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 ($P<0.09$) 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, and severe acute malnutrition (SAM) remains one of the most common presentations of HIV in African children.1,2 Mortality among children with HIV and SAM is 3 times higher compared with children with SAM alone.3,4 Increasing access to antiretroviral therapy (ART) 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.5 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 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.7 In contrast, nucleoside reverse transcriptase inhibitors [e.g., zidovudine (ZDV) and lamivudine (3TC)] are acid labile and may show increased absorption in SAM children.8 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
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. 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). 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. 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 AUC0–12h between cohorts. LPV AUC0–12h coefficient of variation (CV) of 0.4 was assumed based on estimates in similarly aged children, and a 40% difference in AUC0–12h was considered clinically significant. Accounting for possible loss to follow-up (10%), mortality (20%), and variability in AUCn0–12h, 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$_E$ EDTA blood collection tubes. Plasma was separated and stored at −80°C 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 Clirpex 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 evaluation criteria. The laboratory participates in the AIDS Clinical Trial Group Pharmacology Quality Control Program.

PK and Statistical Analysis

The primary PK outcome measures were steady-state AUC0–12h 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/AUC0–12h. 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 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, 25) in the SAM and 18 months (12, 25) 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 ≥ 0.11). Mean 3TC AUC_{0–12h} and CL/F did not differ significantly by cohort at weeks 1 and 24 (Table 2; P ≥ 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 ≥ 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 ≥ 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

| Nutritional cohort subgroup | Severe Malnutrition (N=25) | Mild Malnutrition/Normal Nutrition (N=27) |
|-----------------------------|---------------------------|------------------------------------------|
| 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%)                                 |
| WHOZ weight-for-height Z-Score | -3.4 (-4.0, -3.0)   | -1.0 (-1.8, -0.1)                        |
| Midupper arm circumference (cm) | 11.0 (10.4, 11.5) | 13.9 (12.5, 15.5)                       |
| Log_{10} HIV-1 RNA (copies/mL) | 4.8 (4.2, 5.6)  | 5.6 (4.8, 6.1)                          |
| HIV-1 RNA (copies/mL, categorized) | <400      | 2 (8%)                                   |
| CD4 cell percent            | 15 (9.0, 22.6)            | 23 (17, 31)                              |
| Albumin g/L                 | 70.1 (66.4, 83.4)         | 76.4 (73.2, 79.3)                        |
| Total protein g/L           | 35 (31, 40)               | 41.8 (37, 47)                            |
Viral Load and CD4 Cell Percent

At baseline, 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. Our CL/F values were also comparable with those previously reported in children from both resource rich and poor countries.

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 Kulkanya et al for children using liquid formulations.

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.

Filiekes et al found that age and lower weight were both independently associated with higher ZDV exposures. 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

| Outcome                     | Experienced At Least One Grade 3 or Higher Adverse Event through Study Week 24 | Cohort                              |
|-----------------------------|---------------------------------------------------------------------------------|-------------------------------------|
|                             | (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%)                          |         |

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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REFERENCES

1. UNAIDS. UNAIDS data 2019 (updated 2018 data). 2019. Available at: https://www.unaids.org/en/resources/documents/2019/2019-UNAIDS-data. Accessed November 16, 2019.
2. Cross Continents Collaboration for Kids (3Cs4kids) Analysis and Writing Committee. Markers for predicting mortality in untreated HIV-infected children in resource-limited settings: a meta-analysis. AIDS. 2008;22:97–105.
3. Walker AS, Mulenga V, Sinyinza F, et al; CHAP Trial Team. Determinants of survival without antiretroviral therapy after infancy in HIV-1-infected Zambian children in the CHAP Trial. J Acquir Immune Defic Syndr. 2006;42:637–645.
4. Fergusson P, Tomkins A. HIV prevalence and mortality among children undergoing treatment for severe acute malnutrition in sub-Saharan Africa: a systematic review and meta-analysis. Trans R Soc Trop Med Hyg. 2009;103:541–548.
5. Muenchhoft M, Healy M, Singh R, et al. Malnutrition in HIV-infected children is an indicator of severe disease with an impaired response to antiretroviral therapy. AIDS Res Hum Retroviruses. 2018;34:46–55.
6. Krishnaswamy K. Drug metabolism and pharmacokinetics in malnourished children. Clin Pharmacokinet. 1989;17(suppl 1):68–88.
7. Gilman RH, Partanen R, Brown KH, et al. Decreased gastric acid secretion and bacterial colonization of the stomach in severely malnourished Bangladeshi children. Gastroenterology. 1988;94:1308–1314.
8. Falcon RW, Kakuda TN. Drug interactions between HIV protease inhibitors and acid-reducing agents. Clin Pharmacokinet. 2008;47:75–89.
9. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. 2013. Available at: https://www.who.int/hiv/pub/guidelines/arv2013/en. Accessed June 16, 2020.
10. World Health Organization. Antiretroviral Therapy for HIV Infection in Infants and Children. Recommendations for a Public Health Approach 2010 Revision. World Health Organization, 2010:206.
11. Division of AIDS. DAIDS AE Grading table Version 2.0 dated November 2014, 2014. Available at: https://rsc.niaid.nih.gov/sites/default/files/daids-aes-grading-table-v2-0-nov2014.pdf. Accessed November 16, 2019.
12. World Health Organization. Guideline: Updates on the management of severe acute malnutrition in infants and children. World Health Organization; 2013.

13. Capparelli E, Pinto J, Robbins B, et al. Lopinavir pharmacokinetic (PK) maturational changes and variability in HIV-infected infants beginning Kaletra (LPV/r) therapy at <6 weeks (WK) of age. In: Conference on Retroviruses and Opportunistic Infections, Boston, 2008. 2008.

14. Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry: Bioanalytical Method Validation. FDA; 2013. Available at: http://www.bioagilytix.com/wp-content/uploads/2016/02/FDA-Bioanalytical-Method-Validation-Draft-Guidance-2013.pdf. Accessed November 16, 2019.

15. European Medicines Agency. Guideline on Bioanalytical Method Validation. EMA; 2011. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500109686.pdf. Accessed November 16, 2019.

16. DiFrancesco R, Rosenkranz SL, Taylor CR, et al. Clinical pharmacology quality assurance program: models for longitudinal analysis of antiretroviral proficiency testing for international laboratories. Ther Drug Monit. 2013;35:631–642.

17. Bartelink IH, Savic RM, Dorsey G, et al. The effect of malnutrition on the pharmacokinetics and virologic outcomes of lopinavir, efavirenz and nevirapine in food insecure HIV-infected children in Tororo, Uganda. Pediatr Infect Dis J. 2015;34:e63–e70.

18. Yang J, Nikanjian M, Best BM, et al. Population pharmacokinetics of lopinavir/ritonavir: changes across formulations and human development from infancy through adulthood. J Clin Pharmacol. 2018;58:1604–1617.

19. Kasirye P, Kendall L, Adkison KK, et al; ARROW Trial Team. Pharmacokinetics of antiretroviral drug varies with formulation in the target population of children with HIV-1. Clin Pharmacol Ther. 2012;91:272–280.

20. Chokephaibulkit K, Cressey TR, Capparelli E, et al; IMPAACT P1069 Team. Pharmacokinetics and safety of a new paediatric fixed-dose combination of zidovudine/lamivudine/nevirapine in HIV-infected children. Antivir Ther. 2011;16:1287–1295.

21. Fillekes Q, Kendall L, Kitaka S, et al; ARROW Trial Team. Pharmacokinetics of zidovudine dosed twice daily according to World Health Organization weight bands in Ugandan HIV-infected children. Pediatr Infect Dis J. 2014;33:495–498.

22. Charman WN, Porter CJ, Mithani S, et al. Physiochemical and physiological mechanisms for the effects of food on drug absorption: the role of lipids and pH. J Pharm Sci. 1997;86:269–282.

23. Biressaw S, Abegaz WE, Abebe M, et al. Adherence to antiretroviral therapy and associated factors among HIV infected children in Ethiopia: unannounced home-based pill count versus caregivers’ report. BMC Pediatr. 2013;13:132.