several months to years; 20% of boys reach peak growth velocity during this period

Source: Adapted from reference (121).

ANNEX I: RECOMMENDED TIERED LABORATORY CAPABILITIES FOR ART MONITORING IN RESOURCE-LIMITED SETTINGS

Diagnosis and 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 coinfections 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 cerebrospinal 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]		–	–	+

✓ Essential test.

\+ Desirable but non-essential test.

– Non-essential test.

[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 aged under 18 months; can be performed using dried blood spots (DBSs).

[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 not currently recommended for decision-making on initiation or regular monitoring of ART in resource-limited settings. Tests for HIV-RNA viral load can also be used to diagnose HIV infection (17).

References

1. *WHO/UNAIDS, 2006.*

2. *Brahmbhatt H, Kigozi G, Wabwire-Mangen F, Serwadda D, Lutalo T, Nalugoda F, et al. Mortality in HIV-Infected and Uninfected Children of HIV-Infected and Uninfected Mothers in Rural Uganda. J Acquir Immune Defic Syndr. 2006 Apr 1;41(4):504-8.*

3. *Newell ML, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P, Dabis F. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. Lancet. 2004 Oct 2;364(9441):1236-43.*

4. *WHO. Scaling up ART in resource-limited settings: treatment guidelines for a public health approach; 2003 revision. Geneva, Switzerland; 2004.*

5. *WHO. Interim WHO clinical staging of HIV/AIDS and HIV/AIDS case definitions for surveillance. African Region. Geneva, Switzerland: World Health Orgnization; 2005. Report No: WHO/HIV/2005.02.*

6. *The British HIV Association (BHIVA) treatment guidelines for 2005; 2005.*

7. *Briss PA, Zaza S, Pappaioanou M, Fielding J, Wright-De Aguero L, Truman BI, et al. Developing an evidence-based Guide to Community Preventive Services-methods. The Task Force on Community Preventive Services. Am J Prev Med. 2000 Jan;18(1 Suppl):35-43.*

8. *Chantry CJ, Cooper ER, Pelton SI, Zorilla C, Hillyer GV, Diaz C. Seroreversion in human immunodeficiency virus-exposed but uninfected infants. Pediatr Infect Dis J. 1995 May;14(5):382-7.*

9. *Fischer A, Lejczak C, Lambert C, Servais J, Makombe N, Rusine J, et al. Simple DNA extraction method for dried blood spots and comparison of two PCR assays for diagnosis of vertical human immunodeficiency virus type 1 transmission in Rwanda. J Clin Microbiol. 2004 Jan;42(1):16-20.*

10. *Nesheim S, Palumbo P, Sullivan K, Lee F, Vink P, Abrams E, et al. Quantitative RNA testing for diagnosis of HIV-infected infants. J Acquir Immune Defic Syndr. 2003 Feb 1;32(2):192-5.*

11. *Rouet F, Sakarovitch C, Msellati P, Elenga N, Montcho C, Viho I, et al. Pediatric viral human immunodeficiency virus type 1 RNA levels, timing of infection, and disease progression in African HIV-1-infected children. Pediatrics. 2003 Oct;112(4):e289.*

12. *Pineau F, Ngoubou S, Burgard M, ran-Minh T, Franco-Montoya ML, Rouzioux C, et al. Reliable diagnosis of neonatal HIV-1 infection by Real Time PCR in Congo. 11th Conference on Retroviruses and Opportunistic Infections; 2004; San Francisco, USA; 2004.*

13. *Rouzioux C, Ekouevi D, Burgard M, Chaix M, Dabis F. Is early diagnosis of HIV infection feasible in resource-limited settings? . 12th Conference on Retroviruses and Opportunistic Infections; 2005; Boston, USA; 2005.*

14. *Schupbach J, Boni J, Bisset LR, Tomasik Z, Fischer M, Gunthard HF, et al. HIV-1 p24 antigen is a significant inverse correlate of CD4 T-cell change in patients with suppressed viremia under long-term antiretroviral therapy. J Acquir Immune Defic Syndr. 2003 Jul 1;33(3):292-9.*

15. *Sherman GG, Stevens G, Stevens WS. Affordable diagnosis of human immunodeficiency virus infection in infants by p24 antigen detection. Pediatr Infect Dis J. 2004 Feb;23(2):173-6.*

16. *Zijenah LS, Tobaiwa O, Rusakaniko S, Nathoo KJ, Nhembe M, Matibe P, et al. Signal-boosted qualitative ultrasensitive p24 antigen assay for diagnosis of subtype C HIV-1 infection in infants under the age of 2 years. J Acquir Immune Defic Syndr. 2005 Aug 1;39(4):391-4.*

17. *Rouet F, Ekouevi DK, Chaix ML, Burgard M, Inwoley A, Tony TD, et al. Transfer and evaluation of an automated, low-cost real-time reverse transcription-PCR test for diagnosis and monitoring of human immunodeficiency virus type 1 infection in a West African resource-limited setting. J Clin Microbiol. 2005 Jun;43(6):2709-17.*

18. *Crowe S, Turnbull S, Oelrichs R, Dunne A. Monitoring of human immunodeficiency virus infection in resource-constrained countries. Clin Infect Dis. 2003 Jul 1;37(Suppl 1):S25-35.*

19. *Sherman GG, Stevens G, Jones SA, Horsfield P, Stevens WS. Dried blood spots improve access to HIV diagnosis and care for infants in low-resource settings. J Acquir Immune Defic Syndr. 2005 Apr 15;38(5):615-7.*

20. *Damond F, Descamps D, Farfara I, Telles JN, Puyeo S, Campa P, et al. Quantification of proviral load of human immunodeficiency virus type 2 subtypes A and B using real-time PCR. J Clin Microbiol. 2001 Dec;39(12):4264-8.*

21. *Desire N, Dehee A, Schneider V, Jacomet C, Goujon C, Girard PM, et al. Quantification of human immunodeficiency virus type 1 proviral load by a TaqMan real-time PCR assay. J Clin Microbiol. 2001 Apr;39(4):1303-10.*

22. *Gibellini D, Vitone F, Gori E, La Placa M, Re MC. Quantitative detection of human immunodeficiency virus type 1 (HIV-1) viral load by SYBR green real-time RT-PCR technique in HIV-1 seropositive patients. J Virol Methods. 2004 Feb;115(2):183-9.*

23. *Gueudin M, Plantier JC, Damond F, Roques P, Mauclere P, Simon F. Plasma viral RNA assay in HIV-1 group O infection by real-time PCR. J Virol Methods. 2003 Oct;113(1):43-9.*

24. *Rouet F, Elenga N, Msellati P, Montcho C, Viho I, Sakarovitch C, et al. Primary HIV-1 infection in African children infected through breastfeeding. AIDS. 2002 Nov 22;16(17):2303-9.*

25. *Schutten M, van den Hoogen B, van der Ende ME, Gruters RA, Osterhaus AD, Niesters HG. Development of a real-time quantitative RT-PCR for the detection of HIV-2 RNA in plasma. J Virol Methods. 2000 Jul;88(1):81-7.*

26. *Patton JC, Sherman GG, Coovadia AH, Stevens WS, Meyers TM. The Ultrasensitive HIV-1 p24 Antigen assay modified for use in dried whole blood spots as a reliable, affordable test for infant diagnosis. Clinical and Diagnostic Laboratory Immunology. 2006; Clinical and Vaccine Immunology. 2006 Jan; p152-155*

27. *Sherman GG, Matsebula TC, Jones SA. Is early HIV testing of infants in poorly resourced prevention of mother to child transmission programmes unaffordable? Trop Med Int Health. 2005 Nov;10(11):1108-13.*

28. *Biggar RJ, Miley W, Miotti P, Taha TE, Butcher A, Spadoro J, et al. Blood collection on filter paper: a practical approach to sample collection for studies of perinatal HIV transmission. J Acquir Immune Defic Syndr Hum Retrovirol. 1997 Apr 1;14(4):368-73.*

29. *Comeau AM, Pitt J, Hillyer GV, Landesman S, Bremer J, Chang BH, et al. Early detection of human immunodeficiency virus on dried blood spot specimens: sensitivity across serial specimens. Women and Infants Transmission Study Group. J Pediatr. 1996 Jul;129(1):111-8.*

30. *Sherman GG, Cooper PA, Coovadia AH, Puren AJ, Jones SA, Mokhachane M, et al. Polymerase chain reaction for diagnosis of human immunodeficiency virus infection in infancy in low resource settings. Pediatr Infect Dis J. 2005 Nov;24(11):993-7.*

31. *Moodley D, Bobat RA, Coutsoudis A, Coovadia HM. Predicting perinatal human immunodeficiency virus infection by antibody patterns. Pediatr Infect Dis J. 1995 Oct;14(10):850-2.*

32. *Sherman GG, Jones SA. Oral fluid human immunodeficiency virus tests: improved access to diagnosis for infants in poorly resourced prevention of mother to child transmission programs. Pediatr Infect Dis J. 2005 Mar;24(3):253-6.*

33. *Moodley D, Moodley P, Moodley J, Coovadia H, Esterhuizen T. Use of rapid tests for perinatal HIV infection in resource-limited settings. Journal of Pediatric Infectious Diseases. 2006;1(2).*

34. *Shapiro RL, Holland DT, Capparelli E, Lockman S, Thior I, Wester C, et al. Antiretroviral concentrations in breast-feeding infants of women in Botswana receiving antiretroviral treatment. J Infect Dis. 2005 Sep 1;192(5):720-7.*

35. *WHO. Guidelines for Using HIV Testing Technologies in Surveillance: Selection, Evaluation, and Implementation. 2001(WHO7CDS/CSR/EDC/2001.16).*

36. *UNAIDS/WHO. Revised recommendations for the selection and use of HIV antibody tests. Wkly Epidemiol Rec. 1997 Mar 21;72(12):81-7.*

37. *Horwood C, Liebeschuetz S, Blaauw D, Cassol S, Qazi S. Diagnosis of paediatric HIV infection in a primary health care setting with a clinical algorithm. Bull World Health Organ. 2003;81(12):858-66.*

38. *Jones SA, Sherman GG, Coovadia AH. Can clinical algorithms deliver an accurate diagnosis of HIV infection in infancy? Bull World Health Organ. 2005 Jul;83(7):559-60.*

39. *Fassinou P, Elenga N, Rouet F, Laguide R, Kouakoussui KA, Timite M, et al. Highly active antiretroviral therapies among HIV-1-infected children in Abidjan, Cote d'Ivoire. AIDS. 2004 Sep 24;18(14):1905-13.*

40. *Dabis F, Elenga N, Meda N, Leroy V, Viho I, Manigart O, et al. 18-Month mortality and perinatal exposure to zidovudine in West Africa. AIDS. 2001 Apr 13;15(6):771-9.*

41. *Chintu C, Bhat GJ, Walker AS, Mulenga V, Sinyinza F, Lishimpi K, et al. Co-trimoxazole as prophylaxis against opportunistic infections in HIV-infected Zambian children (CHAP): a double-blind randomised placebo-controlled trial. Lancet. 2004 Nov 20-26;364(9448):1865-71.*

42. *Wade AM, Ades AE. Age-related reference ranges: significance tests for models and confidence intervals for centiles. Stat Med. 1994 Nov 30;13(22):2359-67.*

43. *Shearer WT, Rosenblatt HM, Gelman RS, Oyomopito R, Plaeger S, Stiehm ER, et al. Lymphocyte subsets in healthy children from birth through 18 years of age: the Pediatric AIDS Clinical Trials Group P1009 study. J Allergy Clin Immunol. 2003 Nov;112(5):973-80.*

44. *Embree J, Bwayo J, Nagelkerke N, Njenga S, Nyange P, Ndinya-Achola J, et al. Lymphocyte subsets in human immunodeficiency virus type 1-infected and uninfected children in Nairobi. Pediatr Infect Dis J. 2001 Apr;20(4):397-403.*

45. *Dunn D. Short-term risk of disease progression in HIV-1-infected children receiving no antiretroviral therapy or zidovudine monotherapy: a meta-analysis. Lancet. 2003 Nov 15;362(9396):1605-11.*

46. *Mofenson LM, Harris DR, Moye J, Bethel J, Korelitz J, Read JS, et al. Alternatives to HIV-1 RNA concentration and CD4 count to predict mortality in HIV-1-infected children in resource-poor settings. Lancet. 2003 Nov 15;362(9396):1625-7.*

47. *HIV Paediatric Prognostic Markers Collaborative Study. Use of total lymphocyte count for informing when to start antiretroviral therapy in HIV-infected children: a meta-analysis of longitudinal data. Lancet. 2005 Nov 26;366(9500):1868-74.*

48. *Chokephaibulkit K, Plipat N, Cressey TR, Frederix K, Phongsamart W, Capparelli E, et al. Pharmacokinetics of nevirapine in HIV-infected children receiving an adult fixed-dose combination of stavudine, lamivudine and nevirapine. AIDS. 2005 Sep 23;19(14):1495-9.*

49. *Barlow-Mosha L, Musoke P, Ajuna P, Luttajumwa M, Walabyeki J, Owor M, et al. Early effectiveness of Triomune in HIV-infected Ugandan children, Abstract WeOa0103. Third International AIDS Society Conference on HIV Pathogenesis and Treatment; 2005; Rio de Janeiro, Brazil; 2005.*

50. *Corbett A Hosseinipour M, Nyirenda J et al. Pharmacokinetics between Trade and Generic Liquid and Split Tablet Formulations of Lamivudine Stavudine + Nevirapine in HIV-Infected Malawian Children. Poster H-1106 45th ICAAC Washington 2005; Abstract H-1905.*

51. *King JR, Kimberlin DW, Aldrovandi GM, Acosta EP. Antiretroviral pharmacokinetics in the paediatric population: a review. Clin Pharmacokinet. 2002;41(14):1115-33.*

52. *Eley B, Nuttall J, Davies MA, Smith L, Cowburn C, Buys H, et al. Initial experience of a public sector antiretroviral treatment programme for HIV-infected children and their infected parents. S Afr Med J. 2004 Aug;94(8):643-6.*

53. *Gortmaker SL, Hughes M, Cervia J, Brady M, Johnson GM, Seage GR, 3rd, et al. Effect of combination therapy including protease inhibitors on mortality among children and adolescents infected with HIV-1. N Engl J Med. 2001 Nov 22;345(21):1522-8.*

54. *Kline MW, Matusa RF, Copaciu L, Calles NR, Kline NE, Schwarzwald HL. Comprehensive pediatric human immunodeficiency virus care and treatment in Constanta, Romania: implementation of a program of highly active antiretroviral therapy in a resource-poor setting. Pediatr Infect Dis J. 2004 Aug;23(8):695-700.*

55. *Puthanakit T, Oberdorfer A, Akarathum N, Kanjanavanit S, Wannarit P, Sirisanthana T, et al. Efficacy of highly active antiretroviral therapy in HIV-infected children participating in Thailand's National Access to Antiretroviral Program. Clin Infect Dis. 2005 Jul 1;41(1):100-7.*

56. *Baylor M, Ayime O, Truffa M, Denson A, Johann-Liang R. Hepatotoxicity associated with nevirapine use in HIV-infected children. Abstract #776. 12th Conference on Retroviruses and Opportunistic Infections; 2005; Boston, MA, USA; 2005.*

57. *Handforth J, Sharland M. Triple nucleoside reverse transcriptase inhibitor therapy in children. Paediatr Drugs. 2004;6(3):147-59.*

58. *Arribas JR. The rise and fall of triple nucleoside reverse transcriptase inhibitor (NRTI) regimens. J Antimicrob Chemother. 2004 Sep;54(3):587-92.*

59. *Gulick RM, Ribaudo HJ, Shikuma CM, Lustgarten S, Squires KE, Meyer WA, 3rd, et al. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. N Engl J Med. 2004 Apr 29;350(18):1850-61.*

60. *Staszewski S, Keiser P, Montaner J, Raffi F, Gathe J, Brotas V, et al. Abacavir-lamivudine-zidovudine vs indinavir-lamivudine-zidovudine in antiretroviral-naive HIV-infected adults: A randomized equivalence trial. Jama. 2001 Mar 7;285(9):1155-63.*

61. *Bang LM, Scott LJ. Emtricitabine: an antiretroviral agent for HIV infection. Drugs. 2003;63(22):2413-24; discussion 25-6.*

62. *European Paediatric Lipodystrophy Group. Antiretroviral therapy, fat redistribution and hyperlipidaemia in HIV-infected children in Europe. AIDS. 2004 Jul 2;18(10):1443-51.*

63. *Kline MW, Dunkle LM, Church JA, Goldsmith JC, Harris AT, Federici ME, et al. A phase I/II evaluation of stavudine (d4T) in children with human immunodeficiency virus infection. Pediatrics. 1995 Aug;96(2 Pt 1):247-52.*

64. *Kline MW, Fletcher CV, Harris AT, Evans KD, Brundage RC, Remmel RP, et al. A pilot study of combination therapy with indinavir, stavudine (d4T), and didanosine (ddI) in children infected with the human immunodeficiency virus. J Pediatr. 1998 Mar;132(3 Pt 1):543-6.*

65. *Pollard RB, Tierney C, Havlir D, Tebas P, Fox L, Smeaton L, et al. A phase II randomized study of the virologic and immunologic effect of zidovudine + stavudine versus stavudine alone and zidovudine + lamivudine in patients with >300 CD4 cells who were antiretroviral naive (ACTG 298). AIDS Res Hum Retroviruses. 2002 Jul 1;18(10):699-704.*

66. *Hoggard PG, Kewn S, Barry MG, Khoo SH, Back DJ. Effects of drugs on 2',3'-dideoxy-2',3'-didehydrothymidine phosphorylation in vitro. Antimicrob Agents Chemother. 1997 Jun;41(6):1231-6.*

67. *Paediatric European Network for Treatment of AIDS (PENTA). Comparison of dual nucleoside-analogue reverse-transcriptase inhibitor regimens with and without nelfinavir in children with HIV-1 who have not previously been treated: the PENTA 5 randomised trial. Lancet. 2002 Mar 2;359(9308):733-40.*

68. *Birkus G, Hitchcock MJ, Cihlar T. Assessment of mitochondrial toxicity in human cells treated with tenofovir: comparison with other nucleoside reverse transcriptase inhibitors. Antimicrob Agents Chemother. 2002 Mar;46(3):716-23.*

69. *Gallant JE, DeJesus E, Arribas JR, Pozniak AL, Gazzard B, Campo RE, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. N Engl J Med. 2006 Jan 19;354(3):251-60.*

70. *Karras A, Lafaurie M, Furco A, Bourgarit A, Droz D, Sereni D, et al. Tenofovir-related nephrotoxicity in human immunodeficiency virus-infected patients: three cases of renal failure, Fanconi syndrome, and nephrogenic diabetes insipidus. Clin Infect Dis. 2003 Apr 15;36(8):1070-3.*

71. *Schaaf B, Aries SP, Kramme E, Steinhoff J, Dalhoff K. Acute renal failure associated with tenofovir treatment in a patient with acquired immunodeficiency syndrome. Clin Infect Dis. 2003 Aug 1;37(3):e41-3.*

72. *Verhelst D, Monge M, Meynard JL, Fouqueray B, Mougenot B, Girard PM, et al. Fanconi syndrome and renal failure induced by tenofovir: a first case report. Am J Kidney Dis. 2002 Dec;40(6):1331-3.*

73. *Giacomet V, Mora S, Martelli L, Merlo M, Sciannamblo M, Vigano A. A 12-month treatment with tenofovir does not impair bone mineral accrual in HIV-infected children. J Acquir Immune Defic Syndr. 2005 Dec 1;40(4):448-50.*

74. *Hazra R, Gafni RI, Maldarelli F, Balis FM, Tullio AN, DeCarlo E, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy for pediatric HIV infection. Pediatrics. 2005 Dec;116(6):e846-54.*

75. *Khanlou H, Yeh V, Guyer B, Farthing C. Early virologic failure in a pilot study evaluating the efficacy of therapy containing once-daily abacavir, lamivudine, and tenofovir DF in treatment-naive HIV-infected patients. AIDS Patient Care STDS. 2005 Mar;19(3):135-40.*

76. *Jemsek J, Hutcherson P, Harper E. Poor Virologic Responses and Early Emergence of Resistance in Treatment Naive HIV-infected patients receiving a once daily triple nuceloeside regimen of Didanosine, Lamivudine and Tenofovir DF. 2004.*

77. *Maitland D, Moyle G, Hand J, Mandalia S, Boffito M, Nelson M, et al. Early virologic failure in HIV-1 infected subjects on didanosine/tenofovir/efavirenz: 12-week results from a randomized trial. AIDS. 2005 Jul 22;19(11):1183-8.*

78. *Leon A, Martinez E, Mallolas J, Laguno M, Blanco JL, Pumarola T, et al. Early virological failure in treatment-naive HIV-infected adults receiving didanosine and tenofovir plus efavirenz or nevirapine. AIDS. 2005 Jan 28;19(2):213-5.*

79. *Podzamczer D, Ferrer E, Gatell JM, Niubo J, Dalmau D, Leon A, et al. Early virological failure with a combination of tenofovir, didanosine and efavirenz. Antivir Ther. 2005;10(1):171-7.*

80. *Torti C, Quiros-Roldon E, Regazzi M, Antinori A, Patroni A, Villani P, et al. Early virological failure after tenofovir + didanosine + efavirenz combination in HIV-positive patients upon starting antiretroviral therapy. Antivir Ther. 2005;10(4):505-13.*

81. *Ena J, Amador C, Benito C, Fenoll V, Pasquau F. Risk and determinants of developing severe liver toxicity during therapy with nevirapine-and efavirenz-containing regimens in HIV-infected patients. Int J STD AIDS. 2003 Nov;14(11):776-81.*

82. *Keiser P, Nassar N, White C, Koen G, Moreno S. Comparison of nevirapine- and efavirenz-containing antiretroviral regimens in antiretroviral-naive patients: a cohort study. HIV Clin Trials. 2002 Jul-Aug;3(4):296-303.*

83. *Keiser P, Nassar N, Yazdani B, Armas L, Moreno S. Comparison of efficacy of efavirenz and nevirapine: lessons learned for cohort analysis in light of the 2NN Study. HIV Clin Trials. 2003 Sep-Oct;4(5):358-60.*

84. *Law WP, Dore GJ, Duncombe CJ, Mahanontharit A, Boyd MA, Ruxrungtham K, et al. Risk of severe hepatotoxicity associated with antiretroviral therapy in the HIV-NAT Cohort, Thailand, 1996-2001. AIDS. 2003 Oct 17;17(15):2191-9.*

85. *Martin-Carbonero L, Nunez M, Gonzalez-Lahoz J, Soriano V. Incidence of liver injury after beginning antiretroviral therapy with efavirenz or nevirapine. HIV Clin Trials. 2003 Mar-Apr;4(2):115-20.*

86. *Moyle GJ. NNRTI choice: has 2NN changed our practice? AIDS Read. 2003 Jul;13(7):325-8.*

87. *van Leth F, Phanuphak P, Ruxrungtham K, Baraldi E, Miller S, Gazzard B, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. Lancet. 2004 Apr 17;363(9417):1253-63.*

88. *Teglas JP, Quartier P, Treluyer JM, Burgard M, Gregoire V, Blanche S. Tolerance of efavirenz in children. AIDS. 2001 Jan 26;15(2):241-3.*

89. *Eshleman SH, Mracna M, Guay LA, Deseyve M, Cunningham S, Mirochnick M, et al. Selection and fading of resistance mutations in women and infants receiving nevirapine to prevent HIV-1 vertical transmission (HIVNET 012). AIDS. 2001 Oct 19;15(15):1951-7.*

90. *Mandelbrot L, Landreau-Mascaro A, Rekacewicz C, Berrebi A, Benifla JL, Burgard M, et al. Lamivudine-zidovudine combination for prevention of maternal-infant transmission of HIV-1. Jama. 2001 Apr 25;285(16):2083-93.*

91. *McComsey GA, Leonard E. Metabolic complications of HIV therapy in children. AIDS. 2004 Sep 3;18(13):1753-68.*

92. *Sharland M, Blanche S, Castelli G, Ramos J, Gibb DM. PENTA guidelines for the use of antiretroviral therapy, 2004. HIV Med. 2004 Jul;5 Suppl 2:61-86.*

93. *Haas DW. Pharmacogenomics and HIV therapeutics. J Infect Dis. 2005 May 1;191(9):1397-400.*

94. *Verweel G, van Rossum AM, Hartwig NG, Wolfs TF, Scherpbier HJ, de Groot R. Treatment with highly active antiretroviral therapy in human immunodeficiency virus type 1-infected children is associated with a sustained effect on growth. Pediatrics. 2002 Feb;109(2):E25.*

95. *Lindsey JC, Hughes MD, McKinney RE, Cowles MK, Englund JA, Baker CJ, et al. Treatment-mediated changes in human immunodeficiency virus (HIV) type 1 RNA and CD4 cell counts as predictors of weight growth failure, cognitive decline, and survival in HIV-infected children. J Infect Dis. 2000 Nov;182(5):1385-93.*

96. *McCoig C, Castrejon MM, Castano E, De Suman O, Baez C, Redondo W, et al. Effect of combination antiretroviral therapy on cerebrospinal fluid HIV RNA, HIV resistance, and clinical manifestations of encephalopathy. J Pediatr. 2002 Jul;141(1):36-44.*

97. *Hirsch HH, Kaufmann G, Sendi P, Battegay M. Immune reconstitution in HIV-infected patients. Clin Infect Dis. 2004 Apr 15;38(8):1159-66.*

98. *Jevtovic DJ, Salemovic D, Ranin J, Pesic I, Zerjav S, Djurkovic-Djakovic O. The prevalence and risk of immune restoration disease in HIV-infected patients treated with highly active antiretroviral therapy. HIV Med. 2005 Mar;6(2):140-3.*

99. *Shelburne SA, Visnegarwala F, Darcourt J, Graviss EA, Giordano TP, White AC, Jr., et al. Incidence and risk factors for immune reconstitution inflammatory syndrome during highly active antiretroviral therapy. AIDS. 2005 Mar 4;19(4):399-406.*

100. *Tangsinmankong N, Kamchaisatian W, Lujan-Zilbermann J, Brown CL, Sleasman JW, Emmanuel PJ. Varicella zoster as a manifestation of immune restoration disease in HIV-infected children. J Allergy Clin Immunol. 2004 Apr;113(4):742-6.*

101. *Nuttall JJ, Wilmshurst JM, Ndondo AP, Yeats J, Corcoran C, Hussey GD, et al. Progressive multifocal leukoencephalopathy after initiation of highly active antiretroviral therapy in a child with advanced human immunodeficiency virus infection: a case of immune reconstitution inflammatory syndrome. Pediatr Infect Dis J. 2004 Jul;23(7):683-5.*

102. *Puthanakit T, Oberdorfer P, Akarathum N, Wannarit P, Sirisanthana T, Sirisanthana V. Immune reconstitution syndrome after highly active antiretroviral therapy in human immunodeficiency virus-infected thai children. Pediatr Infect Dis J. 2006 Jan;25(1):53-8.*

103. *Shelburne SA, Montes M, Hamill RJ. Immune reconstitution inflammatory syndrome: more answers, more questions. J Antimicrob Chemother. 2005 Dec 14.*

104. *Mofenson LM, Korelitz J, Meyer WA, 3rd, Bethel J, Rich K, Pahwa S, et al. The relationship between serum human immunodeficiency virus type 1 (HIV-1) RNA level, CD4 lymphocyte percent, and long-term mortality risk in HIV-1-infected children. National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial Study Group. J Infect Dis. 1997 May;175(5):1029-38.*

105. *Florence E, Dreezen C, Schrooten W, Van Esbroeck M, Kestens L, Fransen K, et al. The role of non-viral load surrogate markers in HIV-positive patient monitoring during antiviral treatment. Int J STD AIDS. 2004 Aug;15(8):538-42.*

106. *Floren LC, Wiznia A, Hayashi S, Jayewardene A, Stanley K, Johnson G, et al. Nelfinavir pharmacokinetics in stable human immunodeficiency virus-positive children: Pediatric AIDS Clinical Trials Group Protocol 377. Pediatrics. 2003 Sep;112(3 Pt 1):e220-7.*

107. *Pelton SI, Stanley K, Yogev R, Fletcher CV, McIntosh K, Wiznia A, et al. Switch from ritonavir to indinavir in combination therapy for HIV-1-infected children. Clin Infect Dis. 2005 Apr 15;40(8):1181-7.*

108. *Saez-Llorens X, Violari A, Deetz CO, Rode RA, Gomez P, Handelsman E, et al. Forty-eight-week evaluation of lopinavir/ritonavir, a new protease inhibitor, in human immunodeficiency virus-infected children. Pediatr Infect Dis J. 2003 Mar;22(3):216-24.*

109. *Walmsley S, Bernstein B, King M, Arribas J, Beall G, Ruane P, et al. Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. N Engl J Med. 2002 Jun 27;346(26):2039-46.*

110. *Grub S, Delora P, Ludin E, Duff F, Fletcher CV, Brundage RC, et al. Pharmacokinetics*

and pharmacodynamics of saquinavir in pediatric patients with human immunodeficiency virus infection. Clin Pharmacol Ther. 2002 Mar;71(3):122-30.

111. Kline MW, Brundage RC, Fletcher CV, Schwarzwald H, Calles NR, Buss NE, et al. Combination therapy with saquinavir soft gelatin capsules in children with human immunodeficiency virus infection. Pediatr Infect Dis J. 2001 Jul;20(7):666-71.

112. Hoffmann F, Notheis G, Wintergerst U, Eberle J, Gurtler L, Belohradsky BH. Comparison of ritonavir plus saquinavir- and nelfinavir plus saquinavir-containing regimens as salvage therapy in children with human immunodeficiency type 1 infection. Pediatr Infect Dis J. 2000 Jan;19(1):47-51.

113. King JR, Nachman S, Yogev R, Hodge J, Aldrovandi G, Hughes MD, et al. Efficacy, tolerability and pharmacokinetics of two nelfinavir-based regimens in Human Immunodeficiency Virus-infected children and adolescents: Pediatric AIDS Clinical Trials Group Protocol 403. Pediatr Infect Dis J. 2005 Oct;24(10):880-5.

114. Aboulker JP, Babiker A, Chaix ML, Compagnucci A, Darbyshire J, Debre M, et al. Highly active antiretroviral therapy started in infants under 3 months of age: 72-week follow-up for CD4 cell count, viral load and drug resistance outcome. AIDS. 2004 Jan 23;18(2):237-45.

115. Litalien C, Faye A, Compagnucci A, Giaquinto C, Harper L, Gibb DM, et al. Pharmacokinetics of nelfinavir and its active metabolite, hydroxy-tert-butylamide, in infants perinatally infected with human immunodeficiency virus type 1. Pediatr Infect Dis J. 2003 Jan;22(1):48-55.

116. Johnson M, Nieto-Cisneros L, Horban A, Arasteh K, Gonzalez-Garcia J, Artigas JG, et al. Comparison of gastrointestinal tolerability and patient preference for treatment with the 625 mg and 250 mg nelfinavir tablet formulations. HIV Med. 2005 Mar;6(2):107-13.

117. Ananworanich J, Kosalaraksa P, Hill A, Siangphoe U, Bergshoeff A, Pancharoen C, et al. Pharmacokinetics and 24-week efficacy/safety of dual boosted saquinavir/lopinavir/ritonavir in nucleoside-pretreated children. Pediatr Infect Dis J. 2005 Oct;24(10):874-9.

118. Smith GH, Boulassel MR, Klien M, Gilmore N, MacLeod J, LeBlanc R, et al. Virologic and immunologic response to a boosted double-protease inhibitor-based therapy in highly pretreated HIV-1-infected patients. HIV Clin Trials. 2005 Mar-Apr;6(2):63-72.

119. Kovacs A, Montepiedra G, Carey V, Pahwa S, Weinberg A, Frenkel L, et al. Immune reconstitution after receipt of highly active antiretroviral therapy in children with advanced or progressive HIV disease and complete or partial viral load response. J Infect Dis. 2005 Jul 15;192(2):296-302.

120. Campbell TB, Shulman NS, Johnson SC, Zolopa AR, Young RK, Bushman L, et al. Antiviral activity of lamivudine in salvage therapy for multidrug-resistant HIV-1 infection. Clin Infect Dis. 2005 Jul 15;41(2):236-42.

121. Chintu C, Mwaba P. Tuberculosis in children with human immunodeficiency virus infection. Int J Tuberc Lung Dis. 2005 May;9(5):477-84.

122. Geoghagen M, Farr JA, Hambleton I, Pierre R, Christie CD. Tuberculosis and HIV co-infections in Jamaican children. West Indian Med J. 2004 Oct;53(5):339-45.

123. Lawn SD, Bekker LG, Middelkoop K, Myer L, Wood R. Impact of HIV infection on the epidemiology of tuberculosis in a peri-urban community in South Africa: the need for age-specific interventions. Clin Infect Dis. 2006 Apr 1;42(7):1040-7.

124. Ispas D, Stavri D, Ionescu S, Geafar SL, Zahir S, Paun L. Evidence for tuberculous infection in Romanian HIV-positive children by enzyme-linked immunosorbent assay. Pediatr AIDS HIV Infect. 1996 Apr;7(2):98-102.

125. *Jeena PM, Pillay P, Pillay T, Coovadia HM. Impact of HIV-1 co-infection on presentation and hospital-related mortality in children with culture proven pulmonary tuberculosis in Durban, South Africa. Int J Tuberc Lung Dis. 2002 Aug;6(8):672-8.*

126. *Palme IB, Gudetta B, Degefu H, Bruchfeld J, Muhe L, Giesecke J. Risk factors for human immunodeficiency virus infection in Ethiopian children with tuberculosis. Pediatr Infect Dis J. 2001 Nov;20(11):1066-72.*

127. *Ramirez-Cardich ME, Kawai V, Oberhelman RA, Bautista CT, Castillo ME, Gilman RH. Clinical correlates of tuberculosis co-infection in HIV-infected children hospitalized in Peru. Int J Infect Dis. 2006 Mar 13.*

128. *Zar H, Cotton M, Lombard C, Karpakis J, Strauss S, Hussey G, et al. Early and unexpected benefit of isoniazid in reducing mortality in HIV-infected children in an area of high tuberculosis prevalence; Abstract #: LbOrB12. The XV International AIDS Conference, 2004 Bangkok, Thailand.*

129. *Grimwade K, Swingler GH. Cotrimoxazole prophylaxis for opportunistic infections in children with HIV infection. Cochrane Database Syst Rev. 2006(1):CD003508.*

130. *Grimwade K, Sturm AW, Nunn AJ, Mbatha D, Zungu D, Gilks CF. Effectiveness of cotrimoxazole prophylaxis on mortality in adults with tuberculosis in rural South Africa. Aids. 2005 Jan 28;19(2):163-8.*

131. *Kwara A, Flanigan TP, Carter EJ. Highly active antiretroviral therapy (HAART) in adults with tuberculosis: current status. Int J Tuberc Lung Dis. 2005 Mar;9(3):248-57.*

132. *Patel A, Patel K, Patel J, Shah N, Patel B, Rani S. Safety and antiretroviral effectiveness of concomitant use of rifampicin and efavirenz for antiretroviral-naive patients in India who are coinfected with tuberculosis and HIV-1. J Acquir Immune Defic Syndr. 2004 Sep 1;37(1):1166-9.*

133. *Finch CK, Chrisman CR, Baciewicz AM, Self TH. Rifampin and rifabutin drug interactions: an update. Arch Intern Med. 2002 May 13;162(9):985-92.*

134. *Van Cutsem G, Cohen K, Bedelu M, Sarunchuk P, Hilderbrand K, Coetzee D, et al. TB/HIV coinfected patients on rifampicin-containing treatment have equivalent ART treatment outcomes and concurrent use of nevirapine is not associated with increased hepatotoxicity, Abstract WePp0303 Third International AIDS Conference on HIV Pathogenesis and Treatment; 2005; Rio de Janeiro, Brazil; 2005.*

135. *Jarvis B, Faulds D. Nelfinavir. A review of its therapeutic efficacy in HIV infection. Drugs. 1998 Jul;56(1):147-67.*

136. *Niemi M, Backman JT, Fromm MF, Neuvonen PJ, Kivisto KT. Pharmacokinetic interactions with rifampicin: clinical relevance. Clin Pharmacokinet. 2003;42(9):819-50.*

137. *Carey VJ, Yong FH, Frenkel LM, McKinney RE, Jr. Pediatric AIDS prognosis using somatic growth velocity. AIDS. 1998 Jul 30;12(11):1361-9.*

138. *Johann-Liang R, O'Neill L, Cervia J, Haller I, Giunta Y, Licholai T, et al. Energy balance, viral burden, insulin-like growth factor-1, interleukin-6 and growth impairment in children infected with human immunodeficiency virus. AIDS. 2000 Apr 14;14(6):683-90.*

139. *Arpadi SM, Cuff PA, Kotler DP, Wang J, Bamji M, Lange M, et al. Growth velocity, fat-free mass and energy intake are inversely related to viral load in HIV-infected children. J Nutr. 2000 Oct;130(10):2498-502.*

140. *Miller TL, Easley KA, Zhang W, Orav EJ, Bier DM, Luder E, et al. Maternal and infant factors associated with failure to thrive in children with vertically transmitted human immunodeficiency virus-1 infection: the prospective, P2C2 human immunodeficiency virus multicenter study. Pediatrics. 2001 Dec;108(6):1287-96.*

141. *Rabkin M, El-Sadr W, Abrams E. Care and Treatment of HIV/AIDS in resource-limited settings: The Columbia Clinical Manual New York, USA; 2005.*

142. *WHO. HIV and infant feeding: A guide for health-care managers and supervisors. Geneva, Switzerland; 2003.*

143. WHO. HIV and infant feeding: Guidelines for decision-makers. Geneva, Switzerland; 2003.

144. WHO. Vitamin A supplements: a guide to their use in the treatment and prevention of vitamin A deficiency and xerophthalmia. Second edition. Geneva, Switzerland; 1997.

145. Ashworth A, Khanum S, Jackson A, Schofield C. Guidelines for the inpatient treatment of severely malnourished children. Geneva, Switzerland; 2003.

146. WHO. Management of a child with a serious infection or malnutrition: Guidelines for the care at the first-referral level in developing countries. Geneva, Switzerland: World Health Organization; 2000.

147. WHO. Management of serious malnutrition: A manual for physicians and other senior health workers. Geneva, Switzerland: World Health Organization; 1998.

148. WHO. Nutrient requirements for people living with HIV/AIDS. Report of a technical consultation. World Health Organization, Geneva, 13-15 May 2003. Geneva, Switzerland; 2003.

149. Fawzi W, Msamanga G, Spiegelman D, Hunter DJ. Studies of vitamins and minerals and HIV transmission and disease progression. J Nutr. 2005 Apr;135(4):938-44.

150. Irlam J, Visser M, Rollins N, Siegfried N. Micronutrient supplementation in children and adults with HIV infection. The Cochrane Database of Systematic Reviews 2006(Issue 1).

151. Miller TL. Nutritional aspects of HIV-infected children receiving highly active antiretroviral therapy. AIDS. 2003 Apr;17 Suppl 1:S130-40.

152. Coutsoudis A, Bobat RA, Coovadia HM, Kuhn L, Tsai WY, Stein ZA. The effects of vitamin A supplementation on the morbidity of children born to HIV-infected women. Am J Public Health. 1995 Aug;85(8 Pt 1):1076-81.

153. Fawzi WW, Mbise RL, Hertzmark E, Fataki MR, Herrera MG, Ndossi G, et al. A randomized trial of vitamin A supplements in relation to mortality among human immunodeficiency virus-infected and uninfected children in Tanzania. Pediatr Infect Dis J. 1999 Feb;18(2):127-33.

154. de Martino M, Tovo PA, Galli L, Gabiano C, Chiarelli F, Zappa M, et al. Puberty in perinatal HIV-1 infection: a multicentre longitudinal study of 212 children. AIDS. 2001 Aug 17;15(12):1527-34.

155. Badri M, Wood R. Usefulness of total lymphocyte count in monitoring highly active antiretroviral therapy in resource-limited settings. AIDS. 2003 Mar 7;17(4):541-5.

156. van der Ryst E, Kotze M, Joubert G, Steyn M, Pieters H, van der Westhuizen M, et al. Correlation among total lymphocyte count, absolute CD4+ count, and CD4+ percentage in a group of HIV-1-infected South African patients. J Acquir Immune Defic Syndr Hum Retrovirol. 1998 Nov 1;19(3):238-44.

157. Brettle RP. Correlation between total and CD4 lymphocyte counts in HIV infection. Int J STD AIDS. 1997 Sep;8(9):597.

158. Van Dyke RB, Lee S, Johnson GM, Wiznia A, Mohan K, Stanley K, et al. Reported adherence as a determinant of response to highly active antiretroviral therapy in children who have human immunodeficiency virus infection. Pediatrics. 2002 Apr;109(4):e61.

159. Farley J, Hines S, Musk A, Ferrus S, Tepper V. Assessment of adherence to antiviral therapy in HIV-infected children using the Medication Event Monitoring System, pharmacy refill, provider assessment, caregiver self-report, and appointment keeping. J Acquir Immune Defic Syndr. 2003 Jun 1;33(2):211-8.

160. Watson DC, Farley JJ. Efficacy of and adherence to highly active antiretroviral therapy in children infected with human immunodeficiency virus type 1. Pediatr Infect Dis J. 1999 Aug;18(8):682-9.

161. Gordillo V, del Amo J, Soriano V, Gonzalez-Lahoz J. Sociodemographic and psychological variables influencing adherence to antiretroviral therapy. AIDS. 1999 Sep 10;13(13):1763-9.

162. *Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med. 2000 Jul 4;133(1):21-30.*

163. *Gibb DM, Goodall RL, Giacomet V, McGee L, Compagnucci A, Lyall H. Adherence to prescribed antiretroviral therapy in human immunodeficiency virus-infected children in the PENTA 5 trial. Pediatr Infect Dis J. 2003 Jan;22(1):56-62.*

164. *Dolezal C, Mellins C, Brackis-Cott E, Abrams EJ. The reliability of reports of medical adherence from children with HIV and their adult caregivers. J Pediatr Psychol. 2003 Jul-Aug;28(5):355-61.*

165. *Ledergerber B, Lundgren JD, Walker AS, Sabin C, Justice A, Reiss P, et al. Predictors of trend in CD4-positive T-cell count and mortality among HIV-1-infected individuals with virological failure to all three antiretroviral-drug classes. Lancet. 2004 Jul 3-9;364(9428):51-62.*

166. *Prado JG, Parkin NT, Clotet B, Ruiz L, Martinez-Picado J. HIV type 1 fitness evolution in antiretroviral-experienced patients with sustained CD4+ T cell counts but persistent virologic failure. Clin Infect Dis. 2005 Sep 1;41(5):729-37.*

167. *Nicastri E, Chiesi A, Angeletti C, Sarmati L, Palmisano L, Geraci A, et al. Clinical outcome after 4 years follow-up of HIV-seropositive subjects with incomplete virologic or immunologic response to HAART. J Med Virol. 2005 Jun;76(2):153-60.*

168. *Kaplan SS, Ferrari G, Wrin T, Hellmann NS, Tomaras GD, Gryszowka VE, et al. Longitudinal assessment of immune response and viral characteristics in HIV-infected patients with prolonged CD4(+)/viral load discordance. AIDS Res Hum Retroviruses. 2005 Jan;21(1):13-6.*

169. *Brigido L, Rodrigues R, Casseb J, Custodio RM, Fonseca LA, Sanchez M, et al. CD4+ T-cell recovery and clinical outcome in HIV-1-infected patients exposed to multiple antiretroviral regimens: partial control of viremia is associated with favorable outcome. AIDS Patient Care STDS. 2004 Apr;18(4):189-98.*

170. *Deeks SG, Hoh R, Neilands TB, Liegler T, Aweeka F, Petropoulos CJ, et al. Interruption of treatment with individual therapeutic drug classes in adults with multidrug-resistant HIV-1 infection. J Infect Dis. 2005 Nov 1;192(9):1537-44.*

171. *Tindyebwa D, Kayita J, Musoke P, Eley B, Nduati R, Coovadia H, et al. African Network for the Care of Children Affected by AIDS. Handbook on Paediatric AIDS in Africa Kampala, Uganda; 2004.*

172. *Machado DM, Fernandes SC, Succi RC, Freire WS, Pannuti CS, Gouveia AB, et al. Analysis of HIV- type 1 protease and reverse transcriptase in Brazilian children failing highly active antiretroviral therapy (HAART). Rev Inst Med Trop Sao Paulo. 2005 Jan-Feb;47(1):1-5.*

173. *Eshleman SH, Krogstad P, Jackson JB, Wang YG, Lee S, Wei LJ, et al. Analysis of human immunodeficiency virus type 1 drug resistance in children receiving nucleoside analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir (Pediatric AIDS Clinical Trials Group 377). J Infect Dis. 2001 Jun 15;183(12):1732-8.*

174. *Dunn D. Predictive value of absolute CD4 count for disease progression in untreated HIV-1-infected children. HIV Paediatric Prognostic Markers Study AIDS. submitted.*

175. *Bergshoeff A, Burger D, Verweij C, Farrelly L, Flynn J, Le Prevost M, et al. Plasma pharmacokinetics of once- versus twice-daily lamivudine and abacavir: simplification of combination treatment in HIV-1-infected children (PENTA-13). Antivir Ther. 2005;10(2):239-46.*

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