Children with HIV in Africa - Pharmacokinetics and Adherence of Simple Antiretroviral Regimens CHAPAS 1 STUDY

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On behalf of CHAPAS Study Team

CHAPAS 1 trial design

- A controlled phase I/II trial to assess the appropriate dosing of, and adherence to, a FDC of stavudine, lamivudine and nevirapine in a new formulation specifically developed for children (Pedimune (Triomune Baby/Junior)). CIPLA pharmaceuticals

- Triomune Baby (nevirapine (NVP)50mg ,stavudine (d4T)6mg, lamivudine (3TC)30mg)
- and Junior (double Baby dose).

CHAPAS 1 Trial schema

200 Previously untreated children,
eligible to start ART according to WHO guidelines

randomise

Full dose Pedimune BD
(100)

Half dose Pedimune QD +Lamivir-S QD
for 14 days. Then full dose Pedimune BD
(100)

PK Substudy
12 hour sampling at week 4
N=64

Adherence substudy
Unannounced home
visits/pill counts/adherence
questionnaires
N=96

48 weeks: endpoints

CHAPAS 1 Population inclusion criteria

- Confirmed HIV-infected children
- Age 3 months to 14 years inclusive
- < 30kg in weight
- Willing and able to give informed consent to participate in both the dose escalation and PK substudy if required
- Previously untreated with antiretroviral drugs.
- Fulfiling WHO criteria for initiating treatment

CHAPAS I Population
exclusion criteria

- Cannot or unwilling to regularly attend the CHAPAS clinic
- Severe laboratory abnormalities (contraindicating NVP based regimen)
- Active opportunistic/bacterial infection including TB (children may be enrolled after the acute phase)
- Current treatment with drugs interracting with NVP - EG rifampicin

WHO Criteria for starting ART

- WHO paediatric stage 4 or severe stage 3 disease regardless of CD4 %
- WHO paediatric stage 2 disease or certain stage 3 (TB, LIP, thrombocytopenia, OHL), with consideration of

  CD4 percent:
  - <15% if > 3 years;
  - <20% if 1-3 years;
  - <25% if <1 year of age;
  - Cd4 count <200 if over 5 years
- Treat TB first and re-evaluate
- Treat acute malnutrition first and reassess staging.

Additional criteria for PK substudy

- Not suffer from illnesses that could influence the PK of the ART
- The first 64 eligible children enrolled in the CHAPAS 1 trial were enrolled in the PK substudy.
- (16 per group) according to age:
  - < 3 years
  - 3-6 years
  - 7-10 years
  - 11-14 years

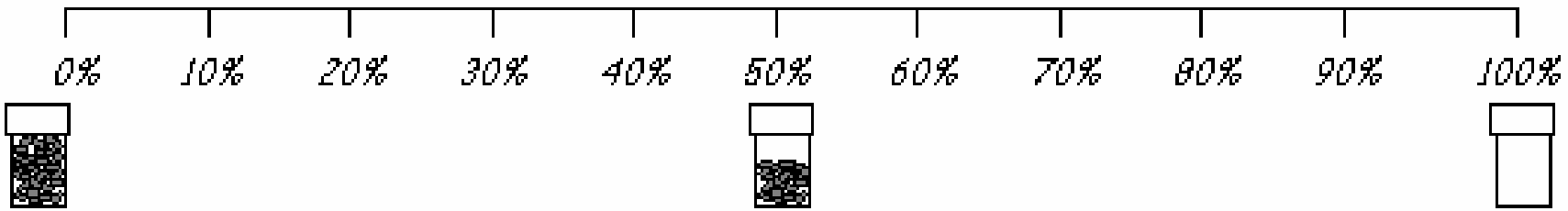
Criteria for Adherence substudy

- fulfill all criteria of the main study protocol.
- They are being enrolled (24 per group) according to age (and can be co-enrolled in the PK substudy):
  - < 3 years
  - 3-6 years
  - 7-10 years
  - 11-14 years

All children to receive MEMS caps:

  -

Visual analogue scale



- Adherence questionnaire for primary carers and children over 10 years:
  - Includes visual analogue
- Unannounced pill counts at home visits
- Memscaps

FOLLOW UP

- –4 wks , screening
- 0 (trial entry/randomisation), 2, 4, 8, 12, 24, 36, and 48 by a doctor.
- 4-weekly to see a nurse and to collect cotrimoxazole and ART medications .

Primary Outcomes

- ***For Dose Escalation Trial (all children)***

  Adverse events (AEs) of grade 3 or 4, possibly or probably related to NVP

- ***For PK Substudy (64 children)***

  Pharmacokinetic parameters (AUC, Cmin, Cmax) of 3TC, d4T and NVP from the full PK curves determined per weight band

Secondary Outcomes

1. ***For Dose Escalation Trial (all children)***
   - oAll AEs (Grade 2,3 or 4) possibly or probably related to NVP
   - oViral load
   - oAdherence and acceptability measurements
   - oMortality, disease progression, growth parameters change in CD4 count and percent from baseline
2. ***For PK Substudy (64 children)***
   - oVariability in pharmacokinetic parameters (AUC, Cmin, Cmax) according to degree of malnourishment

3. ***For Adherence Substudy (96 children)***
   - o Validity of visual analogue scale as a simple measure of adherence

Age group (years	Trial (target = 200)	Died/ LTFU	PK Substudy (target =64)	Adherence Substudy (target = 96)
0-2	76	8	17	30
3-6	44	2	19	31
7-10	53	2	18	28
11-14	27	1	17	19
Total	**198**	**19**	**71**	**108**

Pharmacokinetics of Nevirapine, Stavudine and Lamivudine in HIV-infected Children in Zambia Treated with Paediatric Fixed Dose Combination Tablets

- **Objective**

To determine the pharmacokinetics of nevirapine, stavudine & lamivudine in Zambian HIV-infected children taking Triomune® .

New scored, dispersible FDC tablets for HIV-infected children

(Triomune® Baby & Junior). Cipla pharmaceuticals, India.

Baby: NVP 50mg, d4T 6mg, 3TC 30mg

Junior: NVP 100mg, d4T 12mg, 3TC 60mg

Methods

- 64 children (16 per age group <3, 3-6, 7-10,11-14 years) dosed according to weight group (minimum daily NVP dose: 300mg/m^2).
- ≥ 4 weeks after starting Triomune® : 12 hour pharmacokinetic curve.

PK sampling

- At least 4 weeks of HAART
- 2 mls of blood collected just before and 1, 2, 4, 6, 8 and 12 hours after intake.
- Samples stored at 2-8°C for at most 12 hours until centrifugation.
- Separation of plasma,stored at -80°C, transportation to the Netherlands on dry-ice.

Methods: Summary dosing table

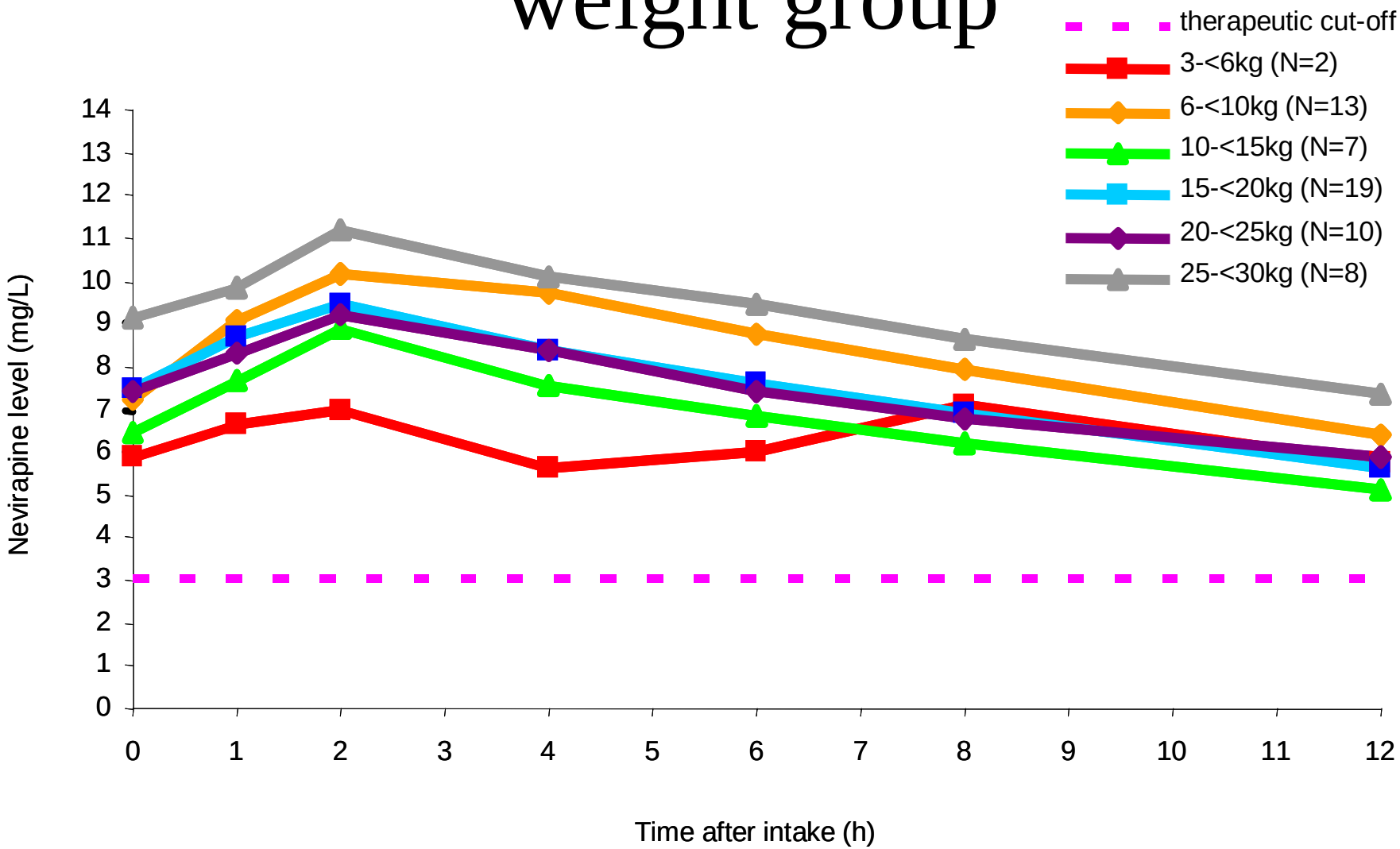
Weight, kg	Type of tablets	Number of tablets daily		Daily dose in mg			Daily dose in mg/kg		Daily dose in mg/m^2 *
		a.m.	p.m.	NVP, mg	d4T, mg	3TC, mg	d4T, mg/kg	3TC, mg/kg	NVP, mg/m^2 †
3-<6	Pedimune (Triomune) Baby (NVP 50mg, d4T 6mg, 3TC 30mg)	1	1	100	12	60	2.0-4.0	10.0-20.0	294-476
6-<10		1½	1½	150	18	90	1.8-3.0	9.0-15.0	306-441
10-<15	Pedimune (Triomune) Junior (NVP 100mg, d4T 12mg, 3TC 60mg)	1	1	200	24	120	1.6-2.4	8.0-12.0	308-408
15-<20		1	1½	250	30	150	1.5-2.0	7.5-10.0	316-385
20-<25		1½	1½	300	36	180	1.4-1.8	7.2-9.0	326-380
25-<30		2	2	400	48	240	1.6-1.9	8.0-9.6	364-435

Results: Demographics

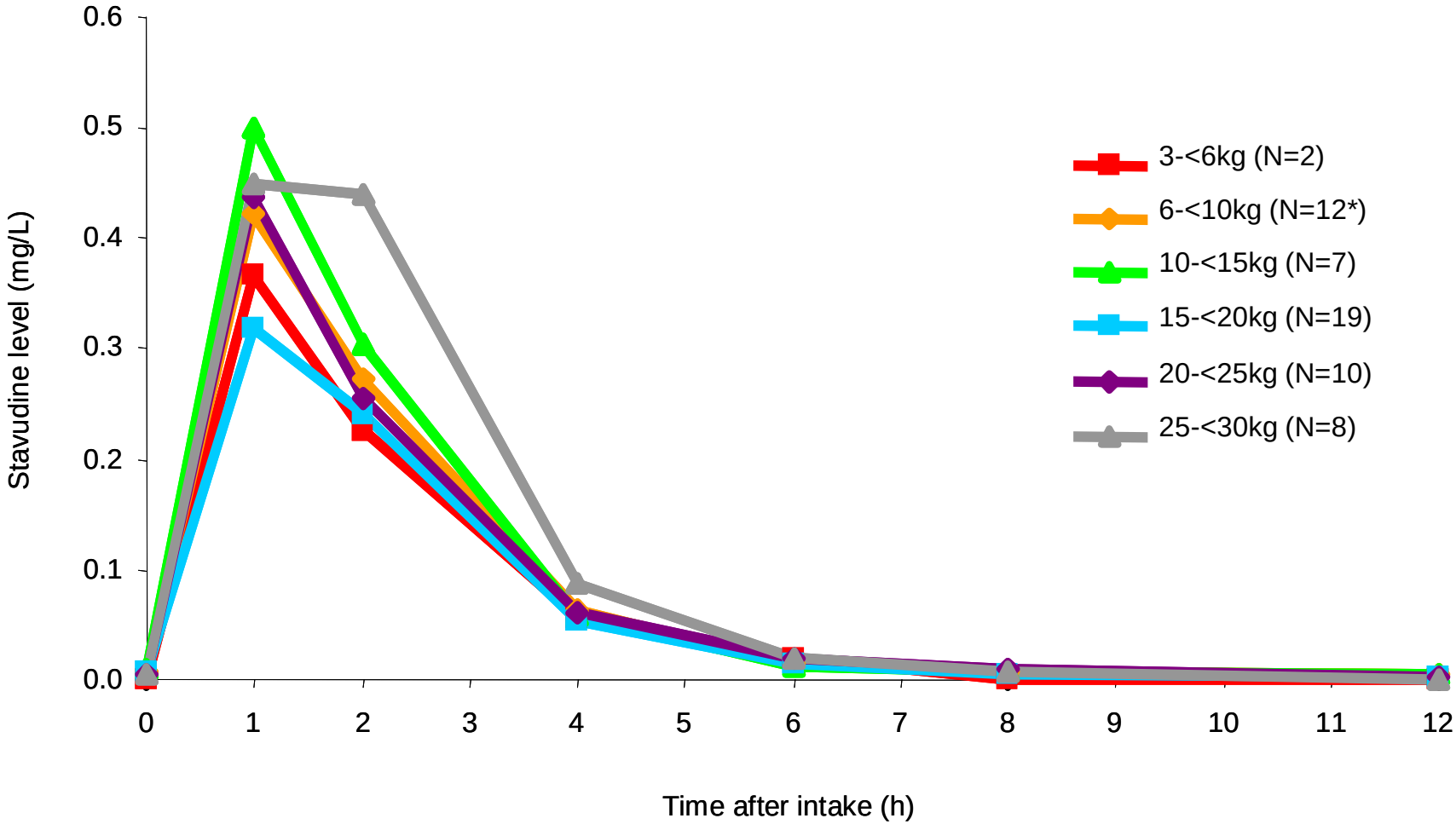
	Weight, kg						Total
	3-<6	6-<10	10-<15	15-<20	20-<25	25-<30	
N	2	13	9	19	12	10	65
Female, n (%)	2 (100%)	4 (31%)	5 (56%)	6 (32%)	4 (33%)	3 (30)	24 (37%)
Age, years	0.8 (0.7,0.8)	1.3 (.5, 4.2.2)	5.2 (3.3,, 6.8)	7.0 (4.8,12.6)	10.2 (7.7,13.5)	12.9 (10.2,14.9)	6.9 (.5,14.9)
Weight-for-age z-score	-7.0 (-9.5,-4.6)	-3.7 (-6.8,-1.3)	-3.8 (-7.0,-1.4)	-3.1 (-5.6,-1.3)	-2.1 (-4.1,-0.7)	-2.2 (-4.3,-1.4)	-3.4 (-9.5,-0.9
Height-for-age z-score	-6.1 (-6.4,-5.8)	-4.1 (-4.5,-3.0)	-3.2 (-4.9,-3.0)	-3.0 (-4.2,-1.9)	-2.0 (-3.3,-1.6)	-2.5 (-3.4,-1.7)	-3.2 (-4.3,-2.0)
BMI-for-age z-score	-4.7 (-9.3,-0.2)	-1.1 -1.9,-0.7)	-0.4 (-2.4,0.0)	-0.9 (-2.7,-0.2)	-1.6 (-3.3,-0.8)	-1.8 (-2.4,-1.0)	-1.2 (-2.2,-0.4)

- Values presented are median (interquartile range) for continuous variables.
- Five children were excluded because C_0 suggested poor adherence

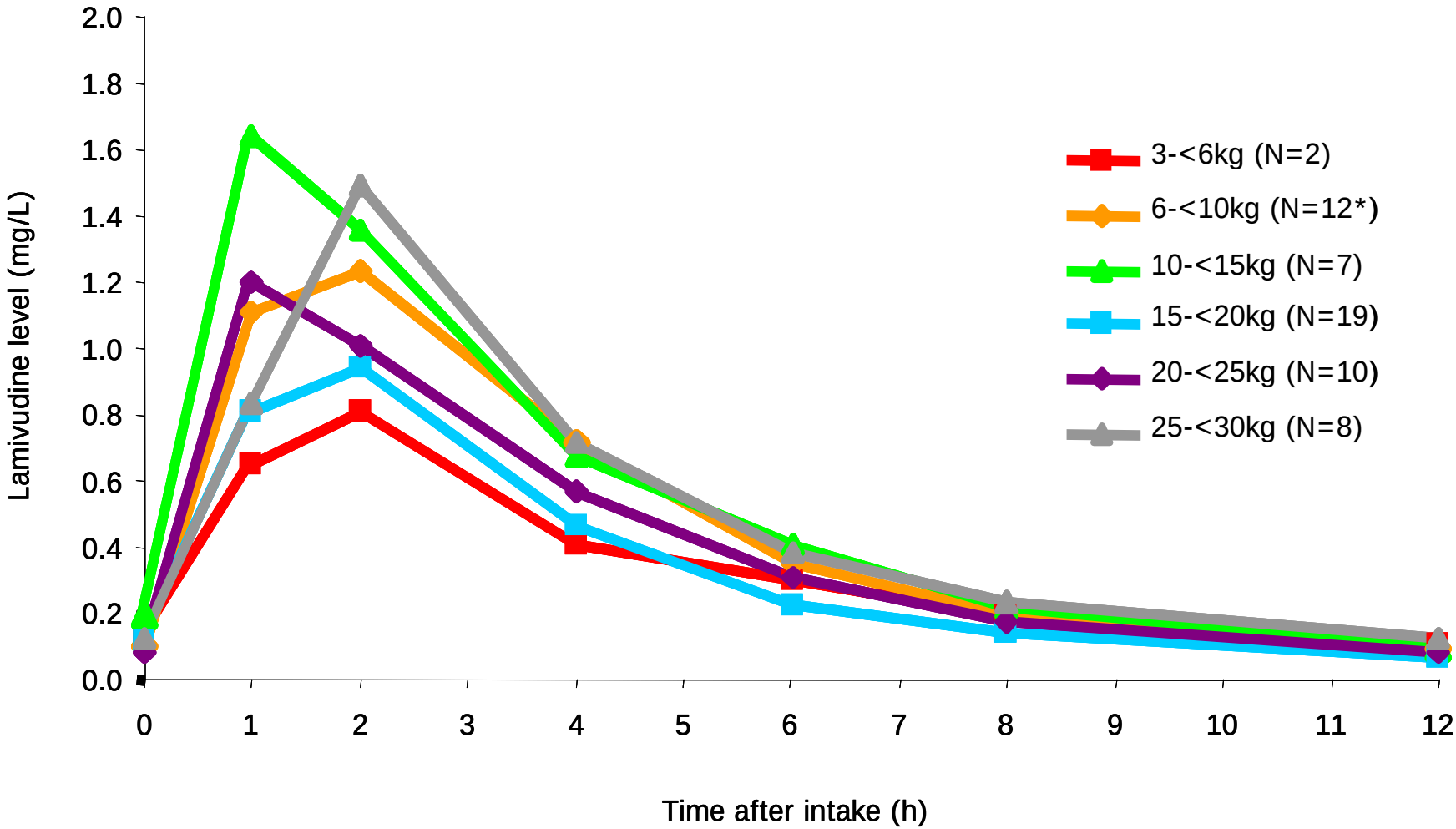
Results: Mean nevirapine levels per weight group



Results: Mean stavudine levels per weight group



Results: Mean lamivudine levels per



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Results: Pharmacokinetic parameters

	CHAPAS trial			Literature data adults
	mean	**(range)**	**[SD]**	
Nevirapine (N=59)				
C_{min} (mg/L)	6.0	(1.4, 16.9)	[3.0]	3.7
C_{max} (mg/L)	10.0	(3.8, 22.5)	[3.]	5.7
AUC_{12h} (mg/L.h)	94.4	(32.1, 232)	[39.4]	54.5
Stavudine (N=58)				
C_{min} (mg/L)	<0.015	(<0.015, 0.11)	[-]	0.009
C_{max} (mg/L)	0.45	(0.09, 0.89)	[0.15]	0.54
AUC_{12h} (mg/L.h)	1.05	(0.35, 2.16)	[0.41]	1.28
Lamivudine (N=58)				
C_{min} (mg/L)	0.09	(<0.05, 0.23)	[-]	0.09
C_{max} (mg/L)	1.33	(0.20, 3.42)	[0.69]	1.2
AUC_{12h} (mg/L.h)	5.42	(1.59, 11.45)	[2.26]	4.7

Results: Pharmacokinetic parameters nevirapine

- Four (7%) children had a subtherapeutic NVP C_{min} *(<3.0 mg/L; one child in each of the weight groups*

  3-<6, 10-<15, 20-<25, 25-<30 kg).

There is no evidence of a difference in NVP AUC_{12h} across the 6 weight groups (p=0.6) or 4 age groups (p=0.2).

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Results: Adverse events

- Three children had a grade 2 NVP rash (resolved after 9-11 days, after temporary discontinuation of NVP).
- Three children had grade 3 raised liver enzymes (all single values since returned to normal on NVP).
- One child had a grade 1 NVP rash (resolved after 7 days) followed by grade 3 raised liver enzymes (since reduced to grade 1); no changes were made to NVP.

One of the excluded children had grade 3 raised liver enzymes (single value since returned to normal on NVP).

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Conclusion

- NVP levels were higher than those previously reported in adults.
- Four (7%) children had a subtherapeutic NVP C_{min} (<3.0 mg/L).
- Pharmacokinetic parameters of d4T and 3TC were comparable to those previously reported in adults.
- The Triomune® Baby and Junior antiretroviral ratio appears to be appropriate for children over the entire range of weights.

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