Too small, too soon: antiretroviral prophylaxis and treatment in preterm and low birth weight infants

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Full Term
Full Term

34 wks
Antiretrovirals used in neonates for:

Prophylaxis

Empiric HIV Therapy

HIV Therapy
Low birth weight (LBW) defined as birth weight below 2500 gm
  • Global prevalence 15.5% of births for ~20 million infants each year
  • 96.5% in developing countries

Two etiologies of LBW:
  • Preterm (PT) delivery - birth before 37 completed weeks of gestation
    – 41% of LBW infants born PT
  • Intrauterine growth restriction (IUGR)
    – 59% of LBW infants are born at term and are small for gestational age (SGA)
Maternal HIV infection contributes to LBW and PTD

- In meta-analysis of 52 cohort studies, maternal HIV infection increased risk of LBW by 73% and PTD by 56%

Estimated that ~20% of infants born to women living with HIV are LBW


https://onlinelibrary.wiley.com/toc/17582652/18/7S6
Pharmacology

Pharmacokinetics
- "What the body does to the drug"
  - Drug Disposition
    - Absorption
    - Distribution
    - Metabolism
    - Elimination

Pharmacodynamics
- "What the drug does to the body"
  - Desired effects - efficacy
  - Undesired effects - toxicity
How is pharmacology different in neonates?

Pharmacokinetics

• **Absorption**: Differences in GI tract function, diet, formulations
• **Distribution**: Changes in body composition/size, plasma proteins
• **Metabolism/Elimination**: Changes in activity of drug metabolism and elimination pathways

Pharmacodynamics

• Is efficacy of ARV’s the same? – immune system development, susceptibility to infection
• Unique neonatal safety issues – hyperbilirubinemia, anemia, growth and development, neonatal specific physiology/diseases
Therapeutic Misadventures in the Nursery

- Penicillin/sulfisoxazole and kernicterus
- Chloramphenicol and grey baby syndrome
- Oxygen and retinopathy/blindness
- Benzyl alcohol and metabolic acidosis, encephalopathy, death
- E-ferol and hepatic toxicity, death
- Dexamethasone and cerebral palsy, developmental delay
- Doxapram and developmental delay
# Antiretroviral Drugs with Formulation and Safety/Dosing Information in Term Infants

<table>
<thead>
<tr>
<th>NRTI</th>
<th>NNRTI</th>
<th>Protease Inhibitors</th>
<th>Entry/Fusion Inhibitors</th>
<th>Integrase Inhibitors</th>
<th>Boosters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>Efavirenz</td>
<td>Atazanavir</td>
<td>Enfuvirtide</td>
<td>Raltegravir</td>
<td>Cobicistat</td>
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<tr>
<td>Didanosine</td>
<td>Nevirapine</td>
<td>Darunavir</td>
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<td>Elvitegravir</td>
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<td>Emtricitabine</td>
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<td>Lopinavir</td>
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<td>Nelfinavir</td>
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<tr>
<td>Tenofovir (TAF)</td>
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<td>Saquinavir</td>
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<tr>
<td>Zidovudine</td>
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<td>Tipranavir</td>
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NRTI: Reverse Transcriptase Inhibitors
NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitors
Protease Inhibitors
Entry/Fusion Inhibitors
Integrase Inhibitors
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**Antiretroviral Drugs with Formulation and Safety/Dosing Information in LBW/PT Infants**
Development of Bilirubin Metabolism and ZDV Clearance


# ZDV Dosing in Premature Infants

<table>
<thead>
<tr>
<th>Gestational Age (Weeks)</th>
<th>Initial Oral Dose Twice Daily Dosing</th>
<th>Continuation Oral Dose Twice Daily Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥35 weeks</td>
<td>Birth to age 4 weeks: 4mg/kg/dose</td>
<td>Age &gt; 4 weeks: 12 mg/kg/dose</td>
</tr>
<tr>
<td>≥30 to &lt;35 weeks</td>
<td>Birth to age 2 weeks: 2 mg/kg/dose</td>
<td>Age &gt; 6-8 weeks: 12 mg/kg/dose</td>
</tr>
<tr>
<td></td>
<td>Age 2 weeks to 6-8 weeks: 3mg/kg/dose</td>
<td></td>
</tr>
<tr>
<td>&lt;30 weeks</td>
<td>Birth to age 4 weeks: 2 mg/kg/dose</td>
<td>Age &gt; 8-10 weeks: 12 mg/kg/dose</td>
</tr>
<tr>
<td></td>
<td>Age 4 weeks to 8-10 weeks: 3 mg/kg/dose</td>
<td></td>
</tr>
</tbody>
</table>

Lamivudine Clearance in Neonates

- Neonatal lamivudine dosing:
  - <4 weeks: 2 mg/kg bid
  - >4 weeks: 4 mg/kg bid

- Data on premature infants limited to a few infants born after gestational age 34 weeks

23 infants with median (range) gest age 36 (28-37) weeks and wt 2100 g (1028-3460)
NVP dosing: 2 mg/kg if < 2000g, 6 mg if >2000g

IMPAACT P1106

• Phase IV prospective PK and safety study of ARV and TB drugs in LBW infants
• Opportunistic study design – all infant dosing by clinician
  • PK visits at Entry and Weeks 4, 6, 10, 16, and 24
• 2 South African sites: FAMCRU - Cape Town; PHRU – Johannesburg
• Enrolled 91 infants from August 2015 - March 2018 with median (Q1-Q3) gest age 34 (32-36) weeks and birth weight 1860 (1525-2250)
• PK data are available for NVP, LPV/r
• Assays pending for ABC, 3TC, ZDV, TMP-SMX and INH
<table>
<thead>
<tr>
<th>Expected Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apnea</td>
</tr>
<tr>
<td>Neonatal abstinence syndrome</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Neurologic compromise (including HIE)</td>
</tr>
<tr>
<td>Congenital abnormalities</td>
</tr>
<tr>
<td>Neutropenia</td>
</tr>
<tr>
<td>Congenital Heart disease (not PDA)</td>
</tr>
<tr>
<td>Patent Ductus Arteriosus</td>
</tr>
<tr>
<td>Electrolyte or metabolic disorder</td>
</tr>
<tr>
<td>Persistent Pulmonary Hypertension</td>
</tr>
<tr>
<td>GI dysfunction (including NEC)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Respiratory insufficiency</td>
</tr>
<tr>
<td>Hypotension</td>
</tr>
<tr>
<td>Retinopathy of prematurity</td>
</tr>
<tr>
<td>Intravascular hemorrhage</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Jaundice</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
</tbody>
</table>
# IMPAACT P1106 EXPECTED EVENT REPORTING WORKSHEET FOR NEONATOLOGIST

**INSTRUCTIONS: FOR NEONATOLOGISTS:**

For each of the expected events in low birth weight infants as listed in Protocol Appendix IV, either note if Normal or Not Evaluated or circle grade for each evaluated event that was identified in participant at the time of the visit (i.e. snapshot approach). Record details of event and any interventions provided to infant under "Additional Comments" column. The objective is to provide enough information within each row for the DATA GROUP to be able to abstract and report into protocol database.

**INSTRUCTIONS: FOR DATA GROUP:**

Abstract information documented from this form onto TGW0004 - IMPAACT P1106 Expected Event Reporting form. Consult with neonatologist on reporting conventions to ensure that enough information is provided to allow data to be abstracted onto Expected Event Reporting form.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Grading Criteria per Protocol Appendix IV Table for Grading Expected Adverse Events (Either check box if Normal or Not Evaluated or circle grade for evaluated event.)</th>
<th>Grade 4 Potentially Life-Threatening</th>
<th>Additional Comments (Complete if needed)</th>
</tr>
</thead>
</table>
| Apnea*            | □ Normal  
□ Not Evaluated  
*Apnea spell defined as apnea event >20s or associated with bradycardia, hypoxia or cyanosis  
6<6 spells* per day or nasal cannula for apnea  
12 or more spells* per day or nasal continuous positive airway pressure (NCPAP) for apnea  
Requires intubation for apnea | Requires packed red cell transfusion, no clinical signs  
Requires packed red cell transfusion, clinical signs of shock |                                       |
| Anemia            | □ Normal  
□ Not Evaluated  
Hgb 8-10 g/dL  
Hgb ≥ 8 g/dL  
Requires packed red cell transfusion, no clinical signs  
Requires packed red cell transfusion, clinical signs of shock |                                   |                                       |
| Congenital Anomalies | □ Normal  
□ Not Evaluated  
Minor (no impairment of function)  
Minor (no impairment of function), future treatment may be needed  
Major (impairment of function), no immediate treatment needed  
Major (impairment of function) immediate treatment needed |                                   |                                       |
P1106: PK of NVP in LBW Neonates (n=56)

2 mg/kg daily for first 2 weeks of life, then 4 mg/kg daily

NVP concentrations - 5%, 95% --- and 50%
NVP Trough Concentration by Post Natal Age and CYP2B6 Metabolism Phenotype
Lopinavir/Ritonavir Oral Solution in Neonates

- LPV/RTV Oral Solution: 80 mg/mL lopinavir and 20 mg/mL ritonavir in 42% ethanol and 15.3% propylene glycol
- 10 infants reported to FDA with serious toxicities
  - 7 female, 3 male
  - 8 preterm with mean gest age 31 wks (range: 28-34 wks)
    - Mean weight (n=6): 1512 g (range: 990-2200 g)
- Clinical Outcomes:
  - Death-1, Life-threatening-2, Hospitalized-4
- Reported events:
  - Cardiac: 4 Bradycardia, 3 Complete AV Block, 5 Heart failure
  - CNS: 1 Hypotonia, 1 Abnormal EEG, 1 CNS Depression
  - Respiratory: 2 Resp failure, 1 Dyspnea/wheezing
  - Renal: 6 Renal failure, 4 Hyperkalemia
  - Metabolic: 2 Hyperlactatemia, 1 Acidosis
- FDA recommendation – do not use prior to age 2 weeks or 42 weeks PMA

Boxwell, et al. Poster #708, CROI 2011
P1106: PK/Safety of LPV/r in neonates (n=23)

LPV/r solution at 300/75 mg/m² twice daily

- LPV/r trough concentrations (C₀)
  - low at 2 weeks
  - similar to adults from 6 weeks

- 13/23 (57%) started LPV/r before 42 weeks PMA
  - range 33.9 - 41.9 weeks

- No toxicity noted

Raltegravir

- First HIV integrase strand transfer inhibitor to be licensed (2007)
- Licensed in US for use in neonates in 2017
- Metabolized via conjugation with glucuronide by UGT1A1, same UGT isoenzyme that metabolizes bilirubin
- Competes with bilirubin for albumin binding sites
In Vitro Study of Effect of Raltegravir on Bilirubin Binding

### Draft WHO PAWG ARV Dosing Recommendations for Neonates

<table>
<thead>
<tr>
<th>Drug</th>
<th>Strength of oral liquid</th>
<th>2-3 kg</th>
<th>3-4 kg</th>
<th>4-5 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AM</td>
<td>PM</td>
<td>AM</td>
</tr>
<tr>
<td>AZT</td>
<td>10 mg/mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1.5 mL</td>
</tr>
<tr>
<td>NVP</td>
<td>10 mg/mL</td>
<td>1.5 mL</td>
<td>1.5 mL</td>
<td>2 mL</td>
</tr>
<tr>
<td>3TC</td>
<td>10 mg/mL</td>
<td>0.5 mL</td>
<td>0.5 mL</td>
<td>0.8 mL</td>
</tr>
<tr>
<td>LPV/r</td>
<td>80/20 mg/mL</td>
<td>0.6 mL</td>
<td>0.6 mL</td>
<td>0.8 mL</td>
</tr>
<tr>
<td>RAL</td>
<td>100 mg sachet (10 mg/mL)</td>
<td>&lt;1 week</td>
<td>0.4 mL (once daily)</td>
<td>0.5 mL (once daily)</td>
</tr>
<tr>
<td></td>
<td>&gt;1 week</td>
<td>0.8 mL</td>
<td>0.8 mL</td>
<td>1 mL</td>
</tr>
</tbody>
</table>
Take Home Points

• To use drugs safely in LBW/PT infants, need to understand the developmental pharmacology (PK and PD) of individual drugs in this population

• Currently have data to allow ARV dosing recommendations in LBW/PT infants for ZDV, 3TC (>34 weeks PMA), NVP (prophylaxis) and LPV/r (>34 weeks PMA)

• Should have LBW/PT PK/safety data soon from P1106 for ABC, 3TC, TMP-SMX, INH

• Study of RAL PK/safety in LBW/PT neonates under development

• Studies of PK/safety in term neonates of MVC is underway and of DTG is under development