

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

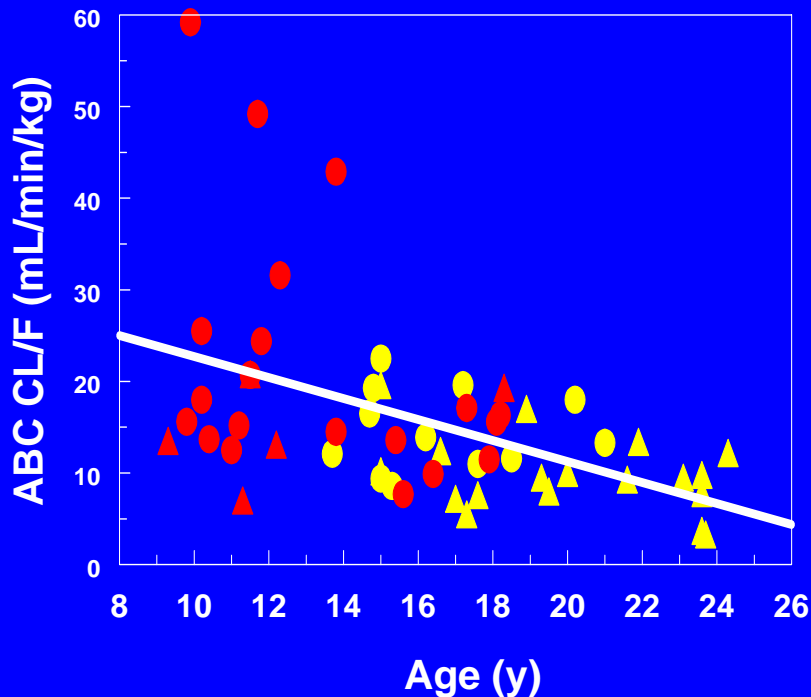
- Various drug clearance and distribution pathways have different age dependency – ideal dosing changes vary by age and drug
- Consequences
 - Expected to result in non approved doses.
 - FDCs not limited to same ratio as adult formulation
 - While aimed at achieving a target dose done with consideration that are actually shooting for a target exposure (labeled doses are not always optimal)
 - Some compromising needed

Sizing Issues and Harmonization

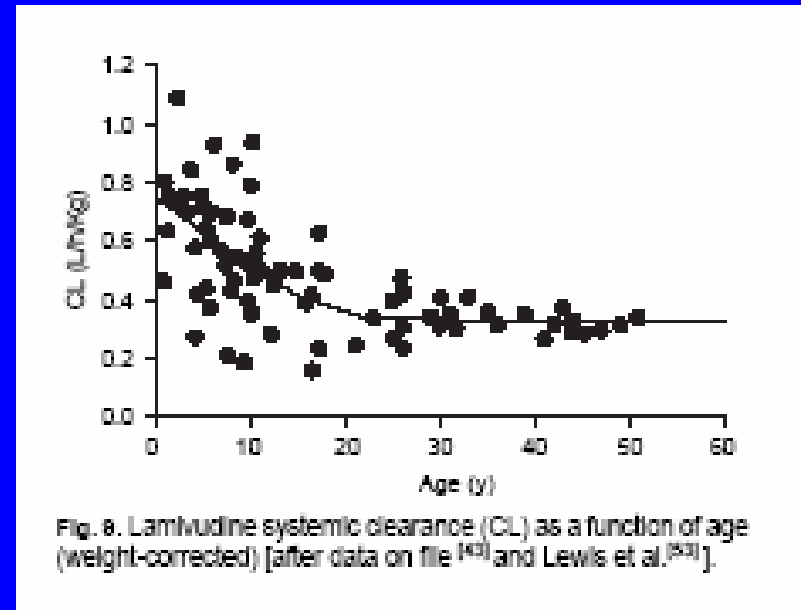
- Although FDA approved dosing is often weight based, CL and exposure (AUC) correlates more closely with BSA –
- True for drugs that are dosed based on weight
- Focused on most critical agent (narrow therapeutic range) and linked dosing for other agents

NRTIs with Weight Based Dosing

ABC Age Effects



3TC Age Effects



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

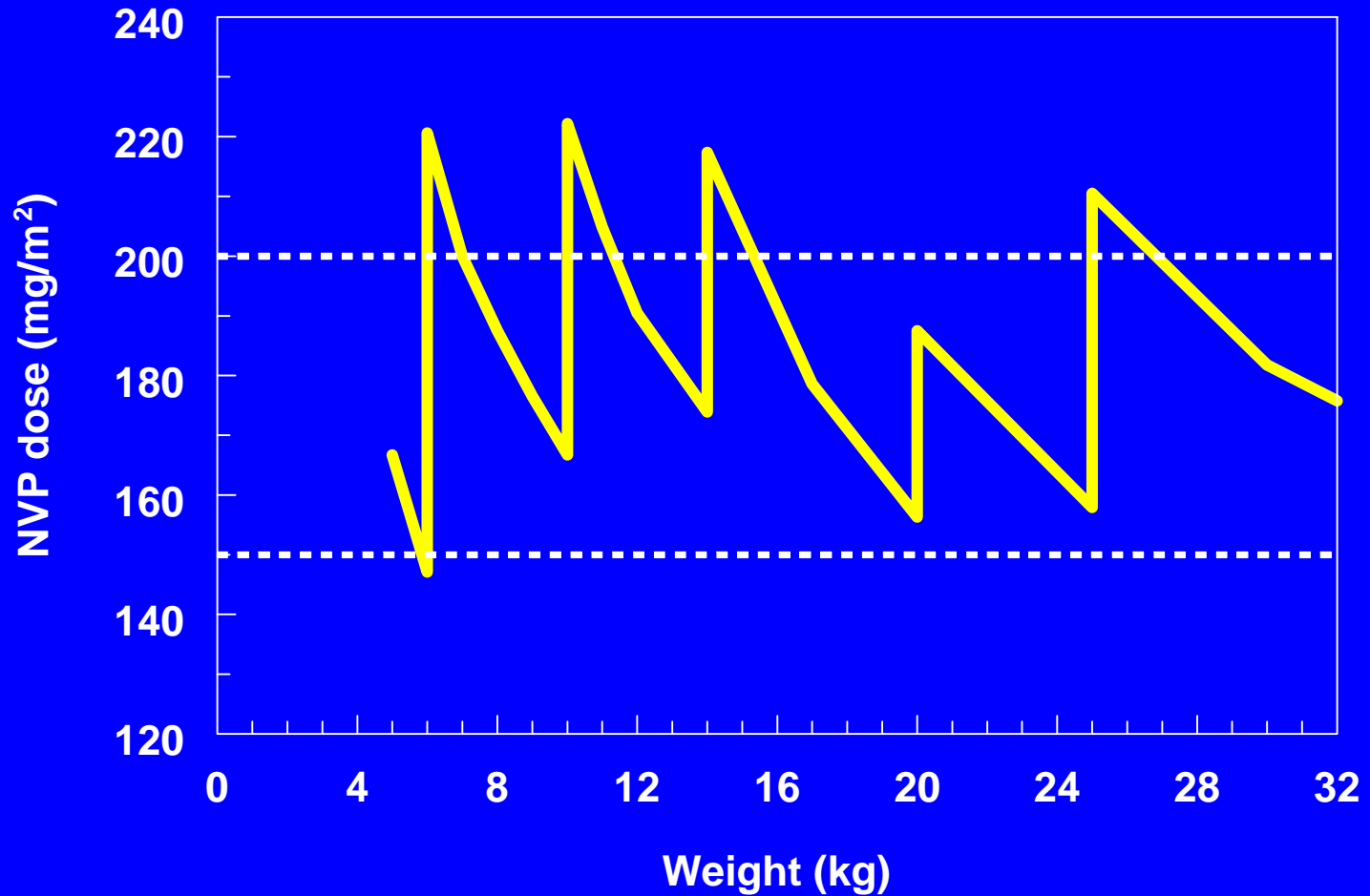
Dose Assessments

- 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

Dose Tables - NRTIs & NVP

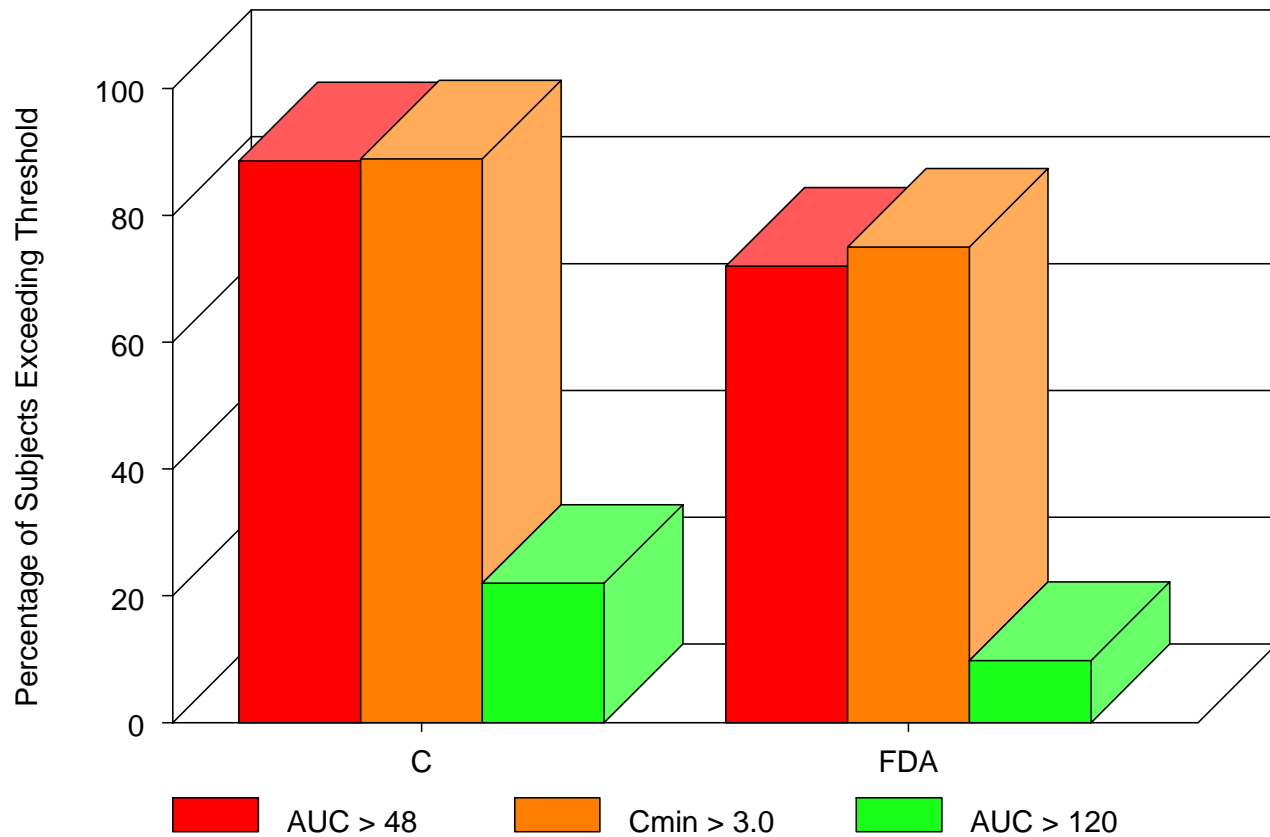
| Drug | Strength of Child Tab (mg) | Number of Tablets by Weight Band (Twice Daily) | | | | | | |
|-------------|----------------------------|--|----------|------------|------------|------------|-------------|------------|
| | | 5-5.9 kg | 6-9.9 kg | 10-13.9 kg | 14-19.9 kg | 20-24.9 kg | Adult | 25-34.9 kg |
| AZT | 60 | 1 | 1.5 | 2 | 2.5 | 3 | 300 | 1 |
| AZT/3TC | 60/30 | 1 | 1.5 | 2 | 2.5 | 3 | 300/150 | 1 |
| AZT/3TC/NVP | 60/30/50 | 1 | 1.5 | 2 | 2.5 | 3 | 300/150/200 | 1 |
| ABC | 60 | 1 | 1.5 | 2 | 2.5 | 3 | 300 | 1 |
| ABC/3TC | 60/30 | 1 | 1.5 | 2 | 2.5 | 3 | 300/150 | 1 |
| ABC/AZT/3TC | 60/60/30 | 1 | 1.5 | 2 | 2.5 | 3 | 300/300/150 | 1 |
| 3TC | 30 | 1 | 1.5 | 2 | 2.5 | 3 | 150 | 1 |
| d4T | 6 | 1 | 1.5 | 2 | 2.5 | 3 | 30 | 1 |
| d4T/3TC | 6/30 | 1 | 1.5 | 2 | 2.5 | 3 | 30/150 | 1 |
| d4T/3TC/NVP | 6/30/50 | 1 | 1.5 | 2 | 2.5 | 3 | 30/150/200 | 1 |
| NVP | 50 | 1 | 1.5 | 2 | 2.5 | 3 | 200 | 1 |

WHO Weight Band Dosing

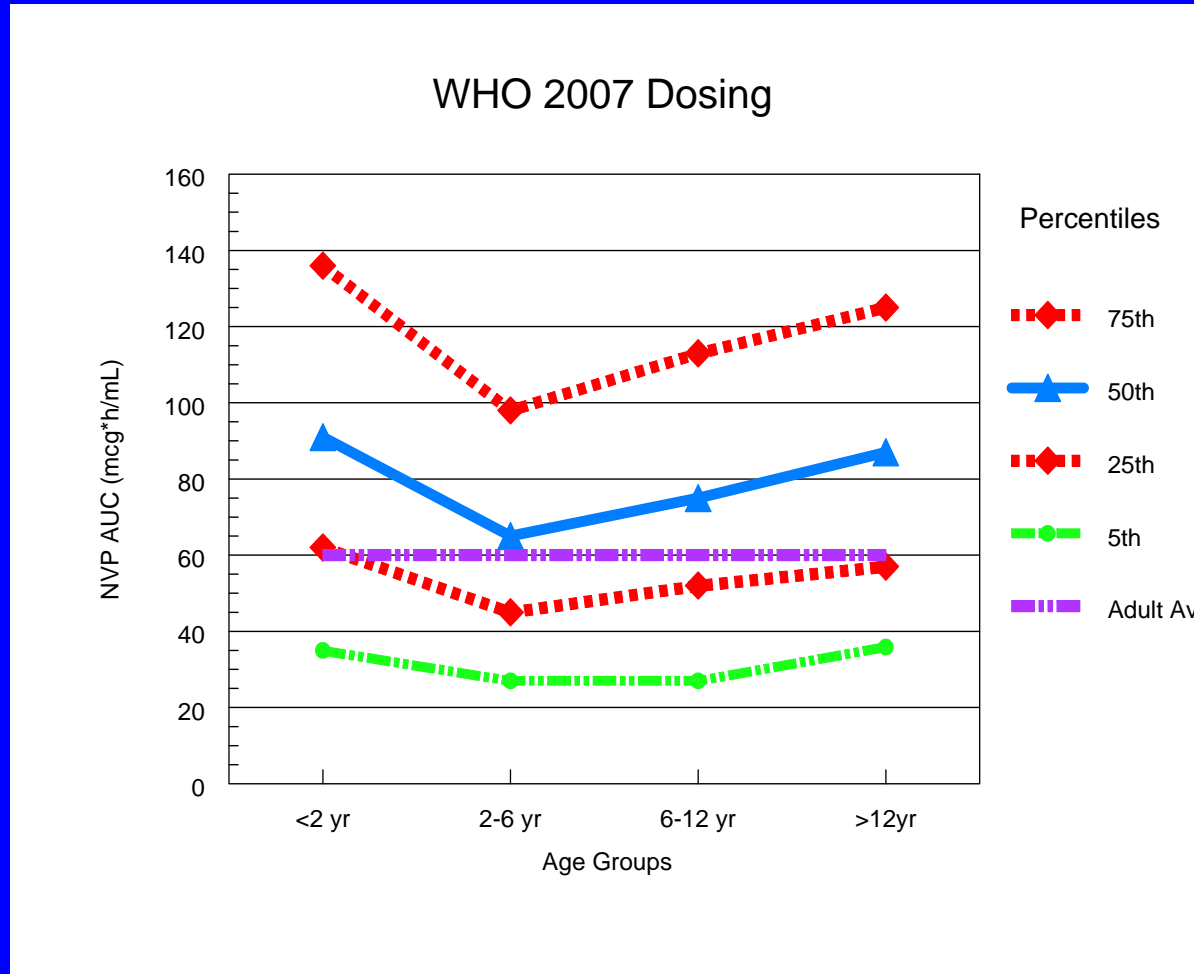


Predicted Exposure if WHO dosing vs FDA

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



NVP MC Exposure by Age Group

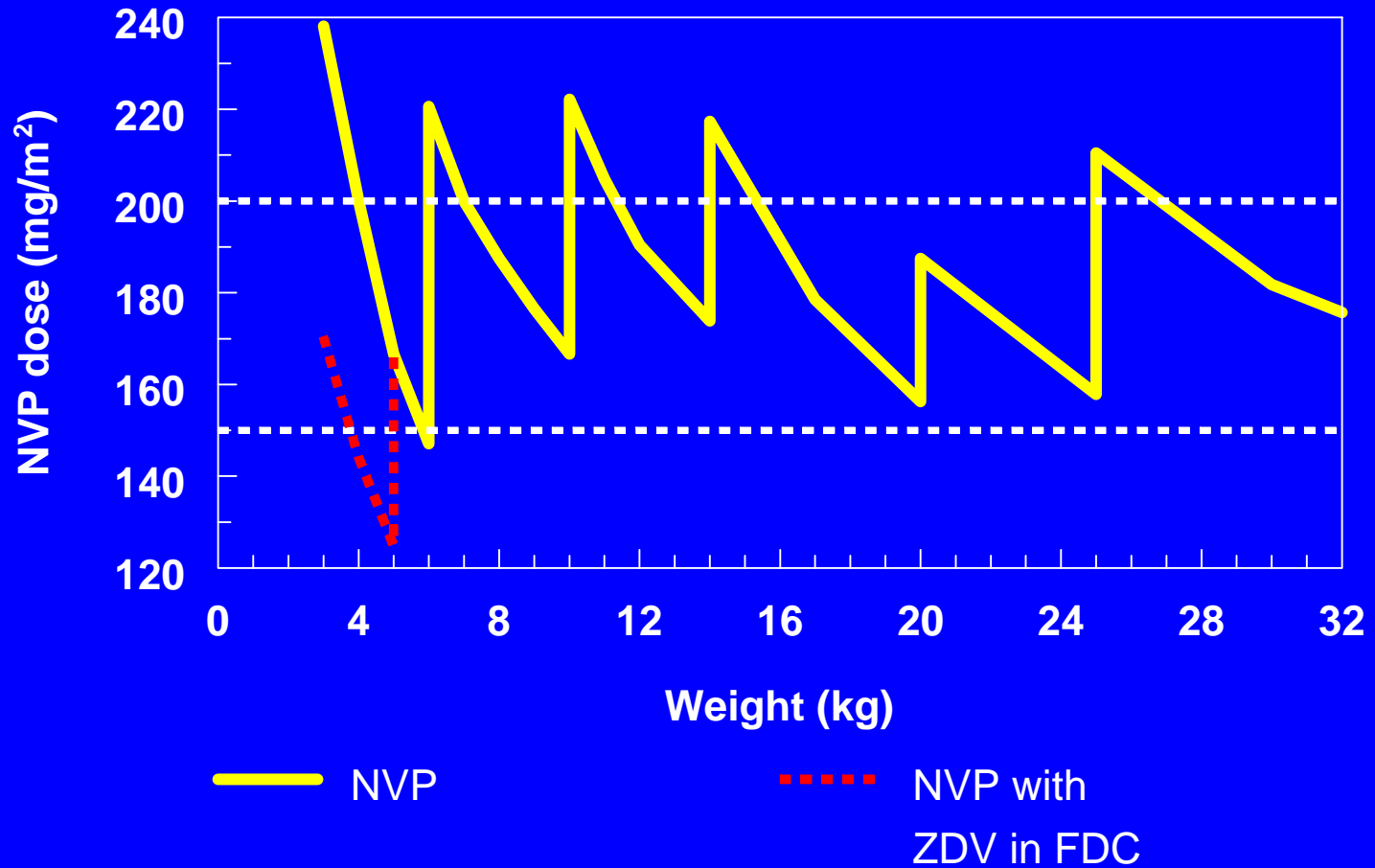


Dose Tables (<6kg)

| Drug | Strength of Child Tab (mg) | Number of Tablets by Weight Band (Twice Daily) | | |
|-------------|----------------------------|--|----------|----------|
| | | 3-3.9 kg | 4-4.9 kg | 5-5.9 kg |
| AZT | 60 | 1* | 1* | 1 |
| AZT/3TC | 60/30 | 1* | 1* | 1 |
| AZT/3TC/NVP | 60/30/50 | 1* | 1* | 1 |
| ABC | 60 | 0.5 | 0.75 | 1 |
| ABC/3TC | 60/30 | 0.5 | 0.75 | 1 |
| ABC/AZT/3TC | 60/60/30 | 0.5 | 0.75 | 1 |
| 3TC | 30 | 1 | 1 | 1 |
| d4T | 6 | 1 | 1 | 1 |
| d4T/3TC | 6/30 | 1 | 1 | 1 |
| d4T/3TC/NVP | 6/30/50 | 1 | 1 | 1 |
| NVP | 50 | 1 | 1 | 1 |

* 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.

WHO Weight Band Dosing



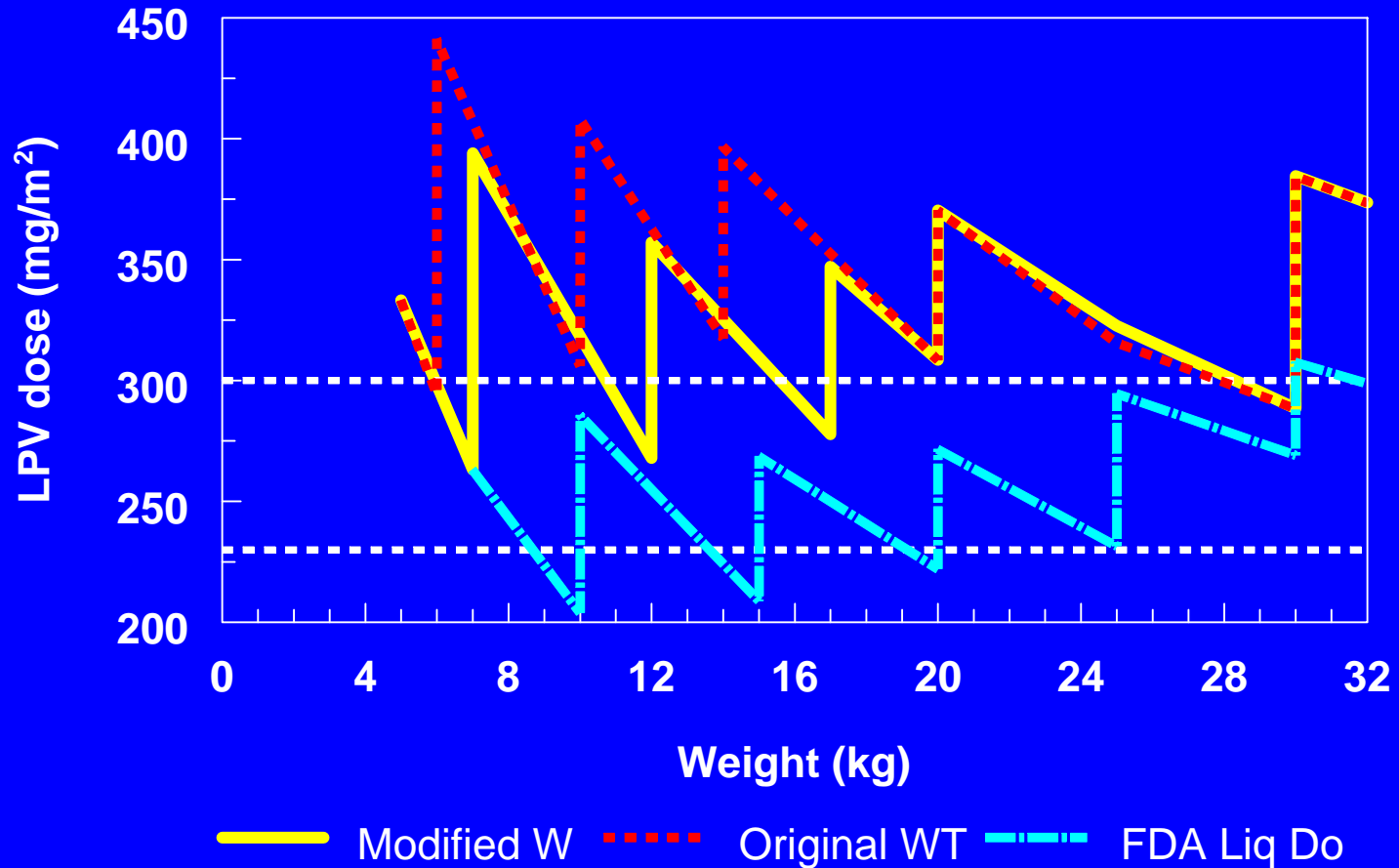
Future Plans

- Approval of simple tables
- New drugs
- Population modeling for NVP, 3TC and d4T
- Evaluate each ARV and incorporate new data

Dosing Tables – LPV/RTV

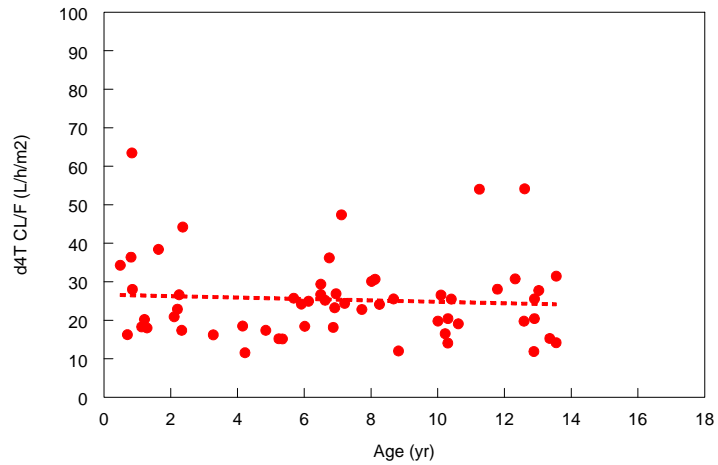
| Drug | Strength of Child Tab (mg) | Number of Tablets by Weight Band (Twice Daily) | | | | | | | | | | |
|-------------|----------------------------|--|----------|----------|-----------|------------|------------|------------|------------|----------------|------------|------------|
| | | 5-5.9 kg | 6-6.9 kg | 7-8.9 kg | 9-11.9 kg | 12-13.9 kg | 14-16.9 kg | 17-19.9 kg | 20-24.9 kg | Adult Strength | 25-29.9 kg | 30-34.9 kg |
| Lop/Rit | 100/25 | 1 | 1 | 1.5 | 1.5 | 2 | 2 | 2.5 | 3 | 200/50 | 1.5 | 2 |
| Rit (boost) | 25 | 0.75 | 1 | 1 | 1.5 | 1.5 | 2 | 2 | 2.5 | 100 | 0.75 | 1 |

WHO Weight Band Dosing for LPV

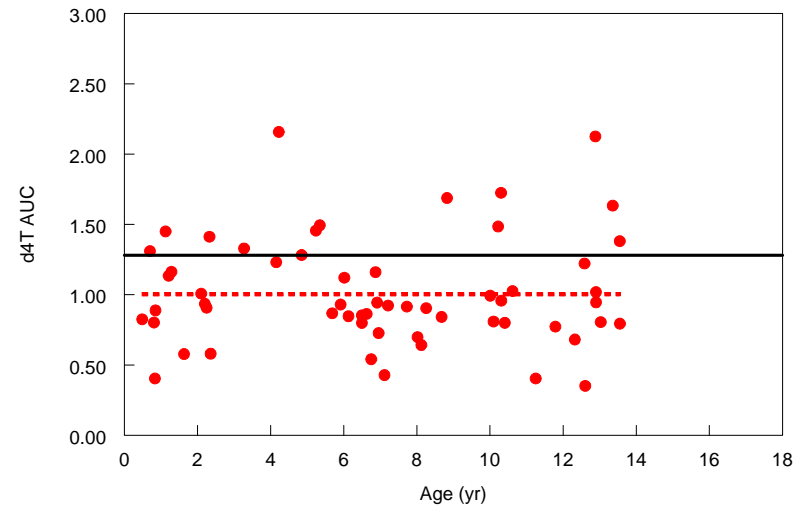


d4T

CHAPAS d4T CL/F by Age

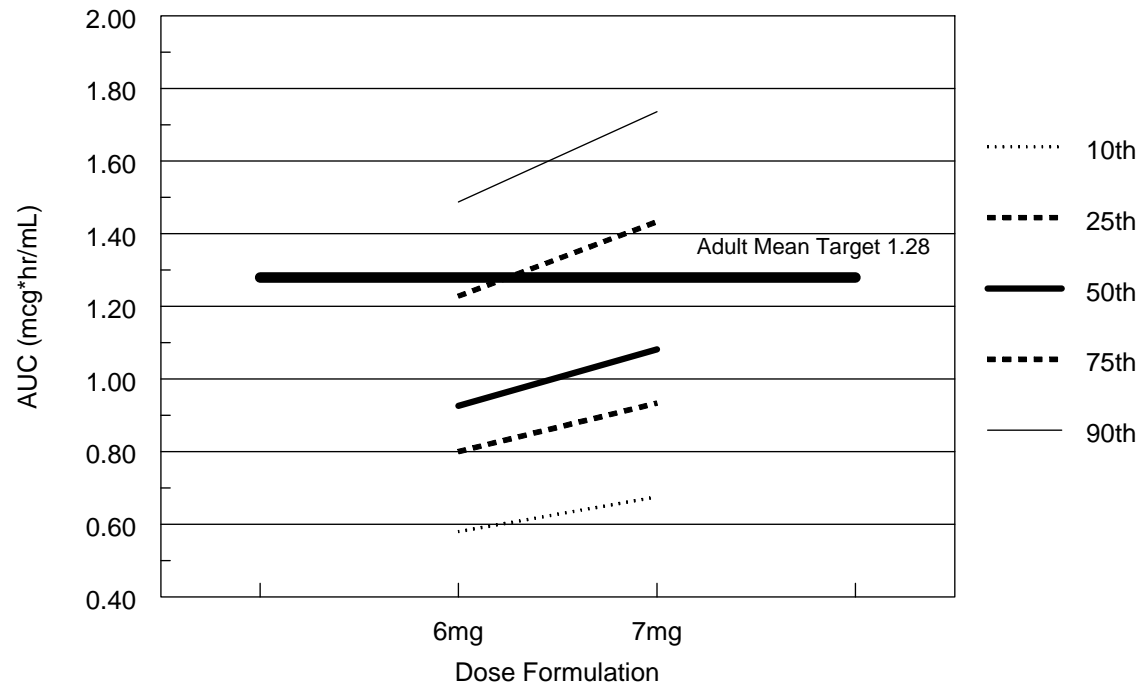


CHAPAS d4T AUC by Age



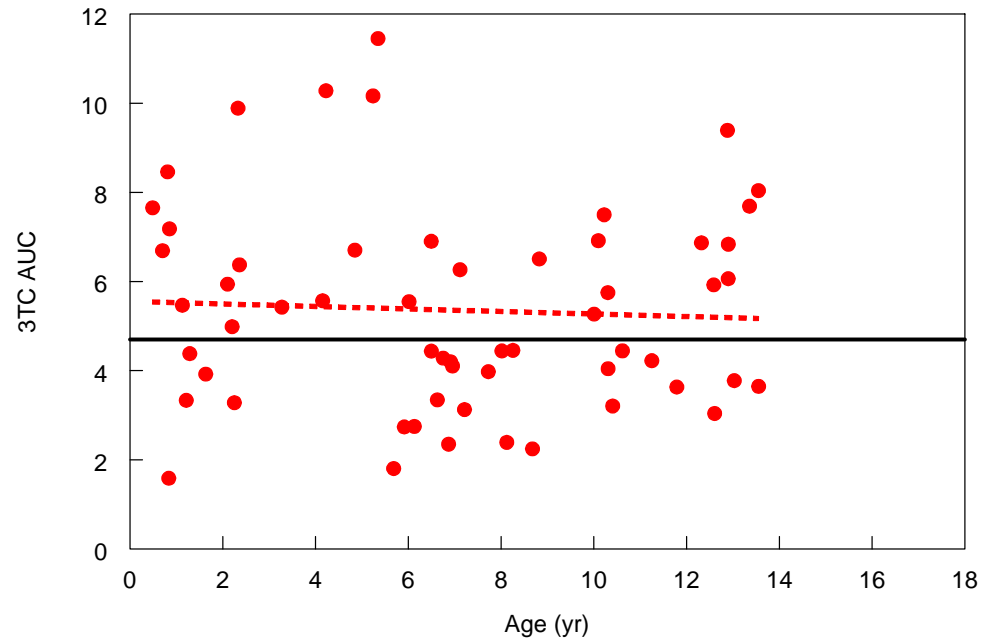
d4T

d4T Exposure from CHAPAS



3TC

CHAPAS 3TC AUC by Age



3TC

3TC Exposure from CHAPAS

