Adaptive Dosing For Studies of Rare Diseases

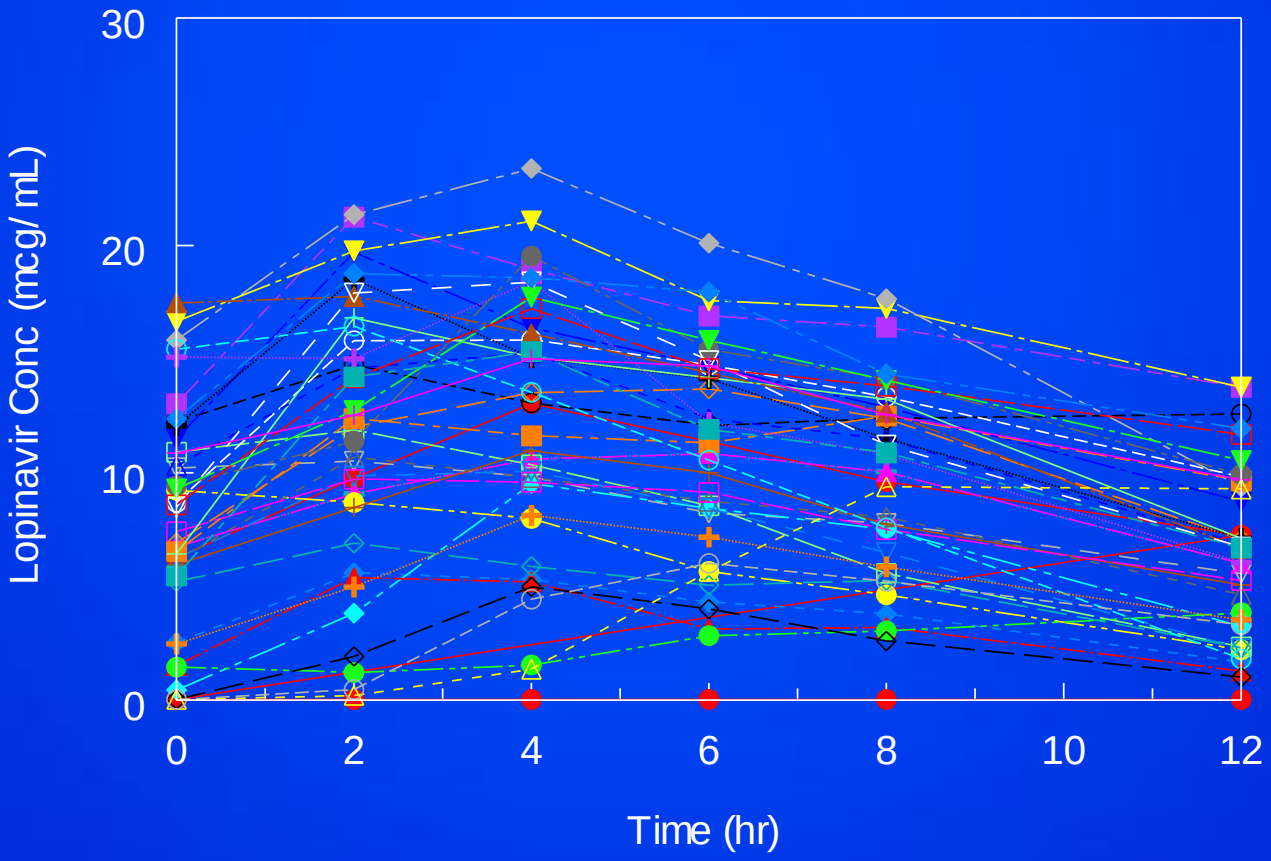
Edmund V. Capparelli, Pharm.D.

UC San Diego, Pediatric Pharmacology and Drug Discovery

School of Medicine and Skaggs School of Pharmacy and Pharmaceutical Sciences

Pharmacokinetic Variability Can Lead to Large Sample Size Requirements

IMPAACT Study P1083



Rationale for Adaptive Dosing in Rare Diseases

- Can determine safety, PK and dosing for target exposure rapidly using few subjects
- Facilitates enrollment with enhanced study subject participation benefit
- Can combine with other study design features to enhanced studies in rare disease

Requirements of Adaptive Dosing in Pediatric Clinical Trials

- Inter-subject variability > intra-subject variability
- Knowledge of exposure-response relationships or mechanistic biomarker – need a priori target and rules
- Laboratory infrastructure for GLP and CAP/CLIA.
- Rapid data capture and clean-up
- Can result in a range of doses studied –
  - Implications: Potential bias for clinical response and toxicity at the typical effective dose.

Drugs for Adaptive Dosing in Clinical Trials

- Narrow Therapeutic Index (TI) Oncologic Agents
- Biologics with Target Mediated Drug Disposition
- Drugs for Inborn Errors of Metabolism
- Immunosuppressants
  - Dosing based on PK and PD
- Pediatric Antiretrovirals

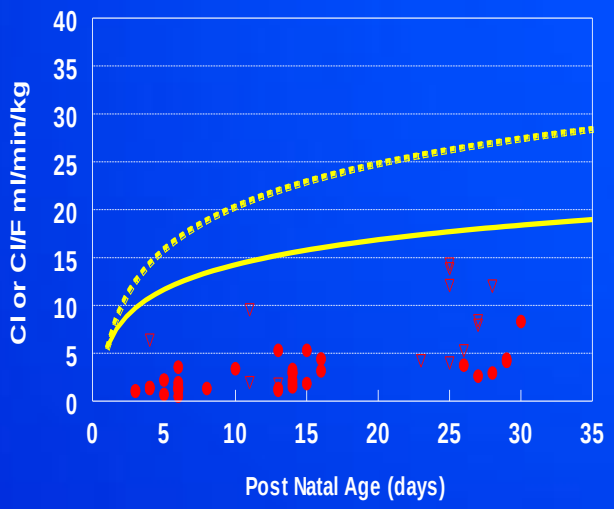
Example of Adaptive Dosing ZDV for HIV Prophylaxis in Premature Infants – PACTG 331

- Combined pre- and post-natal ZDV (6 weeks) is successful in preventing vertical transmission of HIV infection
- Premature infants are at an increased risk for HIV transmission and possibly greater toxicity from ZDV
- ZDV Dosage: Term dosing 2 mg/kg PO q6 hr
- Preterm used 1.5mg/kg (IV or PO) q 12 hr until ~2 weeks of life. Increased to 2mg/kg q 8 hrs from 2-6 weeks of life
- 2-3 Pop PK Samples Collected at Week 1 (DOL 4-6) Week 2 (DOL 12-16) and Week 4 (DOL 28-32)
- ZDV dosage adjusted to maintain:
  - 0.5-2hr Conc > 0.5 uM and
  - Cpre < 3.0 uM

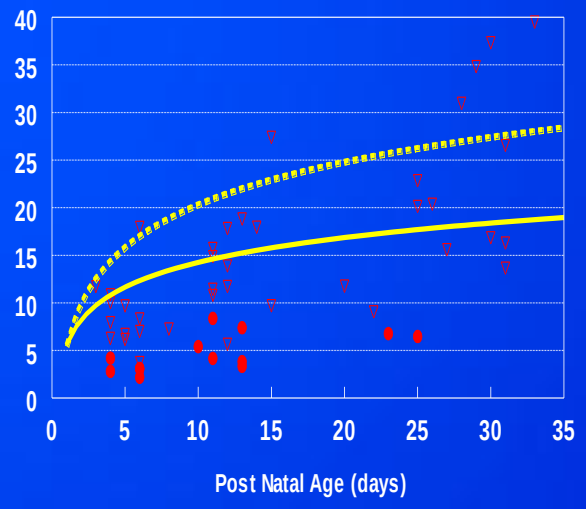
PACTG 331 Results

- **40 subjects enrolled from 20 sites over 2 years -** represents approximately 50% of expected HIV exposed preterm babies within PACTG Study Sites.
- **PK-Adaptive Dosing**
  - **9 Subjects required dose modifications to keep ZDV troughs < 3 µM (8 < 30wks GA / 1 ≥ 30 wks GA)**
- **Dose Recommendations – GA specific**

GA < 30 weeks at birth



GA < 30 weeks at birth



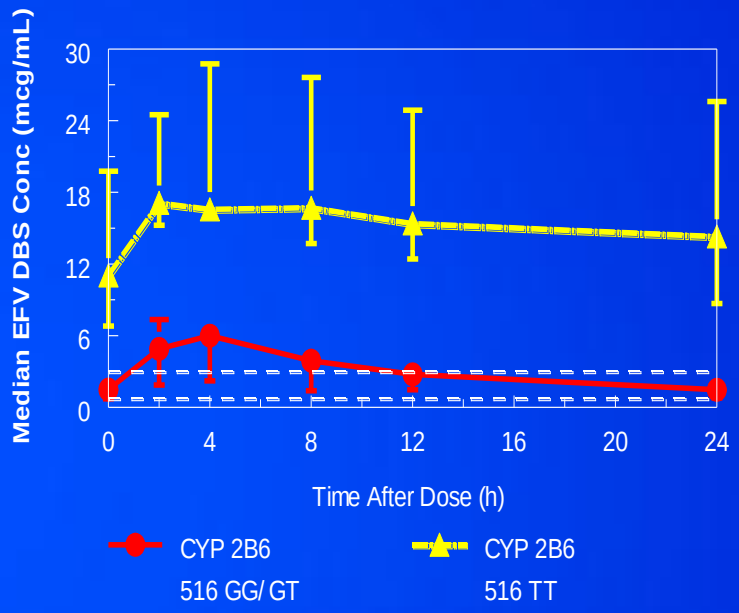
E Capparelli et al J Peds 2003

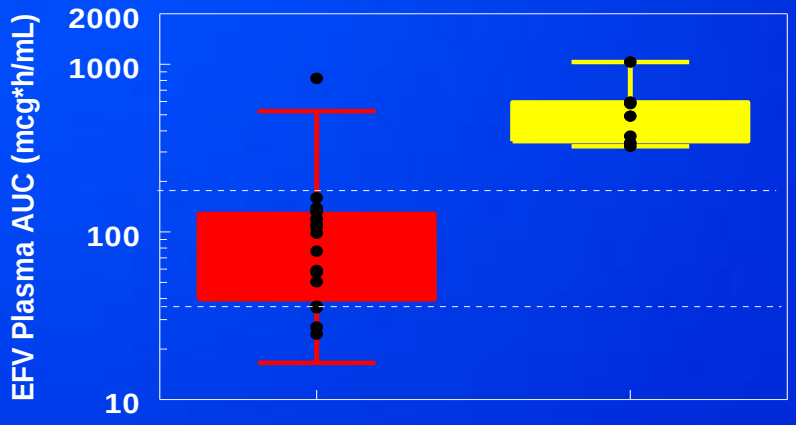
Mini-Cohort Trial Design and Use of Adaptive Dosing Based on Real Time PK

- 2 Stage design per age/formulation cohort
- Progressively younger enrollment
- Stage 1
  - Intensive PK assessed in real time in first 4 subjects in Stage 1 mini-cohort
  - Subjects with individual dose adjustments based of individual exposure
  - Pre-specified dose modification made at cohort level based on mini cohort results
  - Additional subjects enrolled Stage 1 until 10 started at target dose
- Stage 2
  - Additional subjects enrolled at dose found in Stage 1 for safety, response and with population PK objectives

IMPAACT P1070
EFV Real Time PK in Ages < 3 yrs

- Study stratified based on pharmacogenomics
- Initial design: Adaptive Dosing based on AUC and post-hoc analysis of analysis of CYP 2B6 genotype
- CNS AEs
  - 4/8 (50%) CYP 2B6 PM (516TT)
  - 5/36 (14%) CYP 2B6 EM (516 GG/GT)
- CYP 2B6 genotype moved to screening requirement with reduced starting dosing for PMs (ver. 2)





Summary

- Real-time pharmacologic monitoring has become a common component of pediatric ARV drug development
- Adaptive Dosing can minimize risk of prolonged sub-optimal exposure
- Adaptive Dosing increases study complexity but enhances monitoring, promotes enrollment and is an approach that may facilitate development of some rare disease therapies.