Neonatal ART regimens

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Outline

• Rationale for neonatal ART initiation
  – Benefits & risks

• Neonatal ART regimens

• Specific ARVs & use in neonates

• National algorithm for neonatal ART

• Future options
Neonatal ART
Rationale

• Can we reduce both the early and late HIV-associated morbidity & mortality by starting ART during the neonatal period?

• Identification of HIV infection by PCR testing at birth rather than at 6 weeks of age

• Preservation of capacity to respond to routine infant vaccines (Penisieroso, PNAS 2009)
• Rapid control of HIV viraemia in infants can reduce size of HIV reservoir (Persaud, 2012)
• Possibility of later structured ART interruption following very early ART initiation (CHER study)?
• (HIV cure agenda...
Early HIV-associated morbidity & mortality

- Children with HIV Early Antiretroviral Therapy Study (CHER), (Violari, NEJM, 2008)
  - HIV PCR testing at 4 weeks of age
  - Randomised to early or deferred ART
  - Median age at ART start in early arm was 7.4 wks
  - Early ART reduced early infant mortality by 76% and HIV progression by 75% compared to ART deferred until clinical or CD4 criteria were met
  - 33% (10/30) deaths occurred in early ART arm

- Early severe HIV disease precedes early antiretroviral therapy in infants: Are we too late? (Innes, JIAS 2014)
  - Cohort of infants from Soweto & Cape Town
  - Median age at ART start 8.4 wks (IQR 7.2-9.7)
  - 62% (250/403) had advanced HIV disease at time of starting ART
  - Each month increase in age at ART initiation increased the odds of advanced HIV disease at ART initiation (OR: 1.69, CI: 1.05-2.71)
Survival by perinatal vs breastfeeding transmission

Mortality risk peaks at 2-3 months of age

CHER study: early ART improves survival & slows disease progression

Bourne et al. AIDS 2009

Figure 3. Probability of Death or a First Event, According to Treatment Group.

Marston et al. Int. J. Epidemiol. 2011

Violari et al. NEJM 2008
HIV PCR testing at birth

• Detection of intrauterine HIV transmission to infant
  – Associated with rapid HIV disease progression
  – Very early (neonatal) ART initiation offers a window of opportunity to prevent or reduce rapid disease progression

• ARV prophylaxis for HIV-exposed neonates
  – Single (NVP) or dual (AZT+NVP) ARV prophylaxis
  – Transition from ARV prophylaxis to ART (SA & US)
  – ART as prophylaxis and treatment if HIV-infected (UK)
Neonatal ART
What are the risks?

• Safety & efficacy of ART in neonatal population
  – PI vs NNRTI-based regimens
  – Uncertain dosing

• Neonatal pharmacokinetics & pharmacodynamics: immature physiological systems (renal, hepatic, GIT)
  – Premature neonates

• Co-morbidities in neonatal period
  – Congenital syphilis, TB, CMV

• Optimal transition from neonatal ARV prophylaxis to neonatal ART?
  – Maternal ART & neonatal ARV prophylaxis also complicates diagnosis in neonate
### Preferred 1st line ART regimens

<table>
<thead>
<tr>
<th>Age group</th>
<th>SA 2015</th>
<th>WHO 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate (&lt;1 mth)</td>
<td>Not included</td>
<td>Not included</td>
</tr>
<tr>
<td>Infant (1-12 mths) &amp; Child (1-3 yrs)</td>
<td>ABC/3TC/LPV/r</td>
<td>ABC/3TC/LPV/r</td>
</tr>
<tr>
<td>Child (&gt;3-10 yrs)</td>
<td>ABC/3TC/EFV</td>
<td>ABC/3TC/EFV</td>
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<tr>
<td>Early adolescent (10-15 yrs)</td>
<td>ABC/3TC/EFV</td>
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<tr>
<td>Late adolescent (15-19 yrs)</td>
<td>TDF/FTC (or 3TC)/EFV</td>
<td>TDF/FTC (or 3TC)/EFV</td>
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<tr>
<td>Adult (&gt;19 yrs)</td>
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</table>
# Antiretroviral Drug Dosing Chart for Children 2013

Compiled by the Child and Adolescent Committee of the SA HIV Clinicians Society in collaboration with the Department of Health

<table>
<thead>
<tr>
<th>Wt (kg)</th>
<th>Target Dose</th>
<th>Available Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3</td>
<td>3.3-9.0</td>
<td>3ml bd</td>
</tr>
<tr>
<td>4.0-4.9</td>
<td>4ml bd</td>
<td>3ml bd</td>
</tr>
<tr>
<td>5.0-5.9</td>
<td>6ml bd</td>
<td>4ml bd</td>
</tr>
<tr>
<td>6.0-6.9</td>
<td>8ml bd</td>
<td>6ml bd</td>
</tr>
<tr>
<td>7.0-7.9</td>
<td>8ml bd</td>
<td>8ml bd</td>
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<tr>
<td>8.0-8.9</td>
<td>10ml bd</td>
<td>10ml bd</td>
</tr>
<tr>
<td>9.0-9.9</td>
<td>12ml bd</td>
<td>12ml bd</td>
</tr>
<tr>
<td>10.0-10.9</td>
<td>15ml bd</td>
<td>15ml bd</td>
</tr>
<tr>
<td>11.0-11.9</td>
<td>20ml bd</td>
<td>20ml bd</td>
</tr>
<tr>
<td>12.0-12.9</td>
<td>25ml bd</td>
<td>25ml bd</td>
</tr>
<tr>
<td>13.0-13.9</td>
<td>30ml bd</td>
<td>30ml bd</td>
</tr>
<tr>
<td>14.0-14.9</td>
<td>35ml bd</td>
<td>35ml bd</td>
</tr>
<tr>
<td>15.0-15.9</td>
<td>40ml bd</td>
<td>40ml bd</td>
</tr>
</tbody>
</table>

Consult with a clinician experienced in paediatric ARV prescribing for neonates (<28 days of age) and infants weighing <3kg.

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### Cotrimoxazole Dose
- 2.5ml od or 1 tab od
- 5ml od or 1 tab od
- 10ml od or 1 tab od

### Multivitamin Dose
- 2.5ml od
- 5ml od
- 10ml od or 1 tab od

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* Avoid LPV/r solution in any full term infant <14 days of age and any premature infant <14 days after their due date of delivery (40 weeks post conception) or obtain expert advice.

# Weight (kg)
- 3.0-4.9
- 5.0-9.9
- 10.0-13.9
- 14.0-25.9
- ≥20

---

* od = once a day
* bd = twice a day
* usually at night

---
Are we able to recommend a safe and effective neonatal ART regimen...?

- “For neonates and for premature infants (until 42 weeks corrected gestational age), PK data are currently inadequate to formulate an effective complete ART regimen. Although dosing is available for zidovudine and lamivudine, data are inadequate for other classes of ART.

- Providers considering treatment of infants <2 weeks or premature infants should contact a pediatric HIV expert for guidance because the decision about whether to treat and what to use will involve weighing the risks and benefits of using unapproved ART dosing, and incorporating case-specific factors such as exposure to ARV prophylaxis.”

Neonatal ART
Regimen considerations

**ABC/3TC/LPV/r**

- **Safety / toxicity**
  - Abacavir
    - Dosing data lacking <3 mths of age
    - Toxicity not dose-dependent in older infants
  - 3TC
    - Dosing data is available
    - Haematological toxicity
  - LPV/r (Kaletra®)
    - Dosing data is available
    - Serious toxicity reports

- **Efficacy**
  - Unknown in neonatal/early infancy period
  - Superior to NVP-based regimens in older children regardless of perinatal NVP exposure (P1060 study)

**AZT/3TC/NVP**

- **Safety / toxicity**
  - AZT
    - Dosing guidelines are available
    - Haematological toxicity
  - 3TC
  - NVP
    - Lack of dosing data for treatment
    - Potential hepatotoxicity

- **Efficacy**
  - NVP-based regimen may be inferior to PI-based regimen particularly in NNRTI-exposed neonates
  - Transitional regimen
Neonatal ART

Specific ARVs: Zidovudine (AZT)


2. US guidelines, 2015

SA weight-band dosing chart from 4 weeks of age and ≥3 kg
Neonatal ART
Specific ARVs: Lamivudine (3TC)

• 2 mg/kg/dose twice daily for first 4 weeks of life

• At 4 weeks of age
  – 4 mg/kg/dose twice daily
  – Weight band dosing chart from 3 kg body weight

• Haematologic toxicity increases when combined AZT/3TC neonatal prophylaxis is used, with increasing numbers of patients requiring treatment discontinuation or blood transfusions
  (Mandelbrot et al. JAMA 2001)
Neonatal ART
Specific ARVs: Nevirapine (NVP)

• Based on PK modeling, an investigational dose of 6 mg/kg administered twice daily for NVP has been proposed for full-term infants diagnosed as infected in the first few days of life.

• Because modeling data included infants up to 1 month and target values were reached using the investigational dose, a single dosing recommendation of 6 mg/kg/BID for the first month of life was chosen by the Panel to prevent repeated dose changing requirements.

• Pharmacokinetics of NVP using the investigational dose will be evaluated as part of an IMPAACT protocol (P1115).
Neonatal ART
Specific ARVs: Lopinavir/ritonavir (Kaletra®)

• Why would we want to use LPV/r as part of a ART regimen in neonates?

  – IMPAACT P1060 study


  – Arm 2: Virological outcomes were superior with LPV/r compared to NVP-based ART regimens in children 2-36 months of age with no prior exposure to NVP (Violari et al. *N Engl J Med*. 2012)
ARV resistance in young children newly diagnosed with HIV infection

- Genotypic resistance testing in 230 newly diagnosed HIV-infected children <2 yrs of age during 2011 in Jhb
  - 67.4% exposed to maternal ± infant PMTCT intervention

- Among PMTCT-exposed children, 56.8% had NNRTI, 14.8% had NRTI, and 1.3% PI mutations

- In children with no recorded PMTCT exposure, 24% had NNRTI, 10% NRTI, and 1.3% PI resistance mutations

- Findings support 1st line PI-based ART in newly diagnosed infants & young children regardless of PMTCT history

Kuhn, 2014
Neonatal ART
Specific ARVs: Lopinavir/ritonavir (Kaletra®)

Dosing Recommendations
Neonatal Dose (<14 Days):
- No data on appropriate dose or safety in this age group. Do not administer to neonates before a post-menstrual age of 42 weeks and a postnatal age of at least 14 days because of potential toxicities.

Special populations—neonates: Lopinavir/ritonavir should not be used in the immediate postnatal period in premature infants because an increased risk of toxicity in premature infants has been reported. These toxicities in premature infants include transient symptomatic adrenal insufficiency, life-threatening bradyarrhythmias and cardiac dysfunction, and lactic acidosis, acute renal failure, central nervous system depression, and respiratory depression. These toxicities may be from the drug itself and/or from the inactive ingredients in the oral solution, including propylene glycol 15.3%, and ethanol 42.4%. Transient asymptomatic elevation in 17-hydroxyprogesterone levels has been reported in term newborns treated at birth with lopinavir/ritonavir.

Neonatal ART

Specific ARVs: Lopinavir/ritonavir (Kaletra®)

- Approved for use in children ≥14 days old in 2008

- 2011, FDA advisory: 10 reported cases of toxicity in neonates, (8/10 premature), 1 death
  - Cardiac toxicity (bradycardia, heart block, cardiomyopathy, cardiac failure), neuromuscular toxicity (hypotonia, altered LOC, abN EEG), acute renal failure, respiratory & GIT complications
  - 8/10 neonates received Kaletra within 2 days of birth, toxicity developed within 1-6 days
  - Doses administered not provided in report
  - Following discontinuation of Kaletra, 6 neonates recovered within 5 days

- Infants <6 wks of age & premature neonates, doses >300mg/m2/dose 12hrly may be required to achieve plasma LPV trough levels (correlated with efficacy) within the recommended range (1-4mcg/ml)

FDA, 2011
Chadwick, 2009, 2011
Holgate, 2012
Neonatal ART
Lopinavir/ritonavir (Kaletra®)

• Clinical case series on use of LPV/r in preterm infants
  (Holgate et al. *Pediatr Infect Dis J* 2012)

  – Eight premature HIV-infected infants

  – Median age at LPV/r-based cART initiation was 27 days

  – Trough values guided dosing: 5 infants required doses above 300 mg/m²

  – No adverse events were noted, but careful monitoring required
Neonatal ART
Lopinavir/ritonavir (Kaletra®)

• Recommended dose from 14 days-12 months of age: 300mg/m²/dose twice daily (US guidelines 2015)

• SA ARV weight-band dosing chart from 4 weeks of age and ≥3 kg body weight
Protocol for initiation of ART in HIV-infected neonates ≥2.5kg at birth

Refer to documents below where numbered in the protocol:
1. Managing Indeterminate HIV PCR test results guideline
2. Counselling model
3. Dosage chart if <28 days of age
4. SA NDOH dosing chart

Birth HIV PCR test

Indeterminate result: Refer to separate guideline

Positive Birth HIV PCR test
Actively trace and link to care

If neonate weighs < 2.5kg or unwell/ TB/ Syphilis: Discuss with Regional level centre

Baseline Assessment for neonate ≥2.5 kg

Clinical review
Bloods: confirmatory HIV PCR, CD4 count/%
FBC/diff, ALT
( Genotype if mother on failing 2nd/3rd line ART)

Ensure mother is in a treatment pathway;
Advice on breastfeeding

Start ART on same day
(if oral feeding is established)
AZT (4mg/kg/dose BD)
3TC (2mg/kg/dose BD)
NVP (6mg/kg/dose BD)

Post-test and initial adherence counselling for mother / caregiver
Review at 1 week of treatment:
Clinical review & counselling
Check blood results

Review at 2 weeks of treatment:
Clinical review & counselling

Review at 1 month of treatment:
Clinical review & counselling
Bloods: FBC / diff
Start co-trimoxazole prophylaxis
Adjust medication
If ≥ 3kg:
- Switch NVP to LPV/r (Kaletra) and AZT to ABC
- Dose ABC, 3TC, LPV/r as per SA NDOH dosing chart
If still < 3kg:
- Switch NVP to LPV/r (Kaletra): 1ml BD
- Dose AZT 12mg/kg/dose BD, 3TC 4mg/kg/dose BD

If still < 3kg: assess failure to thrive; discuss with Paediatrician if questions / concerns

Review monthly until 6 months of treatment:
Adjust medication using dosing chart
Month 6: Do VL, CD4
# ARV drug dosing chart for children <28 days of age and weighing ≥2.5 kg at birth

<table>
<thead>
<tr>
<th>Target dose</th>
<th>Lamivudine (3TC)</th>
<th>Zidovudine (AZT)</th>
<th>Nevirapine (NVP)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2mg/kg/dose</td>
<td>4mg/kg/dose</td>
<td>6mg/kg/dose</td>
</tr>
<tr>
<td></td>
<td>TWICE daily (BD)</td>
<td>TWICE daily (BD)</td>
<td>TWICE daily (BD)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Available formulation</th>
<th>Lamivudine (3TC)</th>
<th>Zidovudine (AZT)</th>
<th>Nevirapine (NVP)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10mg/ml</td>
<td>10mg/ml</td>
<td>10mg/ml</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Dose in ml</th>
<th>Dose in mg</th>
<th>Dose in ml</th>
<th>Dose in mg</th>
<th>Dose in ml</th>
<th>Dose in mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2.5-&lt;3.0</td>
<td>0.6 ml BD</td>
<td>6 mg BD</td>
<td>1.2 ml BD</td>
<td>12 mg BD</td>
<td>1.8 ml BD</td>
<td>18 mg BD</td>
</tr>
<tr>
<td>≥3.0-&lt;3.5</td>
<td>0.7 ml BD</td>
<td>7 mg BD</td>
<td>1.4 ml BD</td>
<td>14 mg BD</td>
<td>2.1 ml BD</td>
<td>21 mg BD</td>
</tr>
<tr>
<td>≥3.5-&lt;4.0</td>
<td>0.8 ml BD</td>
<td>8 mg BD</td>
<td>1.6 ml BD</td>
<td>16 mg BD</td>
<td>2.4 ml BD</td>
<td>24 mg BD</td>
</tr>
<tr>
<td>≥4.0-&lt;4.5</td>
<td>0.9 ml BD</td>
<td>9 mg BD</td>
<td>1.8 ml BD</td>
<td>18 mg BD</td>
<td>2.7 ml BD</td>
<td>27 mg BD</td>
</tr>
<tr>
<td>≥4.5-&lt;5.5</td>
<td>1.0 ml BD</td>
<td>10 mg BD</td>
<td>2.0 ml BD</td>
<td>20 mg BD</td>
<td>3.0 ml BD</td>
<td>30 mg BD</td>
</tr>
<tr>
<td>≥5.5-&lt;6.5</td>
<td>1.2 ml BD</td>
<td>12 mg BD</td>
<td>2.4 ml BD</td>
<td>24 mg BD</td>
<td>3.6 ml BD</td>
<td>36 mg BD</td>
</tr>
</tbody>
</table>

Caregivers who will be administering ARV medication to the child must be supplied with a syringe (1ml or 2ml) for each of the 3 ARVs and shown how to prepare and administer the correct dose. If possible, bottles and syringes should be colour coded with stickers and a sticker of the relevant colour used to mark the correct dose on the syringe.
<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>3TC</th>
<th></th>
<th></th>
<th></th>
<th>3TC</th>
<th></th>
<th></th>
<th></th>
<th>AZT</th>
<th></th>
<th></th>
<th></th>
<th>NVP</th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Dose in ml</td>
<td>Dose in mg</td>
<td>Dose range: 90-125% of target dose</td>
<td></td>
<td>Dose in ml</td>
<td>Dose in mg</td>
<td>Dose range: 90-125% of target dose</td>
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<td>Dose in ml</td>
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<td></td>
<td>Dose in ml</td>
<td>Dose in mg</td>
<td>Dose range: 90-125% of target dose</td>
</tr>
<tr>
<td>≥2.5&lt;3.0</td>
<td>0.6 ml BD</td>
<td>6 mg BD</td>
<td>2.0-2.4</td>
<td>100-120</td>
<td>1.2 ml BD</td>
<td>12 mg BD</td>
<td>4.0-4.8</td>
<td>100-120</td>
<td>1.8 ml BD</td>
<td>18 mg BD</td>
<td>6.0-7.2</td>
<td>100-120</td>
<td>6mg/kg TWICE daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3.0&lt;3.5</td>
<td>0.7 ml BD</td>
<td>7 mg BD</td>
<td>2.0-2.3</td>
<td>100-117</td>
<td>1.4 ml BD</td>
<td>14 mg BD</td>
<td>4.0-4.7</td>
<td>100-117</td>
<td>2.1 ml BD</td>
<td>21 mg BD</td>
<td>6.0-7.0</td>
<td>100-117</td>
<td>6mg/kg TWICE daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3.5&lt;4.0</td>
<td>0.8 ml BD</td>
<td>8 mg BD</td>
<td>2.0-2.3</td>
<td>100-114</td>
<td>1.6 ml BD</td>
<td>16 mg BD</td>
<td>4.0-4.6</td>
<td>100-114</td>
<td>2.4 ml BD</td>
<td>24 mg BD</td>
<td>6.0-6.9</td>
<td>100-114</td>
<td>6mg/kg TWICE daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥4.0&lt;4.5</td>
<td>0.9 ml BD</td>
<td>9 mg BD</td>
<td>2.0-2.3</td>
<td>100-113</td>
<td>1.8 ml BD</td>
<td>18 mg BD</td>
<td>4.0-4.5</td>
<td>100-113</td>
<td>2.7 ml BD</td>
<td>27 mg BD</td>
<td>6.0-6.8</td>
<td>100-113</td>
<td>6mg/kg TWICE daily</td>
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</tr>
<tr>
<td>≥4.5&lt;5.0</td>
<td>1.0 ml BD</td>
<td>10 mg BD</td>
<td>2.0-2.2</td>
<td>100-111</td>
<td>2.0 ml BD</td>
<td>20 mg BD</td>
<td>4.0-4.4</td>
<td>100-111</td>
<td>3.0 ml BD</td>
<td>30 mg BD</td>
<td>6.0-6.7</td>
<td>100-111</td>
<td>6mg/kg TWICE daily</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Neonatal ART
Are there other ARV options?

• Nucleoside reverse transcriptase inhibitors

  – Stavudine (d4T)
    • Dosing 0.5mg/kg/dose twice daily from 0-<14 days, 1 mg/kg/dose twice daily ≥14 days
    • Little short-term toxicity
    • Liquid formulation requires refrigeration
    • Opened & dispersed capsule contents achieves similar plasma exposure to oral suspension (Innes, 2011)
    • Potentially a useful option if develop AZT toxicity

  – Tenofovir
    • Not approved <2yrs of age
Neonatal ART
Are there other ARV options?

• Non-Nucleoside reverse transcriptase inhibitors
  – Efavirenz
    • Not approved for use in neonates and not generally recommended <3 yrs of age
    • Likely to be less effective than PI-based regimen especially in NNRTI-exposed infants
  – Etravirine & rilpivirine are not approved or recommended for neonates

• Protease inhibitors
  – No other PIs approved or recommended in neonates
  – Darunavir oral suspension (100mg/ml)
    • not registered in SA, Sec 21/compassionate use access
    • not approved for use <3yrs of age/<10kg
Neonatal ART
Are there other ARV options?

• Integrase inhibitors
  – Raltegravir
    • Established role in 3\textsuperscript{rd} line ART regimens
    • Rapid reduction in maternal viral load during pregnancy
    • Crosses placenta, neonatal metabolism variable
    • Emerging role in PMTCT
    • Oral suspension (100mg powder for suspension)
      – Not registered in SA, Sec 21/compassionate use access
      – Not yet approved <4 weeks of age / <3 kg

  – Dolutegravir
Neonatal ART
What about premature neonates?

- Complete lack of safety / dosing data (other than AZT)

- Defer ART initiation until tolerating oral feeds, renal / hepatic / full blood count acceptable
  - No intravenous ART regimen available (only AZT has IV formulation)

- Establish gestational age (early pregnancy ultrasound scan, Ballard score)

- AZT / 3TC / NVP
  - Dosing
    - AZT according to gestational age
    - 3TC 2 mg/kg/dose twice daily
    - NVP 6 mg/kg/dose twice daily

- Continue NVP-based regimen until 42 weeks corrected gestational age (& 2 wks postnatal age) before switching NVP to LPV/r
- May consider switching to LPV/r earlier if renal & liver function is normal, monitoring for toxicity is available and with careful dose calculation (initial dose: 300mg/m²/dose twice daily), monitor trough LPV levels if possible
- Consider substitution of AZT with d4T or ABC if AZT toxicity develops
Resistance to ARV drugs in children

• Transmitted (primary)
  – Mother failing 1\textsuperscript{st} / 2\textsuperscript{nd} / 3\textsuperscript{rd} line ART
    • Antenatally
    • During breastfeeding

• Acquired
  – During PMTCT (NVP ± AZT for 6-12wks)
  – During ART (child failing 1\textsuperscript{st} / 2\textsuperscript{nd} / 3\textsuperscript{rd} line ART)

• NRTI, NNRTI, PI, Integrase inhibitors
HIV-infected neonates
Role of baseline (pre-ART) HIV resistance testing (genotyping)?

• ARV resistance doesn’t currently impact 1st line ART regimen choice in neonates/infants
  – LPV/r-based regimen (initial NVP-based regimen)
  – Transmitted LPV resistance?
    • Likely to be very uncommon at present
    • No effective neonatal/infant ART regimen currently
    • Likely role of integrase inhibitors (dolutegravir)

• Infants <2yrs of age who are newly diagnosed as HIV-positive if their mothers were exposed to PI-based ART during pregnancy or breastfeeding (W Cape guidelines, 2015)
Neonatal HIV case series: challenges in diagnosis & management
Mowbray Maternity Hospital, Cape Town (unpublished, Pillay 2014)

HIV infected neonates (9/117 neonates PCR tested within 48hrs of birth)

<table>
<thead>
<tr>
<th>Case</th>
<th>GA (wks)</th>
<th>Birth weight (g)</th>
<th>Co-morbidities</th>
<th>Baseline CD4 cells/mm³ / (%)</th>
<th>Baseline VL copies/ml (log₁₀)</th>
<th>Age (days) at ART initiation</th>
<th>ARV regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>1740</td>
<td>Congenital syphilis</td>
<td>1026 (22.4%)</td>
<td>16801 (4.23)</td>
<td>25</td>
<td>AZT, 3TC, KLT</td>
</tr>
<tr>
<td>2</td>
<td>36</td>
<td>2310</td>
<td>Congenital CMV</td>
<td>807 (21.41%)</td>
<td>636456 (5.8)</td>
<td>14</td>
<td>AZT, 3TC, KLT</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>1920</td>
<td>None</td>
<td>440 (43%)</td>
<td>9292 (3.92)</td>
<td>4</td>
<td>AZT, 3TC, KLT</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>1380</td>
<td>None</td>
<td>1933 (50%)</td>
<td>6701098 (6.07)</td>
<td>13</td>
<td>AZT, 3TC, NVP</td>
</tr>
<tr>
<td>5</td>
<td>32</td>
<td>1260</td>
<td>None</td>
<td>1933 (50%)</td>
<td>2962535 (6.47)</td>
<td>13</td>
<td>AZT, 3TC, NVP</td>
</tr>
<tr>
<td>6</td>
<td>38</td>
<td>3520</td>
<td>None</td>
<td>3776 (51.88%)</td>
<td>314312 (5.5)</td>
<td>35</td>
<td>ABC, 3TC, KLT</td>
</tr>
<tr>
<td>7</td>
<td>38</td>
<td>3260</td>
<td>× None</td>
<td>1744 (49.06%)</td>
<td>385653 (5.49)</td>
<td>30</td>
<td>AZT, 3TC, KLT</td>
</tr>
<tr>
<td>8</td>
<td>38</td>
<td>3280</td>
<td>× None</td>
<td>942 (39.11%)</td>
<td>343 (2.54)</td>
<td>None</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>29</td>
<td>1245</td>
<td>× None</td>
<td>3880 (52.65%)</td>
<td>1146 (3.06)</td>
<td>None</td>
<td>-</td>
</tr>
<tr>
<td>Median</td>
<td>36</td>
<td>1920</td>
<td></td>
<td><strong>1774 (49.06%)</strong></td>
<td><strong>314312 (5.5)</strong></td>
<td><strong>14</strong></td>
<td></td>
</tr>
</tbody>
</table>
HIV-infected neonates

Deaths

• Three neonates died:
  
  – Two before initiating cART
    • Lethal congenital cardiac anomaly (day 39)
    • Septicaemia / birth weight 1245g (day 13)
  
  – One on cART
    • ART initiated only on day 30
    • Repeated ICU admissions
    • Fungal pneumonia and disseminated Cytomegalovirus infection
Neonatal ART Studies

- International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) studies:
  - P1097: Raltegravir pharmacokinetics & safety in neonates
  - P1106: Pharmacokinetic characteristics of antiretrovirals (ABC, AZT, 3TC, NVP, LPV/r) and tuberculosis medicines (INH, RIF) in low birth weight infants (<2.5 kg)
    - Post-exposure prophylaxis and treatment
    - Weight bands <1400g; 1400-1800g; 1800-2499g
  - P1110: A phase 1 trial to evaluate the safety and pharmacokinetics of raltegravir in HIV-1-exposed neonates (>37 weeks gestation, ≥2 kg) at high risk of acquiring HIV-1 infection
  - P1115: Very early (<48 hrs) intensive treatment (AZT/3TC/NVP/LPV/r) of HIV-infected infants (>34 weeks gestation) to achieve HIV remission: A phase I/II proof of concept study
Neonatal ART

Gaps

• Safety / toxicity
  – Choice of drugs to include in ART regimen
  – Term & preterm neonates

• Efficacy (short & longer term)
  – NNRTI vs PI regimen
  – Role of integrase inhibitors (prophylaxis & treatment)
  – Neonates with LPV-resistant HIV
    • Darunavir approved from 3 yrs of age
    • Raltegravir approved from 4 wks of age
# PRACTICAL ADVICE ON ADMINISTRATION OF ARV DRUGS

<table>
<thead>
<tr>
<th>Abacavir (ABC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caregivers must be warned about potential severe progressive hypersensitivity reaction which may include fever, rash, gastrointestinal &amp; respiratory symptoms. If hypersensitivity occurs it is usually during first six weeks of therapy, symptoms tend to worsen in the hours immediately after the dose and worsen with each subsequent dose. Caregivers or patients should discuss symptoms early with the clinician rather than terminating therapy without consultation. ABC should be stopped permanently if hypersensitivity reaction occurs. Avoid combining ABC and NVP in a regimen and avoid concurrent initiation of ABC and co-trimoxazole. Tablets must not be chewed, divided or crushed; swallow whole with or without food.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Efavirenz (EFV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV is not approved for children &lt;3years/10kg. Tablets must not be chewed, divided or crushed; swallow whole with or without food e.g. yoghurt or banana. Capsules may be opened and powder contents dispersed in water or mixed with a small amount of food (e.g. yoghurt) to disguise peppery taste and immediately ingested. Food, especially high-fat meals, increases absorption. Best given at bedtime to reduce CNS side-effects, especially during first 2 weeks. Consider drug-drug interactions.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Didanosine (ddI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 2 tablets of appropriate strength must be used at any one time for adequate buffering. Tablets may be chewed or crushed and dispersed in 30ml water and immediately ingested. Enteric coated (EC) capsules (250mg) are available for once daily use in children ≥25kg. It is recommended to administer ddI on an empty stomach at least 30 minutes before or 2 hours after meals.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lamivudine (3TC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well tolerated, no food restrictions, oral solution may be stored at room temperature. Tablets are scored and can be easily divided; may be crushed and mixed with a small amount of water or food and immediately ingested.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ritonavir (RTV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only recommended use at present is as booster for lopinavir/ritonavir when co-administered with rifampicin-containing TB treatment. Ritonavir boosting dose is not less than 0.75 x lopinavir/ritonavir dose. Should be taken with food. May be stored at room temperature, limited shelf life of 6 months. May need to use techniques described for Kaletra® to improve tolerance of bitter taste.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stavudine (d4T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well tolerated &amp; palatable but oral solution requires refrigeration after reconstitution. Discard after 30 days. Capsules may be opened and powder contents dispersed in water (stable in solution for 24 hours) or mixed with a small amount of food (e.g. yoghurt). See dosing chart for further details. Consider early drug substitution if toxicity e.g. lipoatrophy develops.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nevirapine (NVP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once-daily dosing during the first 2 weeks of treatment reduces frequency of rash. If a mild rash occurs during the induction period, continue once daily dosing and only escalate dose to twice daily once the rash has subsided and the dose is well tolerated. NVP should be permanently discontinued and not restarted in children who develop severe rash especially if accompanied by fever, blistering or mucosal ulceration. No food restrictions. Tablets can be crushed and mixed with a small amount of water or food and immediately ingested. Avoid NVP if rifampicin is being co-administered. Consider drug-drug interactions.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lopinavir/ritonavir (Kaletra® solution; Aluvia® tablets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose is calculated on lopinavir component. Solution should be taken with food as increases absorption. Solution should be refrigerated however can be stored at room temperature up to 25°C for 6 weeks. May need techniques to increase tolerance &amp; palatability: coat mouth with peanut butter, dull taste buds with ice, follow dose with sweet foods. Tablets must not be chewed, divided or crushed; swallow whole with or without food. Many drug interactions due to RTV inhibition of cytochrome p450.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Zidovudine (AZT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No food restrictions and oral solution may be stored at room temperature. Capsules may be opened and powder contents dispersed in water or mixed with a small amount of food (e.g. yoghurt) and immediately ingested. Currently available tablets are not scored. Use with caution in children with anaemia due to potential for bone marrow suppression.</td>
</tr>
</tbody>
</table>