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Pharmacokinetics and Safety of Zidovudine, Lamivudine, and Lopinavir/Ritonavir in HIV-infected Children With Severe Acute Malnutrition in Sub-Saharan Africa: IMPAACT Protocol P1092

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Background: Severe acute malnutrition (SAM) may alter the pharmacokinetics (PK), efficacy, and safety of antiretroviral therapy. The phase IV study, IMPAACT P1092, compared PK, safety, and tolerability of zidovudine (ZDV), lamivudine (3TC), and lopinavir/ritonavir (LPV/r) in children with and without SAM.

Materials and methods: Children living with HIV 6 to <36 months of age with or without World Health Organization (WHO)-defined SAM received ZDV, 3TC, and LPV/r syrup for 48 weeks according to WHO weight band dosing. Intensive PK sampling was performed at weeks 1, 12, and 24. Plasma drug concentrations were measured using liquid chromatography tandem mass spectrometry. Steady-state mean area under the curve (AUC_{0-12h}) and clearance (CL/F) for each drug were compared. Grade ≥3 adverse events were compared between cohorts.

Results: Fifty-two children were enrolled across 5 sites in Africa with 44% (23/52) female, median age 19 months (Q1, Q3: 13, 25). Twenty-five children had SAM with entry median weight-for-height Z-score (WHZ) −3.4 (IQR −4.0, −3.0) and 27 non-SAM had median WHZ −1.0 (IQR −1.8, −0.1). No significant differences in mean AUC_{0-12h} or CL/F were observed ($P \geq 0.09$) except for lower 3TC AUC_{0-12h} (GMR, 0.60; 95% CI, 0.4–1.0; $P = 0.047$) at week 12, higher ZDV AUC_{0-12h} (GMR, 1.52; 1.2–2.0; $P = 0.003$) at week 24 in the SAM cohort compared with non-SAM cohort. Treatment-related grade ≥3 events did not differ significantly between cohorts (24.0% vs. 25.9%).

Conclusion: PK and safety findings for ZDV, 3TC, and LPV/r support current WHO weight band dosing of syrup formulations in children with SAM.

Key Words: pharmacokinetics, HIV, severe acute malnutrition, children, lopinavir/ritonavir

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Over 90% of the world's 1.7 million children living with HIV reside in sub-Saharan Africa,[1] and severe acute malnutrition (SAM) remains one of the most common presentations of HIV in African children.[2,3] Mortality among children with HIV and SAM is 3 times higher compared with children with SAM alone.[4,5] Increasing access to antiretroviral therapy (ARV) for children living with HIV has improved morbidity and mortality. However, sustained control of viral replication is critical for success and dependent upon adequate ARV drug exposure that may be compromised in children with SAM.

Multiple factors influence the pharmacokinetics (PK) of drugs including, malnutrition, age, sex, and genetic variations.[6] SAM has been associated with villous atrophy of the intestinal lining, reduced gastric acidity, prolonged gastric emptying time, and reduced protein binding due to low-serum albumin concentrations.[6,7] These physiological changes can alter ARV absorption and metabolism. Protease inhibitors [e.g., lopinavir/ritonavir (LPV/r)] prefer an acidic environment for absorption and thus may exhibit reduced exposure in SAM children.[8] In contrast, nucleoside reverse transcriptase inhibitors [e.g., zidovudine (ZDV) and lamivudine (3TC)] are acid labile and may show increased absorption in SAM children. The PK of ARVs in children with HIV and SAM has not been well characterized. This study compared steady-state PK, safety, and tolerability of ZDV, 3TC, and LPV/r in children living with HIV, with and without SAM or moderate malnutrition based on standard of care (SOC) (WHO 2013) treatment guidelines.[9]

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MATERIALS AND METHODS

Study Design

IMPAACT P1092 was a phase IV, multicenter, open label, nonrandomized study conducted at 5 sites in 4 countries (Malawi, Tanzania, Uganda, and Zimbabwe) between October 2015 and September 2017. Study participants received ARVs according to the World Health Organization (WHO) pediatric weight band dosing guidelines.[10] Abacavir (ABC) was allowed to replace ZDV in cases of ZDV intolerance or grade ≥3 hematologic toxicity based on the Division of AIDS Table for Grading Severity of Adult and Pediatric Events (version 2.0 dated November 2014).[11] Participants who prematurely discontinued study treatment continued to be followed in the study.

Enrollment into nutritional cohorts was stratified by age: 6 to <18 months and 18 to <36 months to achieve a balanced distribution. Children with SAM were managed according to WHO nutritional guidelines.[12] They were enrolled 10–18 days of starting nutritional rehabilitation. Non-SAM children were recruited from HIV treatment centers and enrolled within 14 days after screening.

Eligibility criteria included documented HIV-1 infection defined as a positive result from 2 samples collected at different time points. A positive HIV DNA or RNA PCR test was required. A positive serological test (HIV rapid test or ELISA) was also permitted in children above 24 months in age. Children with acute serious infections were stabilized for at least 5 days on antimicrobials. Children with SAM had to demonstrate clinical stability and improvement at enrollment. Exclusion criteria included edematous malnutrition, respiratory distress grade ≥3, and current antituberculosis therapy.

Children were grouped by nutritional status according to WHO standards in weight-for-height Z-score (WHZ) or midupper arm circumference (MUAC). A WHZ > −1 was classified as "normal" nutrition, WHZ > −2 to ≤ −1 as mild malnutrition, and WHZ < −3 or MUAC < 115 mm as severe malnutrition. Children with normal nutrition or mild malnutrition were grouped in the non-SAM cohort. Children with WHO-defined moderate malnutrition were excluded. Children were weighed to the nearest 100 g on scales calibrated daily; lengths were measured to the nearest 0.1 cm using locally built height boards. Study clinic visits occurred at weeks 1, 2, 4, 8, 12, 16, 20, 24, 36, and 48 post enrollment. All visits included nutritional assessments, medical history, and a physical examination. Hematology and Chemistry, CD4 cell count and percentage and plasma HIV-1 RNA (viral load) levels were determined at screening/entry, and weeks 12, 24, 36, and 48.

At enrollment, children initiated ZDV, 3TC, and LPV/r liquid twice daily. At each visit, drug dosing was re-evaluated and adjusted according to the child's weight. Caregivers were given instructions on ARV administration and dose-time documentation.

Cohorts of 17 participants each were calculated to provide 80% power for a 2-sided *t* test with alpha of 0.05 to detect a 40% difference in mean LPV $AUC_{0–12h}$ between cohorts. LPV $AUC_{0–12h}$ coefficient of variation (CV) of 0.4 was assumed based on estimates in similarly aged children,[13] and a 40% difference in $AUC_{0–12h}$ was considered clinically significant. Accounting for possible loss to follow-up (10%), mortality (20%), and variability in $AUC_{0–12h}$ (10%), a sample size of 25 children per cohort was defined.

All ethical committees of participating sites reviewed and approved the protocol. Written informed consent was obtained from caregivers of study participants. The study was registered with Clinical Trials.gov (ClinicalTrials.gov Identifier NCT0818258).

PK Sample Collection

At study weeks 1, 12, and 24, blood was collected for intensive PK sampling. Caregivers were asked to hold the child's morning dose of ARVs before sampling. Blood samples were collected just before an observed morning dose and at 1, 2, 4, 8, and 12 hours postdose. Each time point was documented. Intensive PK sample collection was deferred if any doses were missed within the preceding 72 hours, the most recent hemoglobin was <7.5 g/dL, or the child had diarrhea at the visit. To assure PK samples were collected under steady-state conditions, every effort was made to administer doses approximately every 12 hours for the 48 hours preceding the intensive sampling period. Food intake around week 1, PK sampling was standardized to minimize any potential food effect on PK between the cohorts.

All whole blood samples were collected in Greiner-Mini K_3EDTA blood collection tubes. Plasma was separated and stored at −80ºC until it was shipped for analysis to the Division of Clinical Pharmacology at the University of Cape Town (UCT) in South Africa.

Drug Analysis

Plasma ZDV, 3TC, and LPV/r concentrations were determined with validated liquid chromatography tandem mass spectrometry assays developed at the UCT. Plasma samples for measuring ZDV and 3TC were processed with a liquid-liquid extraction method using 50 µL plasma and 1 mL ethyl acetate. Plasma samples for LPV were processed with a protein precipitation extraction method using 10 µL plasma with 120 µL acetonitrile. Stable isotope-labeled internal standards were used for both assays.

Isocratic chromatographic separation of ZDV and 3TC was achieved on a Higgins Clipeus C18 (150 mm × 3 mm × 5 µm) analytical column. The mobile phase consisted of 0.1% formic acid in water and 0.1% formic acid in methanol (50:50, v/v), delivered at a flow rate of 300 µL/min. Isocratic chromatography for LPV and Ritonavir (RTV) assays was achieved on a Phenomenex Luna PFP (110A, 50 mm × 2 mm × 5 µm) analytical column. The mobile phase consisted of 0.1% formic acid in water and acetonitrile (50:50, v/v) and delivered at a flow rate of 350 µL/min.

An AB Sciex API 3000 mass spectrometer was used to quantify ZDV and 3TC and operated at unit resolution in the multiple reaction monitoring (MRM) mode, monitoring the transition of the protonated molecular ions m/z 268.2 to the product ions at m/z 127.1 for ZDV, and m/z 230.1 to m/z 112.1 for 3TC. An AB Sciex API 4000 mass spectrometer was used to quantify LPV/r and operated at unit resolution in the MRM mode, monitoring the transition of the protonated molecular ions m/z 629.5 to the product ions at m/z 120.2; and m/z 721.5 to m/z 296.1 for LPV and RTV, respectively.

The assays were validated over the concentration ranges of 0.0238–6.10 µg/mL for ZDV and 3TC, 0.0195–20.0 µg/mL for LPV, and 0.00488–5.00 µg/mL for RTV. The accuracy and precision statistics of the quality controls during intra- and interbatch validation were within FDA and EMA validation criteria.[14,15] The laboratory participates in the AIDS Clinical Trial Group Pharmacology Quality Control Program.[16]

PK and Statistical Analysis

The primary PK outcome measures were steady-state $AUC_{0–12h}$ and oral clearance (CL/F) for LPV, RTV, 3TC, and ZDV at study weeks 1, 12, and 24. PK parameters were calculated using a noncompartmental analysis in the software WinNonlin (v8.1). The linear up-log down trapezoidal method was used when calculating the AUC parameter. CL/F was calculated as dose/$AUC_{0–12hr}$. For calculating PK parameters, the first concentration value postdose to fall below the limit of assay quantification (BLQ), was assigned a value of 1/2 BLQ, and a concentration of zero thereafter.

Participants were evaluable for analysis if they had an outcome measure at week 1 and either weeks 12 or 24. The AUC_{0-12h} and CL/F for each study week were compared for each analyte between SAM and non-SAM cohorts using Student's *t* test, assuming unequal variance. PK parameter comparisons were performed on the natural logarithmic scale and differences between cohorts were summarized using a geometric mean ratio (GMR).

The primary safety outcome measures included experiencing at least 1 new grade 3 or higher adverse event related to study treatment through week 24, or experiencing at least 1 new grade 3 or higher adverse event regardless of relationship to treatment through week 24. Adverse events were those that began or increased in grade after study entry. A Fisher's exact test compared grade 3 or higher adverse events.

All statistical tests were 2-sided and performed using SAS 9.4 (Cary, NC). Results were considered statistically significant if the *P* value was less than 0.05.

RESULTS

Baseline Characteristics

Fifty-two participants, 25 in the SAM cohort and 27 in the non-SAM cohort, were enrolled. The median (25th, 75th percentile) age at entry was 19 months[13] in the SAM and 18 months[12] in the non-SAM cohort. SAM participants had a median (25th, 75th percentile) WHZ of −3.4 (−4.0, −3.0) while WHZ was −1.0 (−1.8, −0.1) in the non-SAM cohort (Table 1).

A total of 46 participants (88.5%) completed 48 weeks of study follow-up per protocol.

PK Parameters for LPV/r, 3TC, and ZDV

At least 42 participants (81%) were evaluable for PK analysis of LPV, RTV, and 3TC while, 31 (60%) participants were evaluable for ZDV analysis. Reasons for exclusion in the AUC analysis included: early study discontinuation (n=4) or study treatment discontinuation (n=1) before week 12, and switches from ZDV to ABC before week 12 after experiencing a grade 3 or 4 hematologic toxicity [3 (12%) in the SAM cohort and 5 (18.5%) in the non-SAM cohort].

The mean AUC_{0-12h} or CL/F for LPV and RTV did not differ significantly by cohort at weeks 1, 12, and 24. Although not statistically significant, the SAM cohort consistently had lower LPV and RTV exposures over time (Table 2 and Figure 1A; $P \geq 0.11$). Mean 3TC AUC_{0-12h} and CL/F did not differ significantly by cohort at weeks 1 and 24 (Table 2; $P \geq 0.18$). At week 12, however, the 3TC AUC_{0-12h} was significantly lower in the SAM cohort compared with the non-SAM cohort with a GMR [95% confidence interval (CI)] of 0.60 [(0.4–1.0), $P=0.047$]. For ZDV, there were no significant differences for AUC_{0-12h} or CL/F at weeks 1 and 12 ($P \geq 0.09$). However, at week 24, the SAM cohort had a significantly lower mean ZDV CL/F [GMR, 0.64; 0.5–0.8; $P=0.003$] and a significantly higher AUC_{0-12h} [GMR, 1.52; 1.2–2.0; $P=0.003$] compared with the non-SAM cohort. In a sensitivity analysis, age-group adjusted results were similar.

A repeated measures analysis for each analyte for the AUC and CL/F across the 3 intensive PK weeks among the evaluable participants showed there was no significant evidence that the mean difference between cohorts in AUC or CL/F changed over time ($P \geq 0.35$).

Safety and Tolerability

Overall, 23 (44.2%) participants experienced at least 1 new grade ≧3 adverse event by week 24; this did not differ significantly between cohorts: 13 (52%) [95% CI (31.3%–72.2%)] in the SAM and 10 (37%) [(19.4%–57.6%)] in the non-SAM cohort ($P=0.40$). Similarly, there was no significant difference between cohorts for grade ≧3 adverse events that were at least probably related to study treatment: 6 (24%) [95% CI (9.4%–45.1%)] in SAM and 7 (25.9%) (11.1%–46.3%) in the non-SAM cohort ($P>0.999$). The most common nonmalnutrition events were anemia (n=10), pneumonia or bacterial pneumonia (n=5), decreased hemoglobin (n=11), and decreased neutrophil count (n=6). Three children in the SAM

TABLE 1. Baseline Characteristics

Baseline Characteristics		Cohort: Severe Malnutrition (N=25)	Cohort: 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 (mo)	Median (Q1, Q3)	19 (13, 25)	18 (12, 25)
	6 to <18 mo	11 (44%)	13 (48%)
	≥18 mo	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 (Q1, Q3)	−3.4 (−4.0, −3.0)	−1.0 (−1.8, −0.1)
Midupper arm circumference (cm)	Median (Q1, Q3)	11.0 (10.4, 11.5)	13.9 (12.5, 15.5)
Log_{10} HIV-1 RNA (copies/mL)	Median (Q1, Q3)	4.8 (4.2, 5.6)	5.6 (4.8, 6.1)
HIV-1 RNA (copies/mL, categorized)	<400	2 (8%)	2 (7%)
	400 to <2000	0 (0%)	0 (0%)
	2000 to <10,000	3 (12%)	3 (11%)
	10,000 to <20,000	3 (12%)	1 (4%)
	≥20,000	17 (68%)	21 (78%)
CD4 cell percent	Median(Q1,Q3)	15 (9.0, 22.6)	23 (17, 31)
Total protein g/ L	Median(Q1, Q3)	70.1 (66.4, 83.4)	76.4 (73.2, 79.3)
Albumin g/L	Median(Q1, Q3)	35 (31, 40)	41.8 (37, 47)

TABLE 2. Pharmacokinetic Primary Outcome Measures

			Cohort					
			Severe Malnutrition		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‡	*P*
LPV	AUC (μg*h/mL)	1	22	49.8 (28.5–87.2)	23	64.8 (37.6–111.9)	0.77 (0.4–1.6)	0.49
		12	21	53.0 (26.1–107.5)	23	83.4 (60.4–115.0)	0.64 (0.3–1.4)	0.23
		24	19	64.6 (28.3–147.5)	23	79.4 (56.8–111.0)	0.81 (0.3–2.0)	0.63
	CL/F (L/h)	1	22	2.2 (1.2–3.9)	23	2.0 (1.2–3.5)	1.06 (0.5–2.3)	0.89
		12	21	2.3 (1.1–4.7)	23	1.6 (1.2–2.3)	1.42 (0.7–3.1)	0.37
		24	19	2.1 (0.9–4.8)	23	1.7 (1.2–2.5)	1.23 (0.5–2.9)	0.63
RTV	AUC (μg*h/mL)	1	22	1.6 (1.0–2.5)	23	2.1 (1.2–3.6)	0.76 (0.4–1.5)	0.42
		12	21	1.8 (1.0–3.1)	23	3.0 (2.1–4.5)	0.58 (0.3–1.1)	0.11
		24	19	2.3 (1.3–4.3)	23	3.0 (2.2–4.0)	0.77 (0.4–1.5)	0.44
	CL/F (L/h)	1	22	16.9 (10.5–27.2)	23	15.8 (9.2–27.2)	1.07 (0.5–2.2)	0.84
		12	21	17.3 (9.6–31.0)	23	11.2 (7.6–16.6)	1.54 (0.8–3.1)	0.21
		24	19	14.8 (8.1–27.2)	23	11.5 (8.4–15.7)	1.29 (0.7–2.5)	0.44
3TC	AUC (μg*h/mL)	1	21	4245.0 (2959.3–6089.3)	21	5520.2 (3981.4–7653.7)	0.77 (0.5–1.2)	0.27
		12	20	4365.5 (2743.6–6946.4)	21	7233.0 (5896.4–8872.6)	0.60 (0.4–1.0)	0.047
		24	18	6359.0 (5221.9–7743.8)	20	5849.2 (3453.5–9907.0)	1.09 (0.6–1.9)	0.76
	CL/F (L/h)	1	21	8.7 (6.0–12.7)	21	8.4 (6.2–11.5)	1.03 (0.6–1.7)	0.89
		12	20	9.5 (5.9–15.4)	21	6.8 (5.7–8.1)	1.40 (0.8–2.3)	0.18
		24	18	7.5 (6.2–9.0)	20	8.8 (5.3–14.7)	0.85 (0.5–1.4)	0.53
ZDV	AUC (μg*h/mL)	1	15	2261.0 (1652.0–3094.4)	16	1774.0 (1079.6–2915.1)	1.27 (0.7–2.2)	0.39
		12	12	1826.0 (977.8–3410.0)	16	1335.7 (758.5–2352.2)	1.37 (0.6–3.0)	0.43
		24	13	2449.7 (2053.5–2922.5)	15	1609.3 (1306.7–1981.9)	1.52 (1.2–2.0)	0.003
	CL/F (L/h)	1	15	34.8 (24.4–49.5)	16	58.3 (34.8–97.9)	0.60 (0.3–1.1)	0.090
		12	12	48.8 (24.8–95.8)	16	81.8 (44.9–148.9)	0.60 (0.3–1.4)	0.23
		24	13	40.8 (33.0–50.4)	15	64.0 (51.7–79.1)	0.64 (0.5–0.8)	0.003

*Geometric mean ratio.
†Severe acute malnutrition.
‡Non severe acute malnutrition (mild malnutrition and normal nutrition)

cohort died (2 due to gastroenteritis at weeks 1 and 20, and 1 with probable pneumonia at week 19).

Tolerability of study treatment was assessed as experiencing vomiting or diarrhea through week 24 and permanently discontinuing all study treatment by week 24. Among those who experienced vomiting, 7 (100%) in the SAM cohort were of mild grade. In the non-SAM cohort, 4 (80.0%) were of mild grade and 1 (20.0%) of moderate grade. Four of 9 (44.4%) in the SAM cohort and 2 of 3 (66.7%) in the non-SAM cohort had a moderate grade diarrhea event through week 24. Eight (15.4%) participants permanently discontinued study treatment by week 24: 5 (20%) SAM children [due to deaths unrelated to study treatment,[3] edematous malnutrition,[1] and taking disallowed medication[1]] and 3 (11%) non-SAM children [due to caregiver consent withdrawal,[1] inability to attend clinic,[1] and lost to follow-up[1]].

Viral Load and CD4 Cell Percent

Viral load suppression (≤400 copies/mL) did not differ significantly between cohorts at baseline (8.0% [95% CI (1.0%–26.0%)] in SAM vs. 7.4% (0.9%–24.3%) in non-SAM, $P > 0.999$) or week 12 [34.8% (16.4%–57.3%) in SAM vs. 58.3% (36.6%–77.9%) in non-SAM, $P = 0.15$]. At both weeks 24 and 48, viral load was ≤400 copies/mL in 50.0% (28.2%–71.8%) of SAM versus 78.3% (56.3%–92.5%) of non-SAM children ($P = 0.065$).

At baseline, mean (95% CI) CD4 cell percent was 15.5 (11.9–19.2) in the SAM and 24.5 (20.0–29.0) in the non-SAM cohort. No significant cohort differences of change in CD4 percent from baseline were observed at weeks 12, 24, and 36 ($P \geq 0.18$). At week 48, the SAM cohort had a significantly higher mean (95% CI) change in CD4 cell percent from baseline [12.7 (8.3–17.1)] than the non-SAM group [6.7 (4.2–9.1); $P = 0.018$]. At week 48, the mean (95% CI) CD4 percent was 28.9 (23.2–34.7) in the SAM cohort and 29.0 (25.3–32.8) in the non-SAM cohort.

DISCUSSION

This study showed that SAM and non-SAM children who were dosed according to WHO weight bands had highly variable AUC_{0-12h} and CL/F, particularly for LPV and RTV. On average, each drug's PK parameters did not differ significantly by cohort or time period. While our study did not find a significant difference in mean LPV/r exposure between the 2 cohorts, the SAM cohort had a trend toward lower exposures. This trend was consistent with Bartelink et al who previously reported lower LPV exposure in Ugandan children with a higher prevalence of malnutrition in comparison to European children with a low prevalence of malnutrition.[17] Our CL/F values were also comparable with those previously reported in children from both resource rich and poor countries.[17,18]

For 3TC, the AUC_{0-12h} and CL/F did not differ significantly between cohorts at week 1 or 24. At week 12, SAM children had a significantly lower AUC_{0-12h} than non-SAM children ($P = 0.047$). The finding given was not consistent across study weeks, and it may be a result of other factors, such as adherence, rather than nutritional differences. Our AUC_{0-12h} and CL/F values were similar to those reported by Kasirye et al and Kulkanya et al for children using liquid formulations.[19,20]

At week 24, the SAM cohort had a significantly higher mean ZDV AUC_{0-12h} ($P = 0.003$). While not significantly different, SAM children also had higher AUC_{0-12h} values at weeks 1 and 12. The exposure values were comparable to those reported by Kulkanya et al and within the range of values previously reported in adults.[20] Fillekes et al found that age and lower weight were both independently associated with higher ZDV exposures.[21] We tested for an

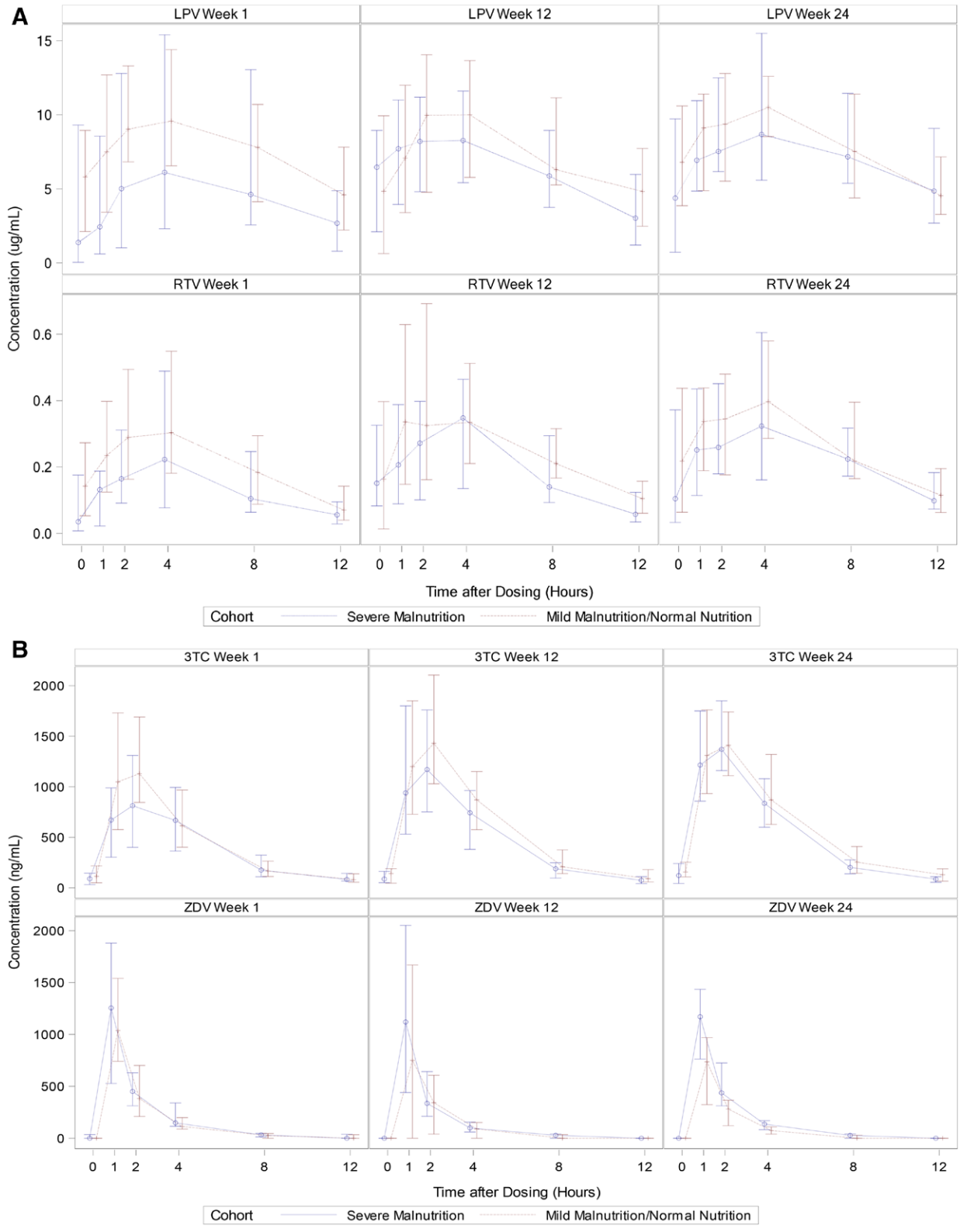

FIGURE 1. A, Plasma concentration—time profile of LPV and RTV in children with severe malnutrition (blue) and mild malnutrition/normal nutrition (red) for study weeks 1, 12, and 24. Data are reported as median (25th and 75th percentile). B, Plasma concentration—time profile of 3TC and ZDV in children with severe malnutrition (blue) and mild malnutrition/normal nutrition (red) for study weeks 1, 12, and 24. Data are reported as median (25th and 75th percentile). 3TC indicates lamivudine; LPV, lopinavir; RTV, ritonavir; ZDV, zidovudine.

TABLE 3. Grade 3 or Higher Adverse Events through Study Week 24 among Participants Evaluable for the Intensive PK Analysis

		Cohort				
		Severe Malnutrition		Mild Malnutrition/ Normal Nutrition		
Outcome	Experienced At Least One Grade 3 or Higher Adverse Event through Study Week 24	n (%)	95% CI	n (%)	95% CI	*P*
All events	Yes	13 (52.0%)	(31.3%–72.2%)	10 (37.0%)	(19.4%– 57.6%)	0.40
	No	12 (48.0%)		17 (63.0%)		
Events related to study treatment	Yes	6 (24.0%)	(9.4%–45.1%)	7 (25.9%)	(11.1%–46.3%)	>0.999
	No	19 (76.0%)		20 (74.1%)		

age effect and found age did not appear to affect the primary PK parameters in our study. Therefore, higher exposure across study weeks among SAM children could be due to weight differences between cohorts. ZDV is an acid-labile compound and malnutrition can lead to increased gastric pH resulting in increased absorption, which might explain our findings.[22] Given the observed ARV exposures in SAM children, the differences in virologic control between the cohorts, although not significant, needs further exploration. One plausible hypothesis is that SAM children have different profile of immune activation.

There were no apparent safety concerns or differences in prevalence of drug-related adverse events between cohorts. More SAM children experienced diarrhea on study. This was not unusual since SAM is associated with coinfections and metabolic complications, which may lead to vomiting and diarrhea, or death.

Strengths of this study included the relatively large numbers of evaluable children in both cohorts for PK parameters. All children received liquid formulation and were of similar ages. In addition, this study recruited participants from 4 countries in eastern and southern Africa, increasing the generalizability of results. Study limitations included children in the SAM cohort receiving nutritional rehabilitation for 2 weeks and showing clinical improvement before study enrollment and during the study. Therefore, improvements to their nutritional status may have reduced differences between the 2 groups. SAM participants also improved after baseline: median (25th, 75th percentile) change in WHZ from baseline to 24 weeks was 2.6 (1.2–3.2) in the SAM cohort and 0.2 (−0.4 to 0.6) in the non-SAM cohort. Given this study did not observe all ARV doses, potential nonadherence could have obscured differences between cohorts.[23] Maternal ARV exposure during breastfeeding may have impacted pharmacokinetic results, albeit the number of potentially exposed infants was small.

In conclusion, we found children with and without SAM had similar AUCs following WHO weight band dosing of ZDV, 3TC, and LPV/r and these doses appeared safe for children with SAM. These PK and safety findings indicate that the current WHO syrup formulation doses provide adequate exposure in children with SAM.

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