WHO recommendations for ARV treatment in infants and children

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HIV in children is likely to be an ongoing problem

- Poor coverage of ANC HIV testing – in 2004 10% up to 18% in 2008 (ie. 82% of women do not get tested)
- Very few of those identified with HIV get ARVs – 34%

**ARV or ART exposure in tested women and their infants**

- % Infant ARV
- % maternal ARV/ART

**Required for universal access by 2010**

% receiving ARV intervention

- 2004
- 2005
- 2006
- 2007
More children are receiving ART

Increased from 75,000 in 2005 to almost 200,000 in 2007

19 of 20 countries with highest PMTCT burden are in sub-Saharan Africa
ART outcomes - good news across the globe

- National programmes reporting good outcomes
- 1 year survival estimated as 93-95%
- 2 year survival 91%
<table>
<thead>
<tr>
<th>Location</th>
<th>Year</th>
<th>N</th>
<th>Baseline Median Age</th>
<th>Baseline Median CD4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janssens/Cambodia</td>
<td>2007</td>
<td>212</td>
<td>6.0 yrs</td>
<td>6%</td>
</tr>
<tr>
<td>George/Haiti</td>
<td>2007</td>
<td>100</td>
<td>6.3 yrs</td>
<td>12%</td>
</tr>
<tr>
<td>Wamawala/Kenya</td>
<td>2007</td>
<td>67</td>
<td>4.4 yrs</td>
<td>6%</td>
</tr>
<tr>
<td>Reddi/S Africa</td>
<td>2007</td>
<td>151</td>
<td>5.7 yrs</td>
<td>8%</td>
</tr>
<tr>
<td>Puthanakit/Thailand</td>
<td>2007</td>
<td>107</td>
<td>7.7 yrs</td>
<td>5%</td>
</tr>
<tr>
<td>Kamya/Uganda</td>
<td>2007</td>
<td>250</td>
<td>9.2 yrs</td>
<td>8.6%</td>
</tr>
<tr>
<td>Rouet/Cote d'Ivoire</td>
<td>2006</td>
<td>78</td>
<td>6.5 yr</td>
<td>8%</td>
</tr>
</tbody>
</table>

Children everywhere are Starting Treatment Late

Meta-analysis 1,195 children from 8 African clinical trials
53% >5 years of age, 70% severe immune deficiency, 12% aged < 12 months (KIDS-ART-LINC)
Arrive 2008
Starting late increases mortality

<table>
<thead>
<tr>
<th>Months from ART start</th>
<th>Probability of Death After Starting ART</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Immune Deficient at Start ART</td>
</tr>
<tr>
<td>6 months</td>
<td>7.8%</td>
</tr>
<tr>
<td></td>
<td>6% excess mortality</td>
</tr>
<tr>
<td>12 months</td>
<td>8.2%</td>
</tr>
</tbody>
</table>

Arrive E et al. 14th CROI, Los Angeles, CA, 2007 Abs. 727

73% median age > 5 years of age, > 50% start with severe immune deficiency, most deaths within 6 months of starting ART

Risk factors for death:
- low CD4
- < 18 months age
- WHO stage 3/4
- viral load greater than 6·0 log
- severe malnutrition

Sutcliffe et al. Lancet Infect Dis 2008;8: 477–89
In 2007:

- only 8% of HIV exposed infants were tested in 1st 2 months of life
- only 4% started on co-trimoxazole
85% infants meet criteria to start ART within 6 months

CHER STUDY: 76% Reduction in the Risk of Death with Immediate Compared to Deferred ART

Most deaths occurred within first 6 months (i.e., before age 10 months)

Nevirapine resistance

Prevalence of NVP resistance

% NVP resistance detected

SD NVP
SD NVP + post partum ARV

mother
baby

Meta analysis: Arrive et al
Response to Antiretroviral Therapy after a Single, Peripartum Dose of Nevirapine


Analysis after 6 months of HAART:
10/13 in SD NVP group and 1/12 placebo group had HIV RNA >400 copies/mL

Median age at start HAART: 8.5 months
2008 revisions
(April + November)

For infants expert panel reviewed:
• When to perform virological testing
• Which tests to use when
• When to start ART
• What ARVs to start in infants with HIV
• ARV dosing for infants
WHO - new recommendations for starting ART in infants

All infants under 12 months of age with confirmed HIV infection should be started on antiretroviral therapy, irrespective of clinical or immunological stage.

GRADE Evidence profile = Moderate

Strength of Recommendation = STRONG

## Revised WHO Guidelines 2008: When to Start Antiretroviral Therapy in HIV-Infected Children

<table>
<thead>
<tr>
<th>&lt; 12 months HIV Confirmed</th>
<th>&lt; 12 months Presumptive Severe HIV*</th>
<th>1–4 yrs</th>
<th>≥ 5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>All regardless of CD4/clinical</td>
<td>All regardless of CD4/clinical</td>
<td>Clinical or immune criteria</td>
<td>Clinical or immune criteria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;20% or</td>
<td>&lt;15% or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12-35 mos: &lt;750/uL</td>
<td>&lt;200/uL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>36-59 mos: &lt;350/uL</td>
<td>(as in adults)</td>
</tr>
</tbody>
</table>

*If Viral test is not possible, use presumptive diagnosis of severe HIV (thrush, severe pneumonia or sepsis) in infants with +ve HIV antibody test and with clinical symptoms of severe HIV – confirm infection status as soon as possible.
What ART to Start in infants – 2008 revision

- No infant or maternal ARV exposure
  - Sd NVP or NNRTI containing ART
    - Baby 18%
  - NVP triple ART
- MTCT ARV Exposure
  - No NNRTI exposure
    - Mum 34%
  - PI triple ART
- Unknown infant maternal MTCT Exposure
  - NVP triple ART

# If no PI is available use NVP triple ART
Children 1 year or over

Clinical and/or immunological criteria to start ART

Standard first line regimen
NNRTI + 2NRTI

< 3 years
NVP + AZT + 3TC

> 3 years
EFV + AZT + 3TC

Standard second line regimen
PI + 2 new NRTI
Distribution of first line regimens in children

Source: WHO AMD Survey 2007
<table>
<thead>
<tr>
<th>Patient group</th>
<th>Preferred first line regimen</th>
<th>Preferred second line regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant not exposed to NVP</td>
<td>NVP + AZT# + 3TC</td>
<td>Boosted PI + 2 new NRTI</td>
</tr>
<tr>
<td>Infant exposed to NVP</td>
<td>Lop/r + AZT # + 3TC</td>
<td>NNRTI + 2 new NRTI</td>
</tr>
<tr>
<td>Infant Unknown NVP exposure</td>
<td>NVP + AZT # + 3TC</td>
<td>Boosted PI + 2 new NRTI</td>
</tr>
<tr>
<td>Children 3 or over</td>
<td>EFV + AZT # + 3TC</td>
<td>Boosted PI + 2 new NRTI</td>
</tr>
</tbody>
</table>

# if anaemia use alternative ABC or d4T
### WHO recommendations for infant ARV prophylaxis

<table>
<thead>
<tr>
<th>Clinical scenario</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal extended pAZT</td>
<td>Sd NVP + 7 days AZT</td>
</tr>
<tr>
<td>Maternal cART</td>
<td>AZT x 7 days</td>
</tr>
<tr>
<td>Less than 4 weeks maternal cART or AZT</td>
<td>Sd NVP + 4 wks AZT</td>
</tr>
<tr>
<td>Mother presents in labour</td>
<td>Sd NVP + 4 wks AZT</td>
</tr>
<tr>
<td>Infant seen in &lt; 72 hrs after birth no maternal ARVs given</td>
<td>Sd NVP + 4 wks AZT</td>
</tr>
<tr>
<td>No infant combination or short course ARV possible</td>
<td>Sd NVP</td>
</tr>
</tbody>
</table>
Ped ARV working group
General Criteria for dosing recommendations

- Maximum number of tablets at any one dose should be no more than three.
- Minimum dose is one half tablet of products that are scored.
- Limit the number of dosing forms for each single ARV or FDC required for prevention and treatment of HIV in adults and children.
- Harmonize dosing schedules and weight-based dose switching points for all products wherever possible – Facilitate FDC switches.
Ped ARV working group (2)

- Attempted to avoid dosing any single ARV component below 90% of intended delivered dose and not more than 25% above intended dose. Better to give a bit too much than too little.
- For nevirapine, the group sought to avoid dosing below (150mg/m²).
- Each individual drug considered was assessed for a range of tablet strengths using the same tool and principles.
- Focused on most critical agent (narrow therapeutic range) and linked dosing for other agents.
Challenges

- Various drug clearance and distribution pathways have different age dependency – ideal dosing changes vary by age and drug

- Consequences
  - Expected to result in non approved doses.
  - FDCs not limited to same ratio as adult formulation
  - While aimed at achieving a target dose done with consideration that are actually shooting for a target exposure (labeled doses are not always optimal)
  - Some compromise needed
Predicted Nevirapine Exposure in Infants < 12 Months

Best fit Weight Band dosing

Simplified liquid = tablet Weight Band Dosing

Source: Mark Mirochnick, MD
Edmund Capparelli, PharmD
Predicted Exposure if WHO dosing vs FDA

Figure 4. Varying NVP Tablet Strength vs FDA Dosing (Liquid)

- AUC > 48
- Cmin > 3.0
- AUC > 120
Proposed WHO unequal LPV Dosing in 10-14 kg weight band

LPV troughs typically maintained above equal 230mg/m² dosing except at highest weight (14 kg)

- but still within 20% (similar to dosing ~2 hr late)

10kg Child

- 200mg am
- 100mg pm
- 230mg/m² am & pm

14kg Child

- 200mg am
- 100mg pm
- 230mg/m² am & pm

Edmund Capparelli, PharmD
# Revised simplified dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Strength of tab (mg) or liquid mg/ml</th>
<th>Number of tablets or ml by weight band (twice daily)</th>
<th>Strength of adult tab (mg)</th>
<th>Number of tablets by weight band (twice daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Children 6 weeks of age and above</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(0.5 BD is delivered as 1 tablet AM and 0.5 tablets PM and 1.5 BD is delivered as 2 tablets AM and 1 tablet PM)</td>
<td>3-3.9 kg</td>
<td>4-4.9 kg</td>
<td>5-5.6 kg</td>
<td>6-6.9 kg</td>
</tr>
<tr>
<td><strong>Drug</strong></td>
<td>3-3.9 kg</td>
<td>4-4.9 kg</td>
<td>5-5.6 kg</td>
<td>6-6.9 kg</td>
</tr>
<tr>
<td>300-10 mg/ml</td>
<td>6 ml</td>
<td>6 ml</td>
<td>6 ml</td>
<td>6 ml</td>
</tr>
<tr>
<td>AZT</td>
<td>60</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>AZT (new annex E)</td>
<td>300, 10 mg/ml</td>
<td>6 ml</td>
<td>6 ml</td>
<td>6 ml</td>
</tr>
<tr>
<td>AZT:3TC</td>
<td>60/30</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>AZT:3TC/NVP</td>
<td>60/30/50</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ABC</td>
<td>60</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ABC (new annex E)</td>
<td>300, 20 mg/ml</td>
<td>3 ml</td>
<td>3 ml</td>
<td>3 ml</td>
</tr>
<tr>
<td>ABC:3TC</td>
<td>60/30</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ABC:3TC/NVP</td>
<td>60/30/50</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ABC/AZT:3TC</td>
<td>60/60/60</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3TC</td>
<td>30</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3TC (new annex E)</td>
<td>150, 10 mg/ml</td>
<td>3 ml</td>
<td>3 ml</td>
<td>3 ml</td>
</tr>
<tr>
<td>d4T</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>d4T (new annex E)</td>
<td>various 1 mg/ml</td>
<td>6 ml</td>
<td>6 ml</td>
<td>6 ml</td>
</tr>
<tr>
<td>d4T:3TC</td>
<td>6/30</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>d4T:3TC/NVP</td>
<td>6/30/50</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>NVP</td>
<td>50</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>NVP (new annex E)</td>
<td>200, 10 mg/ml</td>
<td>6 ml</td>
<td>5 ml</td>
<td>5 ml</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>100/25</td>
<td>n/r</td>
<td>n/r</td>
<td>n/r</td>
</tr>
<tr>
<td>Lopinavir (new annex E)</td>
<td>80/20 mg/ml</td>
<td>1 ml</td>
<td>1.5 ml</td>
<td>1.5 ml</td>
</tr>
</tbody>
</table>

* 3 tablets BD of 100/25 may be substituted with 2 tablets am and 1 tablet pm of 200/50<br>Note: higher doses of Lopivir may be required when co-administered with enzymes-inducing drugs such as NVP, EFV; fosamprenavir, ritampinidin.
WHO FDC ARV tablet regimen superimposed

Most dose adjustments done in 1st year

Same dosing irrespective of FDC, or same dosing for all three single ARV agents

Adapted from T. NUNN
Other outcomes - on ART

**KIDS ART Linc**
- Probability @ 1 year of death 6.0% or loss-to-follow-up 9.5% & at 2 yrs of 6.9% (95% CI 5.9–8.1) 19.2% (95% CI 17.4–21.1)
- WHO review - 12 months, > 86% alive (72-95.7%) and on ART at 12 months.

**D4T toxicity**
- 36M of ART- 57% of children developed clinical lipodystrophy, requiring D4T substitution (AZT). Aupribul et al Thailand

**Patient Retention**
- Kids ART Linc - risk of LTFU was 9.5%, higher in children with severe clinical status.
  - 6 M 2.6%
  - 12 M 4.9%
  - 24 M 9.9%
- 18–24 months
  - Thailand- 91%
  - Kenya 86%

**Switch/Transition to second line**
- Little data - < 3% per annum
- Chris Duncombe review ongoing ? Higher
Guideline issues still under review

- d4T
- Clinical /CD4 algorithms for infant diagnosis
- Recommendations to support adherence
- Second line regimens for children (preferred as FDC)
- Simple standard approaches to using viral load

Related:
- Infant post partum prophylaxis
- TB/HIV- revised dosing for INH
- Malaria –just reviewed
- Immunisation – measles and yellow fever reviews ongoing
Acknowledgments & resources:

- HIV Care Technical Reference group
- Paediatric ARV dosing working group
- Infant Diagnosis Guideline Group

Meeting report summarising these recommendations
Proceedings of the meeting
2006 guidelines (being updated to reflect above)
Tool to assist in developing dosing recommendations
A programming guide – how to scale up Paed care and treatment: