ANTIRETROVIRAL THERAPY FOR CHILDREN WITH HIV INFECTION IN RESOURCE-LIMITED SETTINGS

PART 1: INITIATING AND CHANGING THERAPY

BACKGROUND

Each day, more than 8200 people die of AIDS. Of these, 1400 are children. Without antiretroviral treatment (ART), a significant proportion of children living with HIV in resource-limited settings will die before the age of five (see Figure 1).

Figure 1. Mortality rates in children with HIV infection with no ARV therapy


While access to care and treatment for HIV-infected children is improving, the lack of suitable paediatric formulations in most resource-limited settings remains a significant barrier to access to care for children.

CHILDREN ARE NOT JUST SMALL ADULTS

Baseline viral loads in children typically are higher than those in adults, which may be a barrier to reaching undetectable viral loads. In most paediatric studies, virological response rates to highly active antiretroviral therapy (HAART) are inferior to those in adults, while clinical response rates are good.

In studies of antiretroviral therapy in children, although there are no adequately powered studies to allow direct comparisons of different regimens, good virological responses have been seen in regimens containing protease inhibitors (PIs), in regimens containing nevirapine and in two regimens containing nucleoside reverse transcriptase inhibitors (NRTIs). Triple nucleoside regimens may well offer distinct advantage of once-daily dosing and class sparing, and studies to look at efficacy are ongoing. The tolerability and pill burden of a regimen in younger children may be a more important factor in overall effectiveness. PIs for children in particular are normally unavailable in resource-limited settings.
ANITRETROVIRAL THERAPY

The general principles underlying the use of antiretroviral therapy are similar for all HIV-infected persons. The effectiveness of HAART in reducing HIV-related morbidity and mortality in infants and children is comparable to that observed in adults. However, there are unique considerations for HIV-infected infants and children. These include:

- exposure to zidovudine and nevirapine, which may result in resistance to subsequent ART;
- difficulties in the diagnosis of HIV infection in children <18 months of age in resource-limited settings;
- age-dependent differences in immunologic markers in young children (CD4 percentage, not CD4 count, is used in children);
- differences in the clinical and virologic manifestations of perinatal HIV infection;
- changes in drug pharmacokinetics with age;
- limited expertise in treating children with ART in many countries;
- significant psychosocial support to the child and family, which is required in addition to knowledgeable provision or ART;
- limited number and poor palatability of paediatric formulations of antiretrovirals;
- difficulties in the adherence to combination therapy for many years.
- problems taking medication during sleep time or at school; and
- unwillingness of young children and adolescents to take medication.

The recommendations contained in this section are based on the 2003 revision of WHO's Scaling up antiretroviral therapy in resource-limited settings: Treatment guidelines for a public health approach. References are also made to country guidelines prepared by the Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children (US), revised 30 November 2004, and the Paediatric European Network for Treatment of AIDS (PENTA) 2004 guidelines.

Figure 2. Survival time free of AIDS or death in Thai children

HIV TESTING IN INFANTS AND CHILDREN

VIROLOGICAL TESTING

HIV infection can be definitively diagnosed in infected infants only by using viral diagnostic assays (detection of HIV by DNA or RNA polymerase chain reaction [PCR]). These assays may not be available in resource-limited settings. The preferred virologic method for diagnosing HIV infection during infancy is HIV DNA PCR. Detection of plasma HIV RNA (viral load) is an alternative. If available, virologic testing should be performed between six weeks and six months of age. The same is recommended for breastfed infants, with the additional recommendation that testing should be performed only six weeks after complete cessation of breastfeeding. HIV infection is diagnosed by two positive HIV virologic tests performed on separate blood samples. HIV infection can be reasonably excluded among children with two or more negative virologic tests performed between six weeks and six months of age in non-breastfed infants and six weeks after complete cessation if breastfeeding.

HIV ANTIBODY TESTING

In the absence of viral diagnostic assays, HIV antibody testing is used. However, the diagnosis of HIV infection in infants and children by HIV antibody testing is complicated by the persistence of maternal antibodies in children up to 18 months of age. Breastfeeding infants are at risk of HIV infection during the period of breastfeeding and a negative virologic or antibody test during the breastfeeding period does not exclude the child from becoming infected at a later date. Testing is recommended at any time six weeks after complete cessation of breastfeeding. Two or more negative HIV antibody tests performed at age six months with an interval of at least one month between the tests also can be used to reasonably exclude HIV infection among non-breastfed children with no clinical evidence of HIV infection. HIV infection can be definitively excluded in a non-breastfeeding child if the HIV antibody is negative at 18 months of age. A persistent HIV-positive test result 18 months after delivery confirms HIV infection regardless of breastfeeding.

WHEN TO INITIATE ART IN CHILDREN

The PENPACT 1 trial of early vs. deferred zidovudine monotherapy remains the only randomized trial evaluating when to start ART in children. However, new studies are planned. Recommendations on when to initiate ART in children are still based primarily on a meta-analysis of data from 3941 children in Europe and the United States of America. There is still no adult or paediatric trial evidence on which to base decisions about whether to start with PI- or non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens. This is being studied in the ongoing PENPACT 1 trial.

Figure 3. Probability of a child developing AIDS within the next 12 months by age and current CD4 percentage

Source: Dunn (2003)
Because of the difficulties in making a laboratory diagnosis of HIV infection in children up to 18 months of age, WHO’s recommendations for initiation of ARV therapy in children are divided into categories related to age and availability of virologic diagnostic tests.

When CD4 cell assays are available, CD4 cell percentage rather than absolute CD4 cell count, should be used to determine when to start ARV treatment in children's CD4 cell percentage varies less with age. As in HIV-infected adults, total lymphocyte count significantly correlates with the risk of mortality in HIV-infected children.14,15 When CD4 cell count cannot be assessed, total lymphocyte count may be used as a substitute indication for treatment for infants or children with documented HIV infection in the presence of symptomatic disease.

### Table 1. Draft summary of indications for initiating ART in children (based on the proposed WHO four-stage system)

<table>
<thead>
<tr>
<th>CD4 testing</th>
<th>Age</th>
<th>HIV diagnostic testing</th>
<th>Treatment recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>If CD4 testing is available</td>
<td>Less than 18 months</td>
<td>Positive HIV virologic test</td>
<td>WHO paediatric stage IV (AIDS), irrespective of CD4 percentage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HIV virologic testing not available, but infant is HIV seropositive or born to known HIV-infected mother (repeat HIV test at age 18 months)</td>
<td>WHO paediatric stage IV (AIDS) irrespective of CD4 percentage</td>
</tr>
<tr>
<td></td>
<td>More than 18 months</td>
<td>HIV antibody seropositive</td>
<td>WHO paediatric stage IV (AIDS), irrespective of age or CD4 percentage</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>WHO paediatric stage III consider treatment for all</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>WHO paediatric stages I and II with CD4 &lt;20%</td>
</tr>
<tr>
<td>If CD4 testing is not available</td>
<td>Less than 18 months</td>
<td>Positive HIV virologic test</td>
<td>WHO paediatric stage IV (AIDS) irrespective of age</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HIV virologic testing not available, but infant is HIV seropositive or born to known HIV-infected mother</td>
<td>WHO paediatric stage III consider treatment for all</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment only recommended with presumptive or definitive diagnosis of stage IV clinical events</td>
<td></td>
</tr>
<tr>
<td></td>
<td>More than 18 months</td>
<td>HIV antibody seropositive</td>
<td>WHO paediatric stage IV (AIDS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WHO paediatric stage III consider treatment for all</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>WHO paediatric stages I &amp; II, consider treatment only if TLC &lt;1500 mm$^3$</td>
<td></td>
</tr>
</tbody>
</table>

* For updates on development of this staging system, visit [http://www.who.int/en/](http://www.who.int/en/).

A CD4 cell percentage of <20% corresponds to an absolute CD4 count of approximately <1000/mm$^3$ for children aged <2 months and <750/mm$^3$ for children aged 12-18 months; CD4 <15% corresponds to <500/mm$^3$ for children aged 1-5 years, and <200 mm$^3$ for children aged >6 years. A total lymphocyte count of <2500 mm$^3$ for children aged <18 months or <1500 mm$^3$ for children aged >18 months can be substituted for CD4 percentage when the latter is unavailable and HIV-related symptoms exist. Its utility in asymptomatic
children is unknown. In the absence of CD4 cell testing, asymptomatic HIV-infected children should not be treated because there is currently no other reliable marker available in severely resource-constrained settings. It is preferable that an abnormal total lymphocyte count (TLC) or CD4 cell count/percentage be confirmed with a second test before therapeutic decisions are made, but it is recognized that this may not always be possible.

Research is ongoing to establish the most appropriate TLC cut-off for initiating antiretroviral therapy. In children with clear symptoms of immunosuppression, a TLC above the cut-offs mentioned should not be accepted as a reason not to offer ART. The predictive power TLC may be increased if combined with other standard measurements, e.g. haemoglobin, weight. Accessible and affordable CD4 estimation needs to be promoted.

### Tables 2 and 3. Examples of weight-based paediatric dosing

<table>
<thead>
<tr>
<th>Age or weight (kg)</th>
<th>Oral solution 10mg/ml (ml)</th>
<th>Tablet 150mg</th>
<th>Oral suspension 10mg/ml (ml)</th>
<th>Tablet 200mg</th>
<th>Syrup 10mg/ml (ml)</th>
<th>Capsule (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 kg</td>
<td>1.5</td>
<td>-</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6-10 kg</td>
<td>2.5</td>
<td>-</td>
<td>7.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10-15 kg</td>
<td>5</td>
<td>10</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>15-20 kg</td>
<td>7.5</td>
<td>-</td>
<td>15</td>
<td>-</td>
<td>10.0</td>
<td>1</td>
</tr>
<tr>
<td>20-29 kg</td>
<td>10</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>2</td>
<td>1/2</td>
</tr>
</tbody>
</table>

* Lamivudine (3TC)*
  - 4 mg/kg/dose twice daily for lifetime

<table>
<thead>
<tr>
<th>Age or weight (kg)</th>
<th>Oral solution 10mg/ml (ml)</th>
<th>Capsules (mg)</th>
<th>Syrup 10mg/ml (ml)</th>
<th>Capsules (mg)</th>
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</thead>
<tbody>
<tr>
<td>3-6</td>
<td>1.5</td>
<td>-</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>6-10</td>
<td>2.5</td>
<td>-</td>
<td>7.5</td>
<td>-</td>
</tr>
<tr>
<td>10-15</td>
<td>5</td>
<td>10</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>15-20</td>
<td>7.5</td>
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<td>15</td>
<td>-</td>
</tr>
<tr>
<td>20-29</td>
<td>10</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

* Nevirapine (NVP)*
  - 120 mg/m³ dose once daily for 2 weeks, then twice daily for lifetime

<table>
<thead>
<tr>
<th>Age or weight (kg)</th>
<th>Oral solution 10mg/ml (ml)</th>
<th>Tablet 150mg</th>
<th>Oral suspension 10mg/ml (ml)</th>
<th>Tablet 200mg</th>
<th>Syrup 10mg/ml (ml)</th>
<th>Capsule (mg)</th>
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<td>3-6</td>
<td>1.5</td>
<td>-</td>
<td>4</td>
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<td>-</td>
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</tr>
<tr>
<td>6-10</td>
<td>2.5</td>
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<td>7.5</td>
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<tr>
<td>10-15</td>
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<td>10</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>15-20</td>
<td>7.5</td>
<td>-</td>
<td>15</td>
<td>-</td>
<td>10.0</td>
<td>1</td>
</tr>
<tr>
<td>20-29</td>
<td>10</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>2</td>
<td>1/2</td>
</tr>
</tbody>
</table>

* Zidovudine (ZDV)*
  - 180 mg/m³ dose Give twice daily for lifetime

<table>
<thead>
<tr>
<th>Age or weight (kg)</th>
<th>Oral solution 10mg/ml (ml)</th>
<th>Capsules (mg)</th>
<th>Syrup 10mg/ml (ml)</th>
<th>Capsule (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-6</td>
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<td>-</td>
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<td>15-20</td>
<td>7.5</td>
<td>-</td>
<td>15</td>
<td>-</td>
</tr>
<tr>
<td>20-29</td>
<td>10</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

Antiretroviral Newsletter Issue No.11
Table 4. Proposed WHO staging system a,b

<table>
<thead>
<tr>
<th>STAGE I</th>
<th>STAGE II</th>
</tr>
</thead>
</table>
| • Asymptomatic  
  • Persistent generalized lymphadenopathy (PGL)  
  • Hepatosplenomegaly | • Recurrent or chronic upper respiratory tract infections  
  • Otitis media, otorrhoea, sinusitis, two or more episodes in any six-month period  
  • Papular pruritic eruptions  
  • Herpes zoster (one or more episodes in six months)  
  • Recurrent oral ulcerations (two or more episodes in six months)  
  • Linear gingival erythema (LGE)  
  • Angular chelitis  
  • Parotid enlargement  
  • Seborrhoeic dermatitis  
  • Extensive human papilloma virus infection or molluscum infection (more than 5% body area or disfiguring)  
  • Fungal nail infections |

<table>
<thead>
<tr>
<th>STAGE III</th>
<th>STAGE IV</th>
</tr>
</thead>
</table>
| • Unexplained moderate malnutrition not responding to standard therapy  
  • Unexplained persistent diarrhoea (more than 14 days)  
  • Unexplained persistent fever (intermittent or constant, for longer than one month)  
  • Oral candidiasis (outside neonatal period)  
  • Oral hairy leukoplakia  
  • Pulmonary tuberculosis d  
  • Severe recurrent presumed bacterial pneumonia (two or more episodes in six months)  
  • Acute necrotizing ulcerative gingivitis/periodontitis  
  • Lymphoid interstitial pneumonia (LIP)  
  • Unexplained anaemia (<8gm/dl), neutropenia (<1000/mm 3 ) or thrombocytopenia (<30000/mm 3 ) > than one month  
  • HIV-related cardiomyopathy  
  • HIV-related nephropathy | Conditions where a presumptive diagnosis can be made using clinical signs or simple investigations:  
  • Unexplained severe wasting or severe malnutrition not adequately responding to standard therapy  
  • Pneumocystis pneumonia (PCP)  
  • Recurrent severe presumed bacterial infections (two or more episodes within one year e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)  
  • Chronic orolabial or cutaneous herpes simplex infection (of more than one-month duration)  
  • Extrapulmonary tuberculosis  
  • Kaposi sarcoma  
  • Oesophageal candidiasis  
  • CNS toxoplasmosis  
  • HIV encephalopathy |

| Conditions where confirmatory diagnostic testing is necessary:  
  • CMV infection (CMV retinitis or infection of organ other than liver, spleen, or lymph nodes onset at age one month or more)  
  • Cryptococcal meningitis (or other extrapulmonary disease)  
  • Any disseminated endemic mycosis(e.g. extrapulmonary histoplasmosis, coccidioidomycosis, penicilliosis)  
  • Cryptosporidiosis  
  • Isosporiasis  
  • Disseminated non-tuberculous mycobacterial infection  
  • Candidiasis of trachea, bronchi or lungs  
  • Acquired HIV-related rectovesico fistula |

a For HIV infection in children less than 13 years with confirmed laboratory evidence of HIV infection: HIV antibody age >18 months, HIV-RNA or HIV-DNA <18 months

b For updates on development of this staging system, see http://www.who.int/en/

c Defined as very low weight for age (http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/WHO_FCH_CAH_00.1.htm or http://www.who.int/nut/documents/manage_severe_malnutrition_eng.pdf

d TB may occur at any CD4 count and CD4% should be considered where available

e Defined as very low weight or visible severe wasting or oedema of both feet: (http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/WHO_FCH_CAH_00.1.htm)
PRINCIPLES OF ARV TREATMENT IN CHILDREN WITH CURRENTLY AVAILABLE PRODUCTS

For infants <12 kg, syrups, solutions and dissolvable formulations of ZDV, 3TC, NVP, Abacavir (ABC) and lopinavir/RTV (LPV/r) are the best options. D4T liquid, ddI sachets and NLF powder are not ideal due to problems with dispensing and ease of use. In infants >12 kg, solid formulations of all drugs are preferred. Ideally, tablets should not be broken further than half.

Efavirenz is the NNRTI of choice for children at 3 years of age or older who require ARV therapy and are receiving antituberculosis therapy containing rifampicin. For children younger than 3 years who require ARV therapy while receiving rifampicin, the combination of ZDV/3TC/ABC is recommended.

Drug doses in children are based on either body surface area or weight and dosing must be adjusted as the child grows. Tables of body weight bands are preferred and some have been developed for use in resource-limited settings (Tables 2 and 3). Some ARVs are available with specific child formulations. However, formulations appropriate for use by young children who cannot swallow whole tablets or capsules are not currently widely available in resource-limited settings. The splitting of adult, while suboptimal, should be considered when no other alternatives are available.

Current fixed-dose combination (FDC) formulations may not contain the appropriate doses of each of the component drugs for children on a weight basis. For example, if the adult formulation of the FDC d4T, 3TC and NVP is split for use in children, additional NVP must be taken.

If a mother and child received ARV (usually single dose NVP) to reduce mother-to-child HIV transmission (MTCT), it is possible that the child may have drug-resistant virus. Until more research is conducted, children who require ARV therapy and who have previously received ARV as part of prophylaxis for MTCT should be offered standard NNRTI-based first-line regimens.

**Table 5. Recommended first-line antiretroviral regimens for infants and children**

<table>
<thead>
<tr>
<th>First-line regimen</th>
<th>non-nucleoside reverse transcriptase inhibitor (NNRTI) choice</th>
</tr>
</thead>
</table>
| d4T or ZDV + 3TC + nevirapine (NVP) or efavirenz (EFV) | • age <3 years or weight <10 kg NVP  
• age >3 years or weight >10 kg NVP or EFV |

**ALWAYS GIVE THREE DRUGS**

**Table 6. Drug substitutions for toxicity**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Toxicity</th>
<th>Drug substitution</th>
</tr>
</thead>
<tbody>
<tr>
<td>d4T/3TC/NVP</td>
<td>d4T-related neuropathy, pancreatitis or lipoatrophy</td>
<td>Switch d4T to ZDV</td>
</tr>
<tr>
<td></td>
<td>NVP-related severe hepatotoxicity</td>
<td>Switch NVP to EFV</td>
</tr>
<tr>
<td></td>
<td>NVP-related severe rash</td>
<td>Switch NVP to EFV</td>
</tr>
<tr>
<td>ZDV/3TC/NVP</td>
<td>ZDV-related persistent GI intolerance or severe haematological toxicity</td>
<td>Switch ZDV to d4T</td>
</tr>
<tr>
<td></td>
<td>NVP-related severe hepatotoxicity</td>
<td>Switch NVP to EFV</td>
</tr>
<tr>
<td></td>
<td>NVP-related severe rash</td>
<td>Switch NVP to EFV</td>
</tr>
<tr>
<td>d4T/3TC/EFV</td>
<td>d4T-related neuropathy or pancreatitis d4T-related lipoatrophy</td>
<td>Switch d4T to ZDV</td>
</tr>
<tr>
<td></td>
<td>EFV-related persistent CNS toxicity</td>
<td>Switch d4T to TDF or ABC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Switch EFV to NVP</td>
</tr>
<tr>
<td>ZDV/3TC/EFV</td>
<td>ZDV-related persistent GI intolerance or severe haematological toxicity</td>
<td>Switch ZDV to d4T</td>
</tr>
<tr>
<td></td>
<td>EFV-related persistent CNS toxicity</td>
<td>Switch EFV to NVP</td>
</tr>
</tbody>
</table>
**REASONS FOR SUBSTITUTING AND CHANGING ART IN INFANTS AND CHILDREN**

**TOXICITY**

The management of drug toxicity and the principles on which to base substitutions of ARV for children are similar to those in adults.

**CLINICAL FAILURE**

Clinical signs of drug failure in children:

- lack of growth among children who show an initial response to treatment;
- decline in growth among children who show an initial growth response to therapy;
- a loss of neurodevelopment milestones or the development of encephalopathy;
- occurrence of new opportunistic infection or malignancy signifying clinical disease progression (This must be distinguished from immune reconstitution syndrome, which can occur in the first three months following the initiation of ARV and does not signify treatment failure); and
- recurrence of prior infections, such as oral candidiasis that is refractory to treatment.

Before an ARV regimen is thought to be failing based on clinical criteria, the child should have had a reasonable trial on the therapy (e.g. have received the regimen for at least 24 weeks).

**IMMUNOLOGICAL FAILURE**

Immunological failure is defined as a return in CD4 cell percentage (or for children >6 years of age, absolute CD4 cell count) to pre-therapy baseline or below, in absence of other concurrent infection to explain transient CD4 decrease or a >50% fall from peak level on therapy of CD4 cell percentage (or for children >6 years of age, absolute CD4 cell count), in absence of other concurrent infection to explain transient CD4 decrease.

**SECOND-LINE ART FOR INFANTS AND CHILDREN**

Second-line ARV therapy for children in the event of first-line regimen failure follows the same principles as for adults and includes a change in nucleoside backbone (e.g. from ZDV + 3TC to ABC + ddI) plus a protease inhibitor. Use of protease inhibitors other than LPV/r and NFV is more problematic in children due to:

- lack of suitable paediatric drug formulations for IDV and SQV; and
- lack of appropriate dosing information for ritonavir boosted PIs other than LPV/r.

**Table 7. ARV regimens for infants and children with treatment failure**

<table>
<thead>
<tr>
<th>First-line regimen</th>
<th>Second-line regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>d4T or ZDV Plus 3TC Plus</td>
<td>ABC Plus ddI Plus Protease inhibitor: LPV/r or NFV, or SQV/r if weight &gt;25 kg</td>
</tr>
</tbody>
</table>

**In Part 2 of this edition:**

- Monitoring ART in children
- Complications of ART in children
- Special issues related to adherence in children
WHO Regional Office for the Western Pacific would like to express its sincere thanks to Dr Christopher James Duncombe for drafting this issue and acknowledge the comments provided by Dr Siobhan Crowley.

6 Sharland M et al. for PENTA Steering Committee. Penta Guidelines for the use of antiretroviral therapy. HIV medicine, 2004, 5 (suppl 2); 61–68.
9 Guidelines for the Use of Antiretroviral Agents in Paediatric HIV Infection: The Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children convened by the National Pediatric and Family HIV Resource Center (NPHRC), The Health Resources and Services Administration (HRSA), and The National Institutes of Health (NIH). www.aidsinfo.com
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World Health Organization
Regional Office for the
Western Pacific

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Website: http://www.wpro.who.int