Antiretroviral Drug Dose and Formulation Challenges in Children

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Pediatric Formulations for Antiretroviral Therapies
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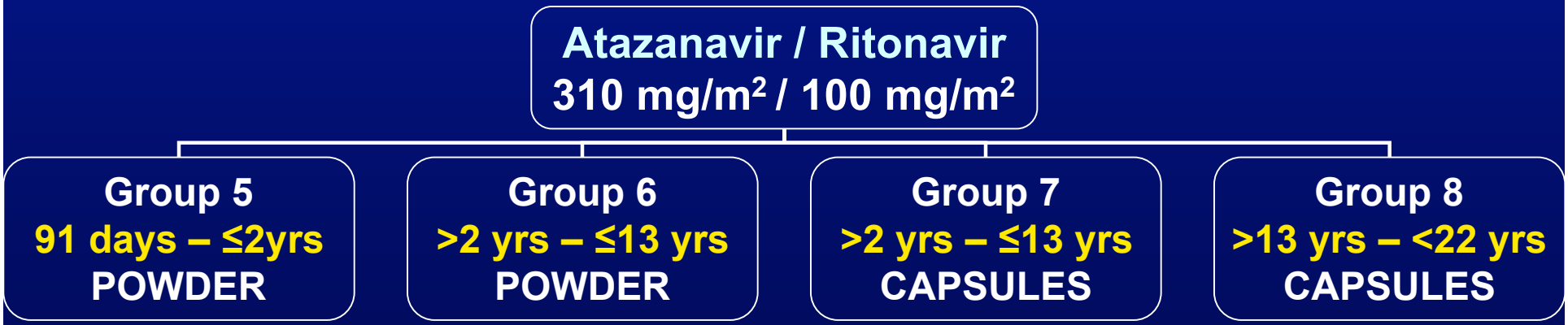
Pediatric Challenges

- Children are not small adults.
- Dosing recommendations cannot be developed for an “average” child
  - –by age or weight
  - –ignores maturational differences in PK
- The challenges of developing an acceptable pediatric formulation are significant
  - –bioavailability in adults ≠ bioavailability in children

PACTG 1020 Study Design

- 8 study groups in 1020
- Groups 1-4 are evaluating unboosted ATV
- Groups 5-8 are evaluating RTV boosted-ATV
- Children undergo 24-hour intensive PK study at week 1
- AUC target 30,000-90,000 ng*hr/mL



ATV Formulations

- Powder
  - 50 mg scoops
  - Cannot accurately dose in smaller increments
  - Those requiring large doses of ATV must take multiple scoops
- Capsules
  - 50, 100, and 200 mg
  - 50 and 100 mg capsules are identical and cannot be used together
  - 200 mg capsules are blue

PACTG 1020 PK Results

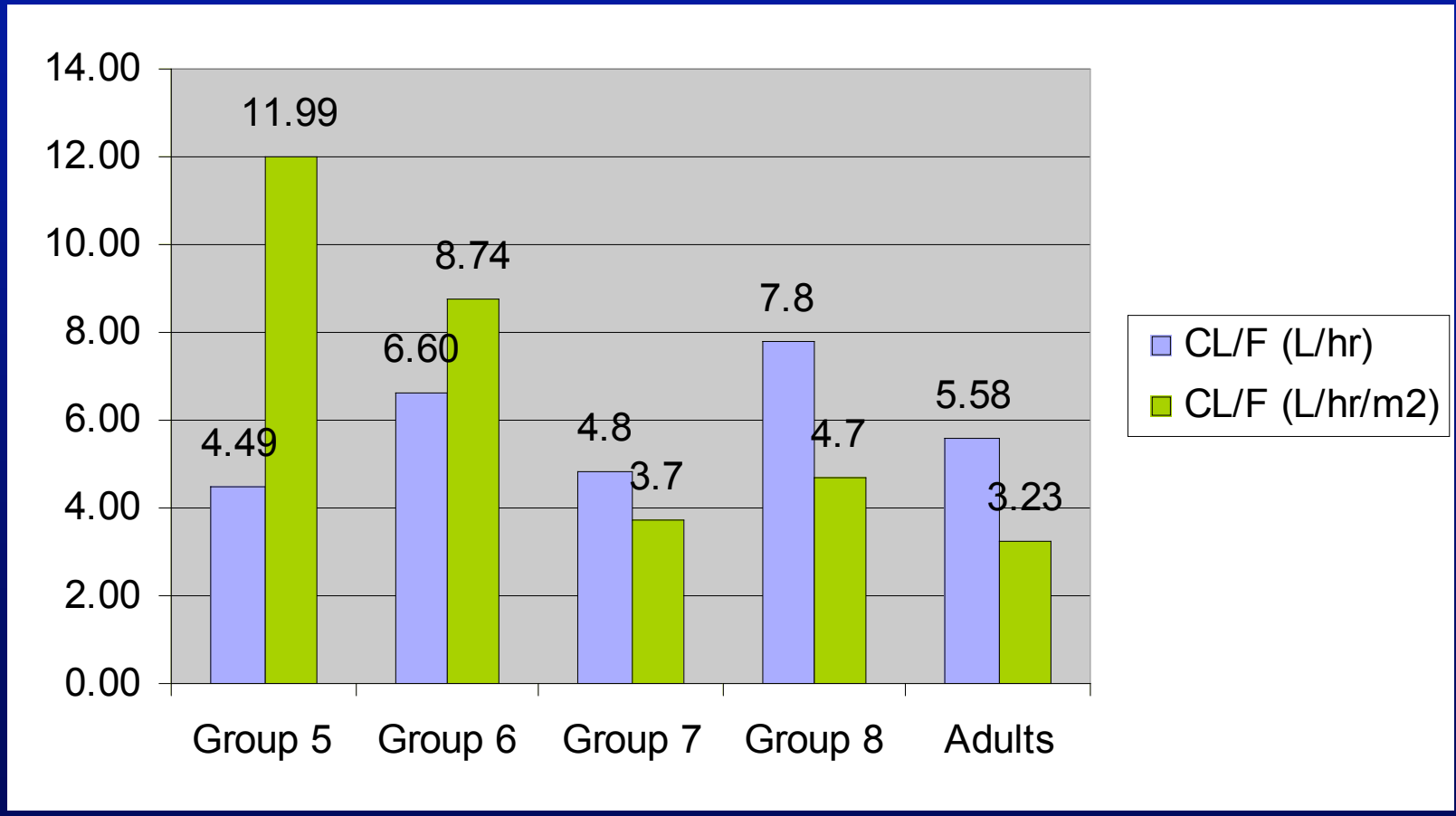
Grp	Form	N	Dose (mg)	Dose (mg/m^2)	Age (yrs)	AUC[a] (mcg*hr/mL)	CL/F[b] ($L/hr/m^2$)
5	Powder	6	125 (50-150)	298 (182-367)	1.0 (0.3-1.3)	53.6 (7.3-110)	8.2 (2.5-35.8)
6	Powder	8	200 (150-500)	313 (268-327)	4.7 (2.6-12.0)	45.1 (17.4-95.4)	7.2 (3.4-18.0)
7	Capsule	5	400 (300-500)	296 (274-349)	10.5 (8.7-11.5)	73.8 (60-134.2)	4.2 (2.2-4.7)
8	Capsule	5	500 (400-600)	286 (281-311)	17.7 (13.1-19.6)	62.4 (51.5-84.7)	4.5 (3.4-6)

Results presented as median (range).

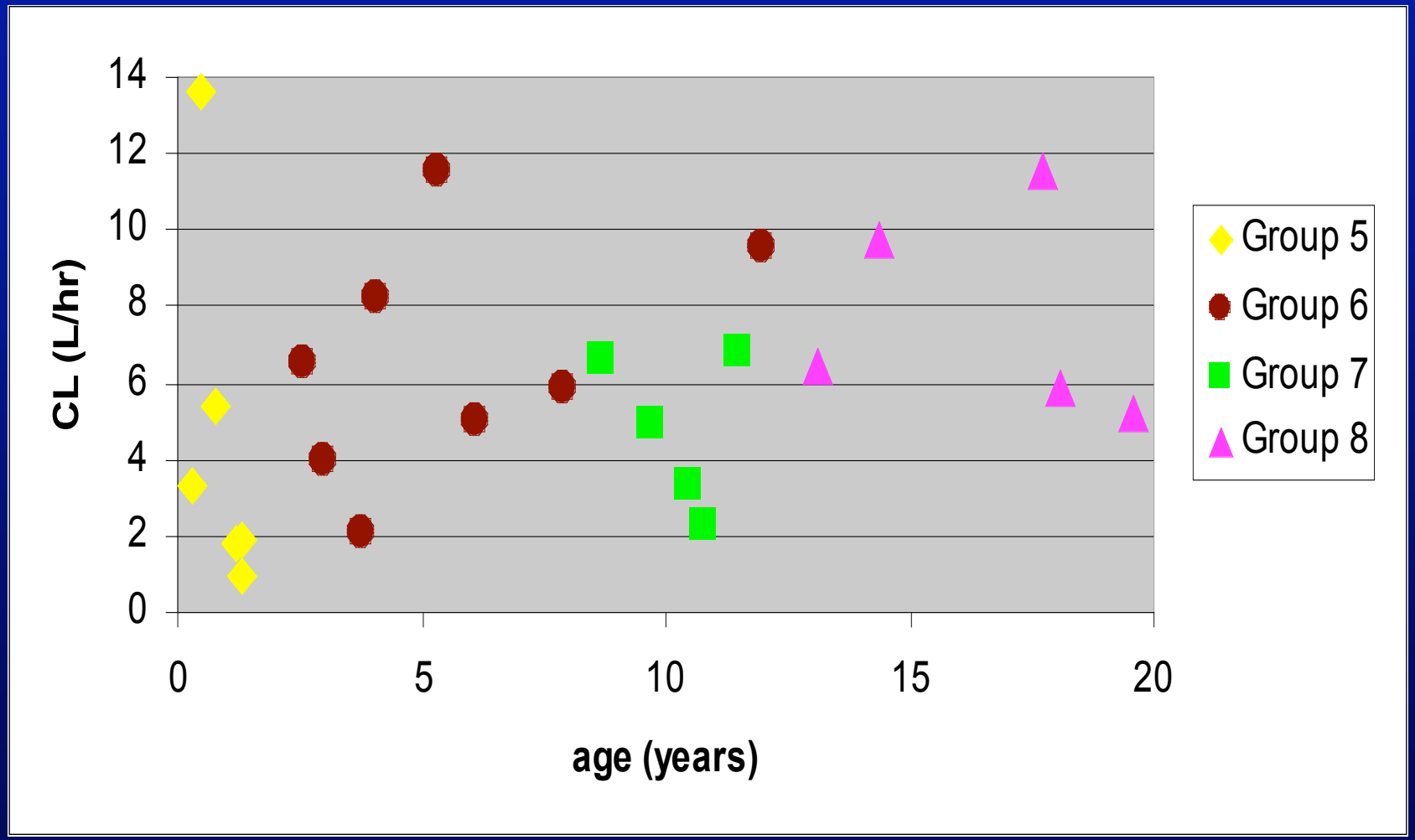
[a]Mean ATV AUC in adults receiving ATV 300 mg plus RTV 100 mg QD is 53.8 mcg*hr/mL

[b]Oral clearance is a combination of total body clearance and bioavailability as an unknown factor

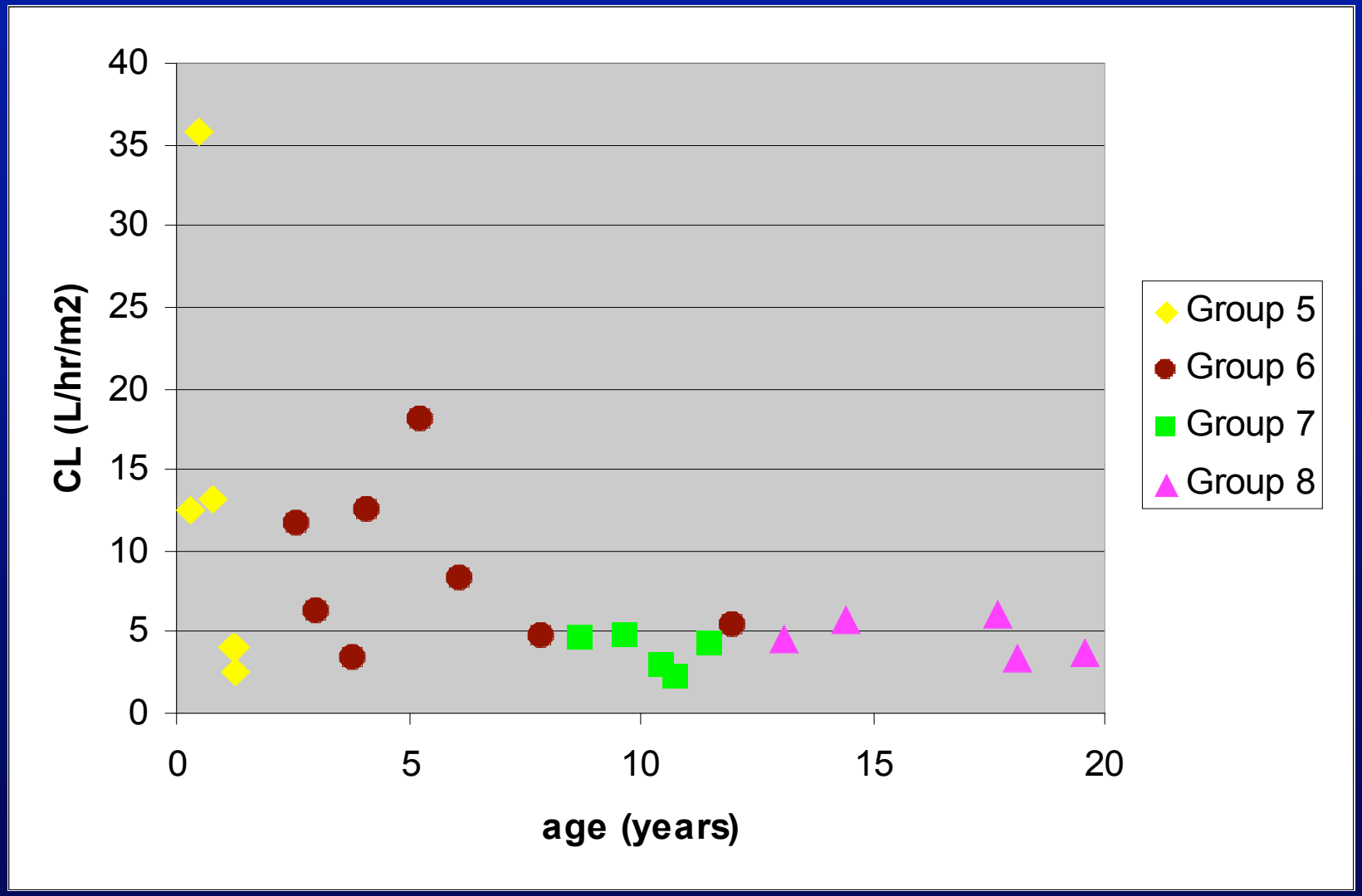
ATV Clearance by Group vs. Adults



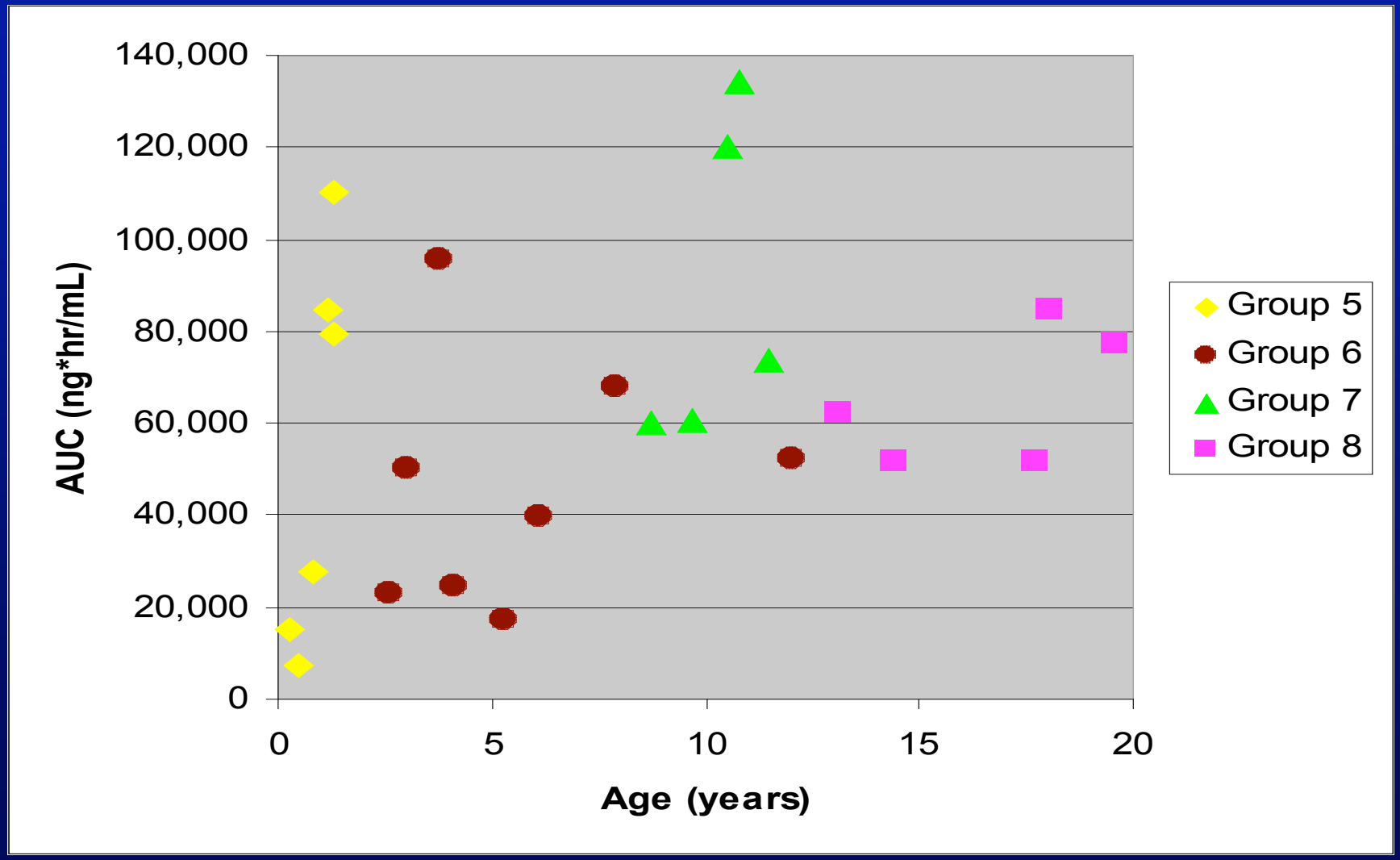
ATV Oral Clearance by Age



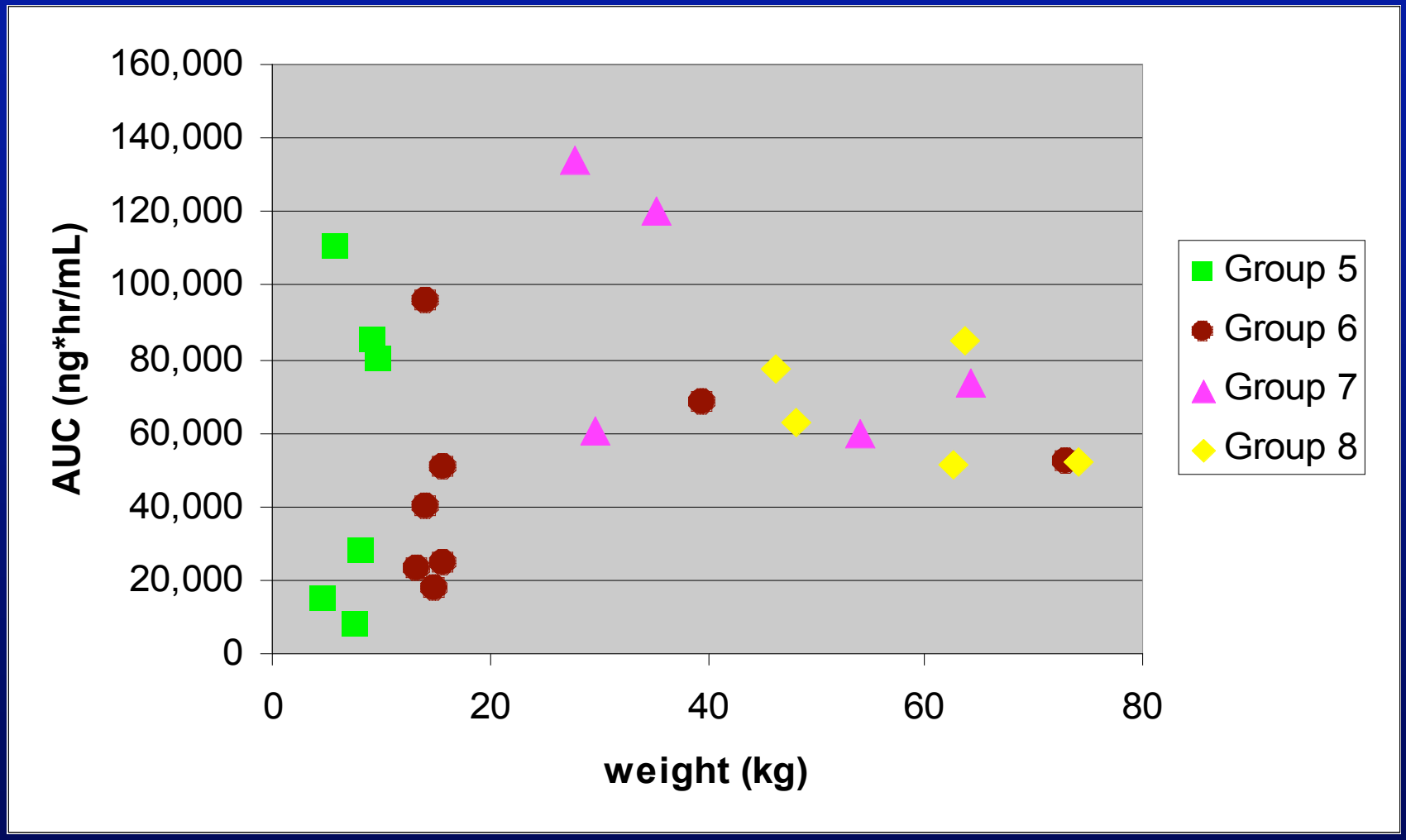
ATV BSA-Normalized CL/F by Age



ATV AUC by Age



ATV AUC by Weight



ATV Powder vs. Capsules

	Group 6	Group 7
Age (years)	4.7 (2.6-12)	10.5 (8.7-11.5)
Dose (mg)	200 (150-500)	400 (300-500)
Dosing Requirements	3-10 scoops	2-3 capsules

Nelfinavir Pharmacokinetics in Children vs. Adults

Parameter	*Children*	*Adults*
	Mean (and % CV)	
Dose	25 mg/kg (23)	750 mg
Age (yrs)	7.9 (40)	- - -
Cmax (mg/L)	3.9 (51)	2.9 (45)
Cmin (mg/L)	1.6 (76)	1.3 (54)
AUC (mg*h/L)	19.9 (53)	16 (48)
CL/F (L/h)	51 (100)	47 (50)
CL/F (L/h/kg)	2.1 (119)	0.67
CL/F (L/h/m^2)	55.1 (109)	27

Nelfinavir Use in Children

- The proportion of children 2-13 years of age achieving an HIV RNA level < 400 cpm through 48 wks ranged from 26-42%.
- Response rates in children < 2 years of age appeared to be poorer than those ≥ 2 years.
- Highly variable exposure remains a significant problem in the use of nelfinavir in pediatric patients.

Viracept Package Insert, March 29, 2004

Lopinavir/r Dosing Recommendations in Children

Weight (kg)	Dose (mg/kg)*	Volume of oral solution BID (80 mg lopinavir/20 mg ritonavir per mL)
Without nevirapine or efavirenz		
7 to <15kg	12 mg/kg BID	
7 to 10 kg		1.25 mL
>10 to <15 kg		1.75 mL
15 to 40 kg	10 mg/kg BID	
15 to 20 kg		2.25 mL
>20 to 25 kg		2.5 mL
>25 to 30 kg		3.0 mL
>30 to 40 kg		3.5 mL
>40 kg	Adult dose	5 mL (or 3 capsules)

* Dosing based on the lopinavir component of lopinavir/ritonavir solution (80 mg/20 mg per mL).
Note: Use adult dosage recommendation for children >12 years of age.

Future Directions

- Thoughtful consideration of pediatric maturational changes in PK during study design and how they are ultimately incorporated into pediatric dosing guidelines
- Studies of formulation bioavailability in children
- Therapeutic drug monitoring of ARV drugs in this population