

Antiretroviral therapy for HIV infection in infants and children:  
Towards universal access

Executive summary of recommendations

Preliminary version for program planning

2010



## Executive summary

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

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

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

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

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

number of HIV-infected children highlights the primary importance of preventing transmission of the virus from mother to child in the first place.

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

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

## Summary of changes

### Earlier, more accurate diagnosis of HIV

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

### Earlier initiation of ART

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

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

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

### What to expect in the first six months of therapy

- Expected signs and symptoms of initial therapy

### Promoting attention to nutrition for children on ART

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

### More strategic monitoring for antiretroviral efficacy and toxicity

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

## Strengthening adherence

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

## List of recommendations

### Establishing a diagnosis of HIV infection in infants and children

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1. It is strongly recommended that HIV **serological assays** used for the purpose of clinical diagnostic testing have a minimum sensitivity of 99% and specificity of 98%, and that the tests are performed by a quality-assured, standardized and validated laboratory.
  - <18 months of age – used as a screening assay to determine HIV exposure
  - >18 months of age – used as a diagnostic assay
2. It is strongly recommended that HIV **virological assays** used for the purpose of clinical diagnostic testing (usually at or after 6 weeks of age) have a sensitivity of at least 95% (ideally greater than 98%), and specificity of 98% or more, and that the tests are performed by a quality-assured, standardized and validated laboratory.
3. It is strongly recommended that HIV virological testing be used to diagnose HIV infection in infants and children less than 18 months of age.
4. In infants and children undergoing virological testing, the following assays (and respective specimen types) are strongly recommended for use:
  - HIV DNA on whole blood specimen or dried blood spots (DBS)
  - HIV RNA on plasma or DBS
  - ultrasensitive p24 antigen (Up24 Ag) on plasma or DBS
5. It is strongly recommended that all HIV-exposed infants have HIV virological testing at 4 to 6 weeks of age or at the earliest opportunity thereafter.
6. In infants with an initial positive virological test result, it is strongly recommended that ART be started without delay and, at the same time, a second specimen be collected to verify the initial positive virological test result. Do not delay ART. In infected infants, immediate initiation of ART saves lives and commencement of ART should not be held while waiting for the results of the verification of the first positive virological result test. (See recommendation 13 if VL is not available)
7. It is strongly recommended that test results from virological testing in infants be returned to the clinic and child/mother/carer as soon as possible, but at the very latest within four weeks of specimen

collection. Positive test results should be fast-tracked to the mother–baby pair as soon as possible to enable prompt initiation of ART.

8. It is strongly recommended that all infants with unknown or uncertain HIV exposure being seen in health-care facilities at or around birth or at the first postnatal visit (usually 4–6 weeks), or other child health visit, have their HIV exposure status ascertained.
9. It is strongly recommended that well, HIV-exposed infants undergo HIV serological testing at around 9 months of age (or at the time of the last immunization visit). Those who have reactive serological assays at 9 months should have a virological test to identify infected infants who need ART.
10. It is strongly recommended that infants with signs or symptoms suggestive of HIV infection undergo HIV serological testing and, if positive (reactive), virological testing.
11. In breastfeeding infants or children, it is strongly recommended that breastfeeding is not discontinued in order to perform any kind of diagnostic HIV test. (see *Rapid Advice on HIV and Infant Feeding*, WHO, 2009.)
12. It is strongly recommended that children aged 18 months or older, with suspected HIV infection or HIV exposure, have HIV serological testing performed according to the standard diagnostic HIV serological testing algorithm used in adults.
13. In sick infants in whom HIV infection is being considered as an underlying cause of symptoms and signs, and virological testing is not available, HIV serological testing and use of the clinical algorithm for presumptive clinical diagnosis of HIV infection is strongly recommended.

### **When to start antiretroviral therapy in infants and children**

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#### **Infants**

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

#### **Children**

2. Initiate ART for all HIV-infected children less than two years of age irrespective of CD4 count or WHO clinical stage.
3. Initiate ART for all HIV-infected children between 24 and 59 months of age with CD4 count of  $\leq 750$  cells/mm<sup>3</sup> or %CD4+  $\leq 25\%$ , whichever is lower, irrespective of WHO clinical stage.
4. Initiate ART for all HIV-infected children more than 5 years of age with a CD4 count of  $\leq 350$  cells/mm<sup>3</sup> (as in adults), irrespective of WHO clinical stage.

5. Initiate ART for all HIV-infected children with WHO HIV clinical stages 3 and 4, irrespective of CD4 count.
6. Initiate ART for any child less than 18 months of age who has been given a presumptive clinical diagnosis of HIV infection.

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

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#### **Infants**

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

#### **Children**

4. For children between 12 and 24 months exposed to maternal or infant NVP or other NNRTIs used for maternal treatment or PMTCT, start ART with lopinavir/ritonavir (LPV/r) + 2 NRTIs.
5. For children more than 24 months and less than 3 years of age, start ART with NVP + 2 NRTIs.
6. For children 3 years of age and above, start ART with NVP or efavirenz (EFV)-containing regimen + 2 NRTIs.
7. For infants and children, the nucleoside backbone for an ART regimen should be one of the following, in preferential order:  
Lamivudine (3TC) + zidovudine (AZT) **or** 3TC + abacavir (ABC) **or** 3TC + stavudine (d4T)

#### **Infants and children with specific conditions**

8. For children more than 3 years of age with tuberculosis (TB), the preferred regimen is EFV + 2 NRTIs.
9. For infants and children less than 3 years of age with TB, the preferred regimens are NVP + 2 NRTIs or a triple nucleoside regimen.
10. For a child or adolescent with severe anaemia (<7.5 g/dl) or severe neutropenia (<500 cells/mm<sup>3</sup>), the preferred regimen is NVP + 2 NRTIs (avoid AZT).
11. For adolescents more than 12 years of age with hepatitis B, the preferred regimen is tenofovir (TDF) + emtricitabine (FTC) + NNRTI.

## **Clinical and laboratory monitoring**

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### **CD4 monitoring**

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

### **Viral load monitoring**

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

### **Routine clinical and laboratory monitoring**

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

## **First-line regimen treatment failure; when to switch regimens**

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1. A switch to a second-line regimen is recommended when:
  - Clinical failure is recognizedand/or
  - Immunological failure is recognizedand/or
  - Virological failure is recognized.

2. Clinical failure is recognized as the appearance or reappearance of WHO clinical stage 3 or stage 4 events after at least 24 weeks on ART in a treatment-adherent child.
3. Immunological failure is recognized as developing or returning to the following age-related immunological thresholds after at least 24 weeks on ART, in a treatment-adherent child:
  - CD4 count of  $\leq 200$  cells/mm<sup>3</sup> or %CD4+  $\leq 10\%$  for a child more than 2 years to less than 5 years of age
  - CD4 count of  $\leq 100$  cells/mm<sup>3</sup> for a child 5 years of age or more.
4. Virological failure is recognized as a persistent VL above 5 000 RNA copies/ml, after at least 24 weeks on ART, in a treatment-adherent child.

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

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

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#### **Considerations for infants and children with tuberculosis and HIV**

##### **Isoniazid preventive therapy**

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

### **Infants and children diagnosed with TB and HIV**

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


### **HIV-infected infants and children who develop TB on ART**

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

### **Considerations for the nutrition for HIV-infected infants and children**

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1. HIV-infected children should be assessed routinely for nutritional status, including weight and height at scheduled visits, particularly after the initiation of ART.
2. HIV-infected children on or off ART who are symptomatic, have conditions requiring increased energy (e.g. TB, chronic lung disease, chronic opportunistic infections [OIs] or malignancies), have weight loss or have evidence of poor growth, should be provided with 25–30% additional energy.
3. HIV-infected children who are severely malnourished should be managed as per the guidelines for uninfected children and provided with 50–100% additional energy.
4. HIV-infected children should receive one recommended daily allowance (RDA) of micronutrients daily. If this cannot be assured through the diet, or there is evidence of deficiency, then supplementation should be given.

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5. HIV-infected infants and children between 6 and 59 months of age should receive high-dose vitamin A supplementation every 6 months, as per the guidelines for uninfected children.
  6. HIV-infected children who have diarrhoea should receive zinc supplementation as a part of management, as per the guidelines for uninfected children.
  7. For infants and young children known to be HIV infected, mothers are strongly encouraged to exclusively breastfeed for 6 months and to continue breastfeeding as per recommendations for the general population (i.e., up to two years of age and beyond).

#### **Adherence to ART**

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