Pharmacokinetics (PK) and safety of zidovudine (ZDV), lamivudine (3TC), and lopinavir/ritonavir (LPV/r) in HIV-infected children with severe acute malnutrition (SAM) in sub-Saharan Africa: IMPAACT Protocol P1092

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Background

Malnutrition is a major problem of children living in resource limited settings and is responsible for over one million deaths per year in children under five years of age. Severe malnutrition remains one of the most common presentations of HIV infection in African children. Severe Acute Malnutrition (SAM) may affect the pharmacokinetics (PK) and safety of antiretroviral therapy (ART) in HIV infected children, increasing their risk for reduced absorption. Limited data are available on PK of ARVs in severe malnutrition. The IMPAACT P1092 study compared the PK, safety and tolerability of zidovudine (ZDV), lamivudine (3TC) and lopinavir/ritonavir (LPVr) between HIV -1 infected children with severe malnutrition and mild/ no malnutrition (non-SAM) in sub-Saharan Africa.

Methods

Design: Phase IV multicenter open label PK study
Population: HIV infected children aged ≥ 6 to < 36 months of age with; severe malnutrition(Cohort I) and mild/no malnutrition(Cohort II)
Study sites: Blantrye & Lilongwe Malawi, Moshi Tanzania, Kampala Uganda, Harare Zimbabwe.
Antiretroviral regimen: Zidovudine, lamivudine and lopinavir/ritonavir liquids according to WHO weight bands for 48 weeks.
Intensive PK sampling: 0, 1, 2, 4, 8 & 12 hours post dose done at study week 1, 12 and 24
Plasma drug concentrations were measured using liquid chromatography tandem mass spectrometry. Drug concentrations were measured using validated liquid chromatography tandem mass spectrometry assays to evaluate steady-state area under the curve ($AUC_{1\text{-}12)}$ and plasma clearance (CL/F) which were compared between Cohort I and II. Frequency and causes of grade ≥3 adverse events (AEs) were evaluated using the DAIDS toxicity table (version 2.0) and tolerability was assessed by frequency of vomiting or diarrhea.

Results

Among 52 children enrolled, 56% were males, median age in months was 19 (IQR13-25) vs 18 (IQR 12-25) and median WHZ (IQR) was -3.4 (-4.0, -3.0) vs -1.0(-1.8,-0.1) for SAM and non-SAM respectively.

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		Cohort	
		Severe Malnutrition (N=25)	Mild Malnutrition/Normal Nutrition (N=27)
Nutritional Cohort Subgroup	Severe Malnutrition	25 (100%)	0 (0%)
	Mild Malnutrition	0 (0%)	15 (56%)
	Normal Nutrition	0 (0%)	12 (44%)
Age (Months)	Median	19	18
	6 - <18 months	11 (44%)	13 (48%)
	≥ 18 months	14 (56%)	14 (52%)
Country	Malawi	12 (48%)	5 (19%)
	Tanzania	7 (28%)	9 (33%)
	Uganda	1 (4%)	1 (4%)
	Zimbabwe	5 (20%)	12 (44%)
Sex	Male	16 (64%)	13 (48%)
	Female	9 (36%)	14 (52%)
WHO Weight-for-Height Z-Score	Median	-3.4	-1.0
Log_{10} HIV-1 RNA (copies/mL)[a]	Median	4.8	5.6
HIV-1 RNA (copies/mL, categorized)	< 400	2 (8%)	2 (7%)
	2,000 - < 10,000	3 (12%)	3 (11%)
	10,000 - < 20,000	3 (12%)	1 (4%)
	≥ 20,000	17 (68%)	21 (78%)
CD4%	N	25	27
	Median	15	23

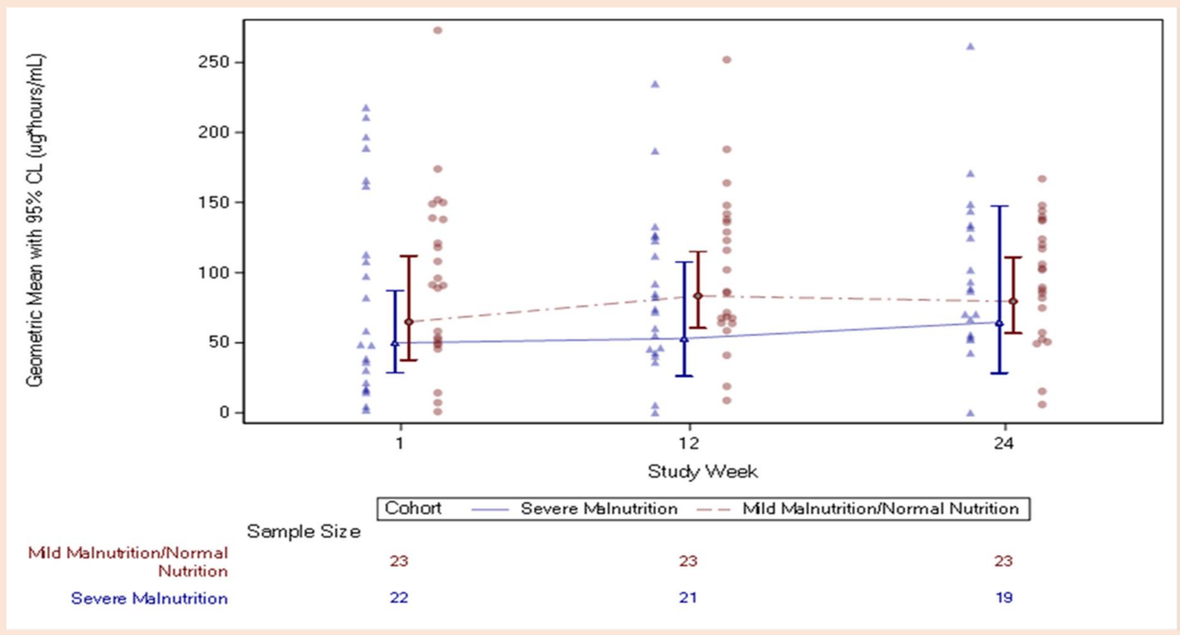
Pharmacokinetic Findings:

			Cohort: Severe Malnutrition		Cohort: Mild Malnutrition/Normal Nutrition				
Analyte	Outcome Measure	Study Visit	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	GMR (95% CI) of SAM/Non-SAM	Difference of Log Means (95% CI)	P-value	Age-Adjusted P-value
LPV	AUC (ug*hrs/mL)	1	22	49.8 (28.5, 87.2)	23	64.8 (37.6, 111.9)	0.77 (0.4, 1.6)	-0.3 (-1.0, 0.5)	0.49	0.56
		12	21	53.0 (26.1, 107.5)	23	83.4 (60.4, 115.0)	0.64 (0.3, 1.4)	-0.5 (-1.2, 0.3)	0.23	0.24
		24	19	64.6 (28.3, 147.5)	23	79.4 (56.8, 111.0)	0.81 (0.3, 2.0)	-0.2 (-1.1, 0.7)	0.63	0.52
	CL/F (L/hrs)	1	22	2.2 (1.2, 3.9)	23	2.0 (1.2, 3.5)	1.06 (0.5, 2.3)	0.1 (-0.7, 0.8)	0.89	0.98
		12	21	2.3 (1.1, 4.7)	23	1.6 (1.2, 2.3)	1.42 (0.7, 3.1)	0.3 (-0.4, 1.1)	0.37	0.41
		24	19	2.1 (0.9, 4.8)	23	1.7 (1.2, 2.5)	1.23 (0.5, 2.9)	0.2 (-0.7, 1.1)	0.63	0.56
RTV	AUC (ug*hrs/mL)	1	22	1.6 (1.0, 2.5)	23	2.1 (1.2, 3.6)	0.76 (0.4, 1.5)	-0.3 (-1.0, 0.4)	0.42	0.48
		12	21	1.8 (1.0, 3.1)	23	3.0 (2.1, 4.5)	0.58 (0.3, 1.1)	-0.5 (-1.2, 0.1)	0.11	0.12
		24	19	2.3 (1.3, 4.3)	23	3.0 (2.2, 4.0)	0.77 (0.4, 1.5)	-0.3 (-0.9, 0.4)	0.44	0.36
	CL/F (L/hrs)	1	22	16.9 (10.5, 27.2)	23	15.8 (9.2, 27.2)	1.07 (0.5, 2.2)	0.1 (-0.6, 0.8)	0.84	0.98
		12	21	17.3 (9.6, 31.0)	23	11.2 (7.6, 16.6)	1.54 (0.8, 3.1)	0.4 (-0.3, 1.1)	0.21	0.24
		24	19	14.8 (8.1, 27.2)	23	11.5 (8.4, 15.7)	1.29 (0.7, 2.5)	0.3 (-0.4, 0.9)	0.44	0.41
3TC	AUC (ng*hrs/mL)	1	21	4,245.0 (2,959.3, 6,089.3)	21	5,520.2 (3,981.4, 7,653.7)	0.77 (0.5, 1.2)	-0.3 (-0.7, 0.2)	0.27	0.32
		12	20	4,365.5 (2,743.6, 6,946.4)	21	7,233.0 (5,896.4, 8,872.6)	0.60 (0.4, 1.0)	-0.5 (-1.0, -0.0)	0.047	0.047
		24	18	6,359.0 (5,221.9, 7,743.8)	20	5,849.2 (3,453.5, 9,907.0)	1.09 (0.6, 1.9)	0.1 (-0.5, 0.6)	0.76	0.83
	CL/F (L/hrs)	1	21	8.7 (6.0, 12.7)	21	8.4 (6.2, 11.5)	1.03 (0.6, 1.7)	0.0 (-0.4, 0.5)	0.89	0.93
		12	20	9.5 (5.9, 15.4)	21	6.8 (5.7, 8.1)	1.40 (0.8, 2.3)	0.3 (-0.2, 0.8)	0.18	0.20
		24	18	7.5 (6.2, 9.0)	20	8.8 (5.3, 14.7)	0.85 (0.5, 1.4)	-0.2 (-0.7, 0.4)	0.53	0.57
ZDV	AUC (ng*hrs/mL)	1	15	2,261.0 (1,652.0, 3,094.4)	16	1,774.0 (1,079.6, 2,915.1)	1.27 (0.7, 2.2)	0.2 (-0.3, 0.8)	0.39	0.58
		12	12	1,826.0 (977.8, 3,410.0)	16	1,335.7 (758.5, 2,352.2)	1.37 (0.6, 3.0)	0.3 (-0.5, 1.1)	0.43	0.48
		24	13	2,449.7 (2,053.5, 2,922.5)	15	1,609.3 (1,306.7, 1,981.9)	1.52 (1.2, 2.0)	0.4 (0.2, 0.7)	0.003	0.005
	CL/F (L/hrs)	1	15	34.8 (24.4, 49.5)	16	58.3 (34.8, 97.9)	0.60 (0.3, 1.1)	-0.5 (-1.1, 0.1)	0.090	0.15
		12	12	48.8 (24.8, 95.8)	16	81.8 (44.9, 148.9)	0.60 (0.3, 1.4)	-0.5 (-1.4, 0.3)	0.23	0.27
		24	13	40.8 (33.0, 50.4)	15	64.0 (51.7, 79.1)	0.64 (0.5, 0.8)	-0.4 (-0.7, -0.2)	0.003	0.007

No AUC or CL/F significant differences were observed between groups (p ≥0.11) except for:

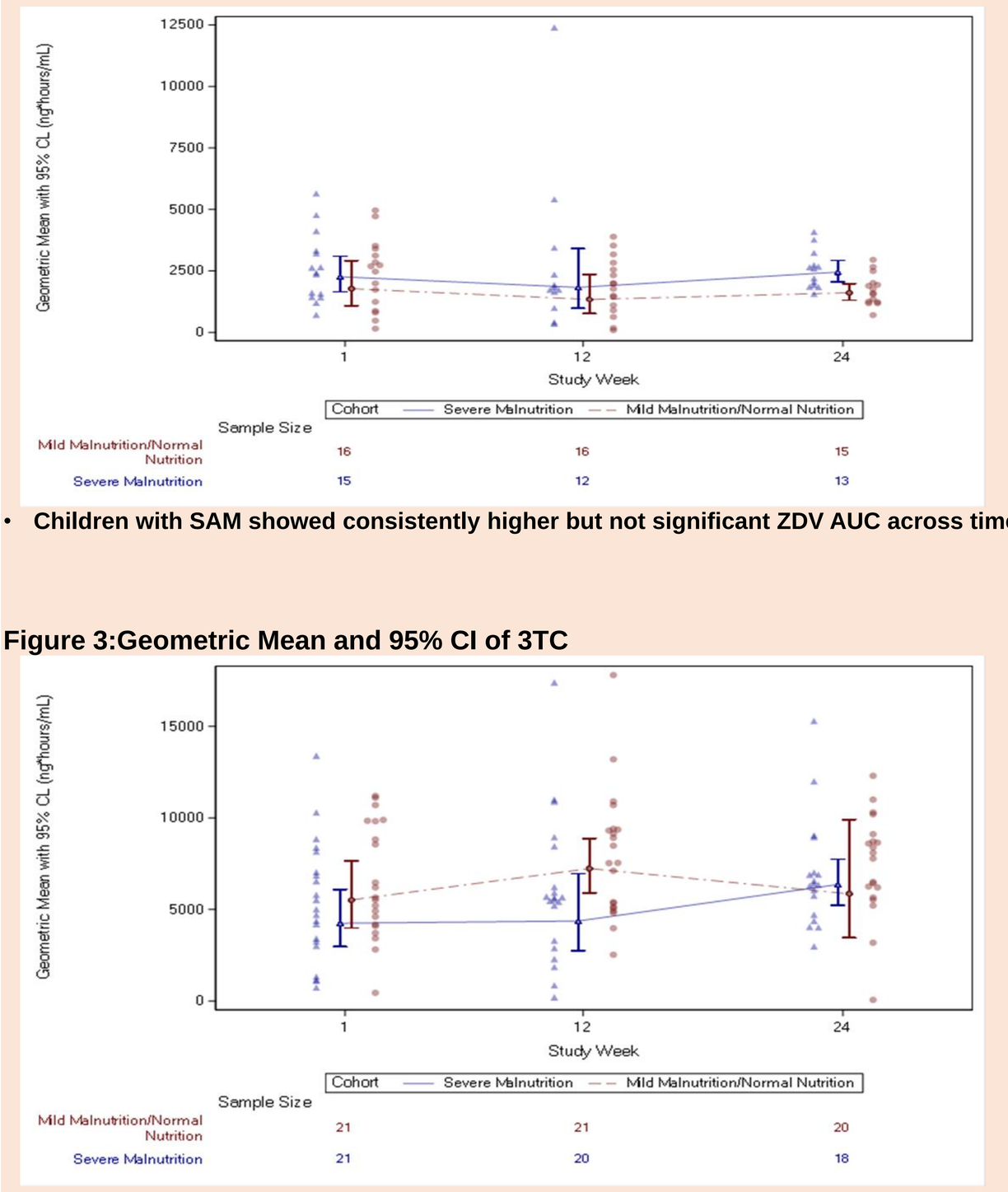
- Lower 3TC AUC at study week 12 (mean 4,365.5 vs. 7,233.0 ng*hr/mL; p=0.047)
- Higher ZDV AUC at study week 24 (2,449.7 vs. 1,609.3 ng*hr/mL; p=0.003)
- Lower ZDV CL/F at study week 24 (40.8 vs. 64.0 L/hr; p= 0.003) in SAM.

Figure 1:Geometric Mean and 95% CI of LPVr AUC



- **Children with SAM showed consistently lower but not significant LPVr AUC across time**

Figure 2:Geometric Mean and 95% CI of ZDV



- **Children with SAM showed consistently higher but not significant ZDV AUC across time**

Figure 3:Geometric Mean and 95% CI of 3TC

- **Children with SAM had lower 3TC at only study week 12**

Safety and tolerability

- Treatment-related grade ≥3 toxicity through study week(SW) 24 did not differ significantly between the 2 groups(24.0% vs. 25.9%).

- Treatment discontinuations through SW 24 were comparable:
  5 (20%) SAM vs 3 (11%) non-SAM.
  (3 deaths in SAM unrelated to study treatment: 2G/E and I pneumonia)

- SAM children experienced more vomiting (28%) and diarrhea (36%) compared to non-SAM (18.5% and 11.1%).

Conclusions

- WHO weight band dosing of ZDV, 3TC and LPVr syrups in SAM children appeared generally safe.
- Drug exposures were generally similar between the groups but SAM AUC exposure tended to be lower for LPV/r and higher for ZDV.

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