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 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, lamivudine and lopinavir/ritonavir (LPV/r) 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 < 36 months of age with severe malnutrition(Cohort I) and mild/no malnutrition(Cohort II)
Study sites: Blantyre & 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.
Pharmacokinetic Findings:

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

Figure 1: Geometric Mean and 95% CI of LPV/r AUC

• Children with SAM showed consistently lower but not significant LPV/r 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

Pharmacokinetic (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

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/mL/L; p=0.047)
- Higher ZDV AUC at study week 24 (2,449.7 vs. 1,609.3 ng/mL/L; p=0.003)
- Lower ZDV CL/F at study week 24 (40.8 vs. 44.0 L/hr; p= 0.003) in SAM.

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. 25.8%).
- Treatment discontinuations through SW 24 were comparable:
  - 3 (3 deaths in SAM unrelated to study treatment: 2GE I and 1 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 LPV/r 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.

Acknowledgements
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