



# Antiretroviral drugs for the treatment of HIV infection in infants and children in resource-limited settings



World Health  
Organization

## Recommendations for a Public Health Approach (2005 Revision)

### Technical Reference Group

#### Brief Meeting Report

*Geneva, Switzerland  
20-21<sup>st</sup> June 2005*

WHO convened a Technical Consultation in Geneva, Switzerland, on 20-21 June 2005 to review the existing treatment guidelines for ART in children. The Technical Reference Group (TRG) was asked to assess new data and experience of scaling up paediatric ART and HIV care as well as make recommendations for revisions of the current WHO ART guidelines for children. The consultation participants also considered the need to harmonize the guidelines with that of the adult and Prevention of Mother to Child Transmission (PMTCT) ARV guidelines, and to simplify them to facilitate implementation at country level.

Simple and evidence-based guidelines ensure that the largest number of HIV-infected and exposed children requiring HIV care, including ART, can benefit from appropriate interventions. In countries which carry the highest burden from HIV disease, ART for children can and must be delivered in settings with limited capacity. ARV regimens may need to be adapted, and the existence of malnutrition and co-infections such as tuberculosis may require additional considerations.

The existing WHO guidelines 'Scaling up ART in resource-limited settings: treatment guidelines for a public health approach; 2003 revision' (considerations for the treatment of children, pages 31-42) were reviewed at the consultation.

In making its recommendations the TRG considered four overarching principles:

1. Infants and children in need of ARV treatment according to national and international guidelines should initiate treatment as soon as practicable;
2. The best evidence should inform the selection of ARV treatment regimens;
3. Programmes should be built around available resources, the availability of drugs, and a common regimen needed by the majority of children as this facilitates implementation and management;
4. Harmonization of the guidelines with the adult and PMTCT ARV guidelines is desirable.

The participants at the consultation agreed that the following considerations should guide the process of revising the current guidelines:

- Stand alone guidelines for children help programmes to understand the need to incorporate the treatment and care of infants and children into ongoing ART scale up activities;
- Guidelines should provide evidence-based recommendations but at the same time enable countries to adapt and implement the guidelines according to the prevailing local situation;
- Introducing new ARV drugs to first and second-line regimens recommended in the guidelines stimulates the production of recommended ARV formulations. However revisions to current recommendations should not disrupt the scale-up efforts already underway in countries. Continued support to national efforts in providing ART to children (and adults) will be important to ensure further expansion of coverage;
- Any revisions to the current guidelines should aim to enable all children needing treatment to receive it; reserving initiation of treatment only for those children with the most severe stage of HIV disease (i.e. HIV clinical disease stage IV) would result in many lost lives as treatment at this stage would often come too late;

- The availability of HIV testing for young children as well as immunological assays such as CD4 cell count or percentage and viral load to assist in decision-making on initiation of ART may be limited in some settings. Implications are as follows:
  - Early infant diagnosis is crucial for timely initiation of ART in infants and children. The inability to diagnose HIV infection early in children, especially through PMTCT programmes, severely limits access to treatment;
  - The use of CD4 cell percentage instead of CD4 cell counts is recommended in children under the age of 5 years. However, not all CD4 assay technology provides CD4 cell percentage; calculating CD4 percentage requires additional effort and skill;
  - Viral load testing for monitoring treatment is not currently an essential requirement for ART scale up within the current WHO guidelines for a public health approach; revised guidelines should retain this approach;
- Monitoring of side effects of ARV drugs needs to be integral part of ART;
- The recently revised WHO Staging for HIV Clinical Disease in Children was considered to be a useful tool for *a)* guiding initiation of treatment and *b)* monitoring treatment outcomes at the individual level.

The technical group emphasized that the guidelines are intended primarily to provide technical guidance at the national level. At the same time, global-level recommendations supported by evidence and experience of experts are a powerful tool to advocate for greater access to ART for infants and children, including increased availability of ARVs suitable for infants and children, reduced cost of drug formulations, and expanded access to and use of early HIV diagnosis and CD4 cell assays. The need to treat an increasing number of HIV-infected children also highlights the importance of preventing the transmission of the virus to the child in the first place. Increased demand by major international donors for the presence of paediatric ART on the national agenda will complement current efforts to increase coverage of treatment and care of HIV-infected infants and children.

The meeting concluded with the following key recommendations:

## 1. When to start treatment

### a) Clinical criteria: Infants and children with confirmed HIV infection

- WHO Paediatric Clinical Stage IV Disease: treat all children irrespective of laboratory parameters; or
- WHO Paediatric Clinical Stage III Disease: treat all children irrespective of CD4; in children aged over 18 months treat guided by CD4 where available, especially in children with lymphocytic interstitial pneumonia, oral hairy leukoplakia, or low platelet count; or
- WHO Paediatric Clinical Stage II Disease: treat CD4-guided or where CD4 is not available, guided by total lymphocyte count; or
- WHO Paediatric Clinical Stage I Disease: treat only guided by CD4; where CD4 is not available, children should not be initiated on ARV therapy.

### b) Clinical criteria: Symptomatic infants and children with unconfirmed HIV infection

For infants and children **aged under 18 months** where virological testing or p24 antigen is not available to confirm HIV infection status, WHO recommends the use of a *presumptive diagnosis* of Clinical Stage IV HIV disease. This should be made if:

- The child's HIV-exposure is confirmed by antibody testing;
- The child is symptomatic with two or more of the following:

- Oral thrush;
- Severe pneumonia (as defined in IMCI);
- Severe wasting/malnutrition (as defined in IMCI);
- Severe sepsis (as defined in IMCI) ;
- CD4 percentages, where available, below 25% ;

Other factors that support presumptive diagnosis of clinical stage IV HIV disease in an HIV-seropositive infant include:

- Recent HIV-related maternal death
- Advanced HIV disease in the mother

A presumptive diagnosis of stage IV HIV disease warrants the appropriate management of the presenting acute illnesses and institution of or referral for, management of presumed HIV infection, this may include initiation of ART. Use of a presumptive clinical diagnosis of infection in a child under the age of 18 months should be accompanied by immediate efforts to confirm the HIV diagnosis with the best nationally or locally available test for age. Initiation of ART based on presumptive diagnosis of clinical stage IV HIV disease is not recommended for use by clinical care providers who are not appropriately trained or experienced in HIV care or administration of antiretroviral therapy.

The algorithm for presumptive diagnosis should not be used in children aged 18 months and older as HIV infection can be confirmed by antibody testing.

### c) Laboratory parameters for guidance on decision-making

Immunological marker <sup>1</sup>	Age-specific recommendation to initiate ART		
	<18 months	18 months - 5 years	≥ 5 years
CD4% <sup>2</sup>	<25%	<15%	<10%
CD4 count <sup>2</sup>	<1500 cells/mm <sup>3</sup>	<500 cells/mm <sup>3</sup>	<200 cells/mm <sup>3</sup>
Total lymphocyte count (where CD4 assays are not available)	<3400 cells/mm <sup>3</sup>	<2300 cells/mm <sup>3</sup>	<1200 cells/mm <sup>3</sup>

<sup>1</sup>) Immunological markers supplement clinical staging.

<sup>2</sup>) CD4 cell percentage is preferred in children aged under 5 years; for all other children CD4 count should be used.

The technical group will explore ways for graphical presentation of laboratory parameters in order to simplify their use by clinicians.

## 2. What to start with - recommended first-line regimens

- Preferred option

**The combination of two nucleoside reverse transcriptase inhibitors (NRTI) plus one non-nucleoside reverse transcriptase inhibitor (NNRTI) should continue to be the preferred 1<sup>st</sup> line ART regimen.** In view of data on treatment outcomes, toxicity profiles and patterns of resistance it was proposed to add abacavir (ABC) as an additional NRTI option in 1<sup>st</sup> line regimens.

- **Dual NRTI backbone:** the use of zidovudine (AZT), stavudine (d4T), ABC or lamivudine (3TC) results in several possible dual nucleoside combinations including AZT + 3TC; d4T + 3TC; ABC + 3TC; AZT + ABC; and d4T + ABC. It is important to note that AZT should not be given in combination with d4T.

**PLUS**

- **NNRTI** nevirapine and efavirenz (NVP or EFV): the use of NVP is preferred in infants and children aged less than 3 years; EFV can be used in infants and children older than 3 years of age.
- **Alternative option**
  - A triple nucleoside regimen (i.e. AZT or d4T + 3TC + ABC) should remain an option, especially for those children who are receiving treatment for tuberculosis.

### 3. What to switch to – recommended second-line regimens in the event of failure on first-line regimens

The second-line choice depends on the first line regimen that has been given; the cornerstone for any second-line treatment is a Protease Inhibitor (PI):

For failure on 1 <sup>st</sup> line regimen	Change to 2 <sup>nd</sup> line regimen	
	NRTI component	PI component
AZT or d4T + 3TC + NVP or EFV <sup>1</sup>	ddl + ABC	+
ABC +3TC + NVP or EFV <sup>1</sup>	ddl + AZT	
AZT or d4T + 3TC + ABC	ddl + EFV <sup>1,4</sup> or NVP	
		LPV/r or SQV/r <sup>2</sup> or NFV <sup>3</sup>

Notes:

<sup>1</sup>) EFV should not be used in children aged less than 3 years or weighing less than 10 kg.

<sup>2</sup>) saquinavir/ritonavir (SQV/r) should not be used in children weighing less than 25kg.

<sup>3</sup>) nelfinavir (NFV) can be used instead of lopinavir/ritonavir LPV/r or SQV/r where no cold chain is in place.

<sup>4</sup>) Tenofovir (TDF) is currently not approved for clinical use in infants and children.

### 4. Expansion of current guidelines for children

The revised guidelines will include sections with additional considerations for the treatment of adolescents; children co-infected with HIV and tuberculosis; infants who have received ARV for MTCT prevention; and malnourished children. Other sections will address ART and nutrition, adherence to therapy, viral resistance, clinical and laboratory monitoring of therapy, as well as salvage strategies.

### 5. Agreed next steps

A writing committee was established at the meeting to elaborate the guidelines. WHO will develop a draft of the guidelines for the TRG to review. Members of the writing committee will add allocated sections.

A public web-based review of the first complete draft is planned as soon as it becomes available (October/November 2005). Based on the feedback received, the final draft will be produced.