Pediatric ARV Working Group
Dosing Recommendations
Overall Goals

• To develop pediatric weight band dosing for ARVs that would simplify dosing and produce therapeutic drug exposure

• Recommend dosing strengths for manufacturers for individual agents and FDCs
Guiding Principles

• 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.
General Criteria

- 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.
Challenge

- 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 a achieving a target dose done with consideration that are actually shooting for a target exposure (labeled doses are not always optimal)
- Some compromising needed
Sizing Issues and Harmonization

- Although FDA approved dosing is often weight based, CL and exposure (AUC) correlates more closely with BSA –
- True for drugs that are dosed based on weight
- Focused on most critical agent (narrow therapeutic range) and linked dosing for other agents
Accepted higher dosing for children < 3 years based on PK:
Nevirapine, Lamivudine, Stavudine, Abacavir, Lopinavir.
Approach to Challenge

• In FDC priority placed on achieving target NVP doses due to correlation with Cmin (>3) and treatment success.
• FDCs dosing established first to harmonize mg doses between FDCs and non-FDC.
  – The doses for individual components should be the same.
• Established BSA based targets for all drugs
• Quadratic BSA estimator from Weight
Weight Bands

- 3-3.9kg*
- 4-4.9kg*
- 5-5.9 kg
- 6-9.9 kg
- 10-13.9kg
- 14-19.9kg
- 20-24.9kg

*some differences based on age
Dose Assessments

- Developed Excel Template to provide visual guidance of proposed tablet strength and dose weight bands – (Tony Nunn)
- Additional assessment performed applying recommended to existing PK data for NVP from CHAPAS, PACTG-US, IMPAACT-Thailand. (Observed * WTBND/Actual)
- Monte Carlo simulations on population model
<table>
<thead>
<tr>
<th>Drug</th>
<th>Strength of Child Tab (mg)</th>
<th>Number of Tablets by Weight Band (Twice Daily)</th>
<th>5-5.9 kg</th>
<th>6-9.9 kg</th>
<th>10-13.9 kg</th>
<th>14-19.9 kg</th>
<th>20-24.9 kg</th>
<th>Adult</th>
<th>25-34.9 kg</th>
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<td>2</td>
<td>2.5</td>
<td>3</td>
<td>300</td>
<td>1</td>
</tr>
<tr>
<td>AZT/3TC</td>
<td>60/30</td>
<td></td>
<td>1</td>
<td>1.5</td>
<td>2</td>
<td>2.5</td>
<td>3</td>
<td>300/150</td>
<td>1</td>
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<tr>
<td>AZT/3TC/NVP</td>
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<td>1</td>
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<td>2</td>
<td>2.5</td>
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<td>300/150/200</td>
<td>1</td>
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<tr>
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<td>2</td>
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<td>3</td>
<td>300</td>
<td>1</td>
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<td>60/30</td>
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<td>300/150</td>
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</tr>
<tr>
<td>ABC/AZT/3TC</td>
<td>60/60/30</td>
<td></td>
<td>1</td>
<td>1.5</td>
<td>2</td>
<td>2.5</td>
<td>3</td>
<td>300/300/150</td>
<td>1</td>
</tr>
<tr>
<td>3TC</td>
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<td>1.5</td>
<td>2</td>
<td>2.5</td>
<td>3</td>
<td>150</td>
<td>1</td>
</tr>
<tr>
<td>d4T</td>
<td>6</td>
<td></td>
<td>1</td>
<td>1.5</td>
<td>2</td>
<td>2.5</td>
<td>3</td>
<td>30</td>
<td>1</td>
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<tr>
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<td>1.5</td>
<td>2</td>
<td>2.5</td>
<td>3</td>
<td>30/150</td>
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<td></td>
<td>1</td>
<td>1.5</td>
<td>2</td>
<td>2.5</td>
<td>3</td>
<td>30/150/200</td>
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<tr>
<td>NVP</td>
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<td>1.5</td>
<td>2</td>
<td>2.5</td>
<td>3</td>
<td>200</td>
<td>1</td>
</tr>
</tbody>
</table>
Predicted Exposure if WHO dosing vs FDA

Figure 4. Varying NVP Tablet Strength vs FDA Dosing (Liquid)
NVP MC Exposure by Age Group

WHO 2007 Dosing

NVP AUC (mcg*h/mL)

Age Groups

Percentiles

- 75th
- 50th
- 25th
- 5th
- Adult Ave.
# Dose Tables (<6kg)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Strength of Child Tab (mg)</th>
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<th>3-3.9 kg</th>
<th>4-4.9 kg</th>
<th>5-5.9 kg</th>
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</thead>
<tbody>
<tr>
<td>AZT</td>
<td>60</td>
<td></td>
<td>1*</td>
<td>1*</td>
<td>1</td>
</tr>
<tr>
<td>AZT/3TC</td>
<td>60/30</td>
<td></td>
<td>1*</td>
<td>1*</td>
<td>1</td>
</tr>
<tr>
<td>AZT/3TC/NVP</td>
<td>60/30/50</td>
<td></td>
<td>1*</td>
<td>1*</td>
<td>1</td>
</tr>
<tr>
<td>ABC</td>
<td>60</td>
<td></td>
<td>0.5</td>
<td>0.75</td>
<td>1</td>
</tr>
<tr>
<td>ABC/3TC</td>
<td>60/30</td>
<td></td>
<td>0.5</td>
<td>0.75</td>
<td>1</td>
</tr>
<tr>
<td>ABC/AZT/3TC</td>
<td>60/60/30</td>
<td></td>
<td>0.5</td>
<td>0.75</td>
<td>1</td>
</tr>
<tr>
<td>3TC</td>
<td>30</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>d4T</td>
<td>6</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>d4T/3TC</td>
<td>6/30</td>
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</tr>
<tr>
<td>d4T/3TC/NVP</td>
<td>6/30/50</td>
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<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>NVP</td>
<td>50</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

* Except in the infant < 6m of age where 3-3.9 kg 0.5/0.5 and 4-4.9 kg 1/0.5 is recommended.
Future Plans

• Approval of simple tables
• New drugs
• Population modeling for NVP, 3TC and d4T
• Evaluate each ARV and incorporate new data
## Dosing Tables – LPV/RTV

<table>
<thead>
<tr>
<th>Drug</th>
<th>Strength of Child Tab (mg)</th>
<th>Number of Tablets by Weight Band (Twice Daily)</th>
<th>Adult Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5-5.9 kg</td>
<td>6-6.9 kg</td>
</tr>
<tr>
<td>Lop/Rit</td>
<td>100/25</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Rit (boost)</td>
<td>25</td>
<td>0.75</td>
<td>1</td>
</tr>
</tbody>
</table>
WHO Weight Band Dosing for LPV
d4T

CHAPAS d4T CL/F by Age

CHAPAS d4T AUC by Age
d4T

d4T Exposure from CHAPAS

AUC (mcg*h/mL)

Dose Formulation

Adult Mean Target 1.28
3TC

CHAPAS 3TC AUC by Age
3TC

3TC Exposure from CHAPAS

AUC (mcg*hr/mL)

10th
25th
50th
75th
90th

Adult Mean Target 4.7

30mg
Dose Formulation