Title

The Effect of Malnutrition on the Pharmacokinetics and Virologic Outcomes of Lopinavir, Efavirenz and Nevirapine in Food Insecure HIV-infected Children in Tororo, Uganda

Journal

The Pediatric Infectious Disease Journal, 34(3)

ISSN

0891-3668

Authors

Bartelink, Imke H
Savic, Rada M
Dorsey, Grant
et al.

Publication Date

2015-03-01

DOI

10.1097/inf.0000000000000603

Peer reviewed

HHS Public Access

Author manuscript

Pediatr Infect Dis J. Author manuscript; available in PMC 2016 March 01.

Published in final edited form as:

Pediatr Infect Dis J. 2015 March ; 34(3): e63–e70. doi:10.1097/INF.0000000000000603.

The Effect of Malnutrition on the Pharmacokinetics and Virologic Outcomes of Lopinavir, Efavirenz and Nevirapine in Food Insecure HIV-Infected Children in Tororo, Uganda

Imke H. Bartelink, PharmD, PhD[1,2], **Rada M. Savic, PhD**[2], **Grant Dorsey, PhD**[3], **Theodore Ruel, MD**[4], **David Gingrich**[1], **Henriette J. Scherpbier, MD, PhD**[10], **Edmund Capparelli, PhD**[11], **Vincent Jullien, PhD**[12], **Sera L. Young, PhD**[6], **Jane Achan, MMed**[7], **Albert Plenty, PhD**[5], **Edwin Charlebois, MPH, PhD**[5], **Moses Kamya, MMed, PhD**[8], **Diane Havlir, MD**[3], and **Francesca Aweeka, PharmD**[1]

[1]Department of Clinical Pharmacy, University of California, San Francisco, California, United States of America [2]Department of Bioengineering & Therapeutic Sciences, University of California, San Francisco, California, United States of America [3]Department of Medicine, University of California, San Francisco, California, United States of America [4]Department of Pediatrics, University of California, San Francisco, California, United States of America [5]Center for AIDS Prevention Studies, University of California, San Francisco, California, United States of America [6]Division of Nutritional Sciences, Cornell University, Ithaca, New York, United States of America [7]Department of Pediatrics and Child Health, Makerere University Kampala, Uganda [8]Department of Medicine, Makerere University Kampala, Uganda [10]Department of Pediatric Immunology and Infectious Diseases, Emma Children's Hospital AMC, The Netherlands [11]University of California San Diego, La Jolla, California, United States of America [12]Department of Pharmacology, Hôpital Européen Georges Pompidou, Paris Descartes, France

Abstract

Background—Malnutrition may impact the pharmacokinetics (PK) of antiretroviral medications and virologic responses in HIV-infected children. We therefore evaluated the PK of nevirapine (NVP), efavirenz (EFV) and lopinavir (LPV) in associations with nutritional status in a cohort of HIV-infected Ugandan children.

Methods—Sparse dried blood spot (DBS) samples from Ugandan children were used to estimate plasma concentrations. Historical PK data from children from three resource-rich countries (RRC) were utilized to develop the PK models.

Results—Concentrations in 330 DBS from 163 Ugandan children aged 0.7–7 years were analyzed in reference to plasma PK data (1189 samples) from 204 children from RRC aged 0.5–12 years. Among Ugandan children 48% was malnourished (underweight, thin or stunted). Compared to RRC, Ugandan children exhibited reduced bioavailability of EFV and LPV; 11% (P=0.045) and 18% (P=0.008) respectively. In contrast, NVP bioavailability was 46% higher in Ugandan children

Corresponding author: Francesca Aweeka, Pharm.D. Department of Clinical Pharmacy, University of California, San Francisco, 521 Parnassus Avenue, San Francisco, California, 94143-0622, faweeka@sfghsom.ucsf.edu, Phone 415-476-0339.

(P<0.001) with a trend towards greater bioavailability when malnourished. Children receiving LPV, EFV or NVP had comparable risk of virologic failure. Among children on NVP, low height and weight for age Z-scores were associated with reduced risk of virologic failure (p=0.034, p=0.068 respectively).

Conclusions—Ugandan children demonstrated lower EFV and LPV and higher NVP exposure compared to children in RRC, perhaps reflecting the consequence of malnutrition on bioavailability. In children receiving NVP, the relation between exposure, malnutrition and outcome turned out to be marginally significant. Further investigations are warranted using more intensive PK measurements and adequate adherence assessements, to further assess causes of virologic failure in Ugandan children.

Background

More than 90% of the world's 2.3 million HIV-infected children live in sub-Saharan Africa.[1] The pharmacokinetics (PK) of antiretroviral medications (ARV) in children in general, and those residing in sub-Saharan Africa specifically, have not been well characterized.[2] ARV exposure in these children may be affected by both developmental changes due to growth[3] as well as malnutrition;[4–6] with the latter far more common in sub-Saharan Africa then in resource-rich countries (RRC).[7] Food insecurity, an upstream determinant of malnutrition, can result in decreased adherence to ARV.[8,9] This is a more blatant contributor to variability in ARV exposure beyond any potential effects of nutritional status on drug absorption and metabolism. PK variability for ARV has serious implications for clinical outcomes. Erratic exposure to nevirapine (NVP) efavirenz (EFV) or boosted lopinavir (LPV) is associated with increased risks for virologic failure and/or drug resistance[10–20] and may elucidate why malnutrition is associated with worsening the clinical course of HIV infection.[8,21–25]

Previous studies investigating ARV exposures in malnourished children are inconclusive.[26–30] Studies suggest that WHO dosing guidelines for ARV based on weight yield suboptimal exposure to ARV in children, specifically for LPV and EFV.[31–33] Additionally, early studies report further reduced concentrations of ARV in sub-Saharan children.[26–28,30,34] Since it remains unknown why WHO dosing guidelines leads to suboptimal exposures in sub-Saharan children and whether malnutrition alters pediatric ARV exposures, more information is needed. Ultimately this knowledge may help guide optimal ARV treatment in malnourished children. To determine the effects of malnutrition on ARV PK in children, we investigated the PK of NVP, EFV and LPV in a cohort of HIV-infected children with diverse nutritional status residing in Tororo, Uganda. To determine if malnutrition was affecting the PK in Ugandan children, we evaluated levels following treatment in a model developed using datasets from RRC children and determined whether, within this cohort, measures of malnutrition were predictive of PK differences. To also explore the clinical impact of PK variability due to malnutrition, we compared virologic outcomes by treatment arm.

Methods

Sparse DBS samples from EFV, LPV and NVP from Ugandan children were collected. Datasets from the United States, The Netherlands and France, referred from this point forward as "resource-rich countries" (RRC) were utilized to develop a PK model that enables study of the effect of malnutrition on ARV PK of Ugandan children.[31,35,36]

Study population and sample collection

For this analysis, children were drawn from the "HIV Protease Inhibitors for the Prevention of Malaria in Ugandan Children" trial (PROMOTE-PEDS, NCT00978068, http://clinicaltrials.gov/show/NCT00978068). PROMOTE-PEDS was a prospective randomized clinical trial that enrolled Ugandan children between 2 months and 5 years of age. ARV details and procedures for the clinical study have been described previously.[37] Briefly, the purpose of PROMOTE-PEDS was to evaluate differences in malaria and HIV outcomes among children randomized to receive either a non-nucleoside reverse transcriptase inhibitor-based (NVP or EFV) or HIV protease inhibitor (boosted LPV) based- ARV regimen. Uncomplicated malaria was treated using artemether-lumefantrine, and complicated malaria using quinine. Children who were already receiving ARV were randomly assigned to continue their current regimen or to switch to LPV while continuing the same nucleoside analogue backbone. ARV-naïve children or their mothers who had received any dose of NVP in the past 24 months were excluded. Dosing was performed according to the Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children,[38] as summarized in Table 1.

Children were followed at the study clinic with monthly routine visits; CD4 counts and percentages, and HIV RNA levels were determined every 12 weeks for the first year and every 24 weeks thereafter as previously described.[39] Weight and age were obtained at each sampling time point for all patients Z-scores - calculated using WHO growth standards (2007)[40] - lower than −2 was used to classify low weight-for-age (WAZ, underweight), low height-for-age (HAZ, stunting) [41] and low BMI for age (BAZ, thinness).[42] Malnutrition was defined as underweight, stunting and/or thinness. 8. Food insecurity was measured using the Household Food Insecurity Access Scale (HFIAS), [43] and household hunger using the Household Hunger Scale (HHS).[44] All covariates are listed in Table 1. All parents/guardians of the children provided written informed consent. The study protocol was approved by the Faculty of Medicine's Research and Ethics Committee at Makerere University, the Uganda National Council of Science and Technology, and the Committee on Human Research at the University of California San Francisco.

Dried blood spots (DBS) for EFV, LPV and NVP measurements were collected during regularly scheduled monthly visits between May and August 2011. As samples were obtained after a minimum of 4 weeks after the start of treatment, all children were expected to have reached steady state ARV at the time of DBS sampling. At each visit, a single DBS was obtained and the time of collection was recorded. DBS were collected using a standardized amount of blood on Whatman™ Classic cards, Whatman™ 903 Cards, or chromatography paper. The samples were stored at −20°C and shipped on dry ice, in zip lock bags with a desiccant packet in each bag and considered stable.[45] Time of the last ARV

dose was determined per parent/guardian-report. DBS samples from Ugandan children were analyzed for EFV, LPV and NVP using a validated liquid chromatography-mass spectrometry method as described previously with similar assay conditions for NVP; [46] lower limits of quantification (LLOQ) for EFV, LPV and NVP were 0.1 mg/L, 0.01 mg/L and 0.01 mg/L, respectively. DBS concentrations were corrected to estimate the corresponding plasma concentrations as described previously.[46]

Historical pediatric datasets from RRC and corresponding population PK models—We developed the PK model for EFV using rich sampled data with up to six plasma samples collected over a dosing interval and the corresponding population PK model from a previously published Dutch study evaluating the efficacy and safety of EFV, abacavir, didanosine and lamivudine in children, aged 0.9 to 19 years.[31] For our analysis, children >12 years of age were excluded.

The PK model for LPV was developed using a sparse sampled dataset using single plasma samples obtained during routine clinical practice visits and the corresponding population PK model from a French study,[36] that included children, aged 0.5 to 7.9 years who were receiving LPV for the treatment of HIV infection or the prevention of mother-to-child transmission and underwent therapeutic drug monitoring for LPV concentrations as part of clinical care. The PK model for NVP was developed using a rich sampled dataset with up to wevern plasma samples collected in one dosing interval from a phase I/II study in the USA; International Maternal Pediatric and Adolescent AIDS Clinical Trials Network (IMPAACT) 377.[47] HIV-infected children from 4 months to 17 years were randomly assigned to one of four stavudine-containing regimens, three of which contained NVP. The validated literature-based population PK model of NVP, used in the current analysis, was based on a larger dataset of NVP PK data from eight pediatric clinical trials,[35] while only the USA data were available for our analysis of Ugandan and RRC children. Children >12 years of age were excluded from the analysis.

Pharmacokinetic analyses

Using the validated literature-based models for EFV, LPV and NVP,[31,35,36] we first evaluated whether measures of nutritional status in the RRC children could explain variability in oral clearance (CL/F) and volume of distribution (V/F). Therefore, WAZ and other measures of malnutrition, if available, were plotted independently against the individual PK parameters predicted by the previously published models.

This was followed by an analysis of the current data generated in Ugandan children. First, the differences in PK profiles of the three drugs between children from RRC countries and Uganda were studied using visual predictive checks (VPC). Using a VPC we compared the observations and simulated predictions to assess ability of the validated PK-models to reproduce the central tendency and the variability in the observed Ugandan data. A total of 1000 simulations were run based on dosing regimens of the patients, and using the PK-parameter values (including the inter- and intra-individual variability) obtained from the validated literate-based models of the RRC data.[31,35,36] CYP2B6 polymoprhisms at published allele frequencies were incorporated into the NVP and EFV model and was

assumed to be the same in RRC and Ugandan children.[48] In order to determine whether nutritional status explained the difference between RRC and Ugandan children, we joined the RRC data and Ugandan data in one analysis. The literature-based models were refitted to the RRC and Ugandan datasets and all parameters were re-estimated (joint base model). Differences in Cl/F and V/F were studied between the estimations in RRC children dataset and the joint Uganda + RRC datasets. We determined whether measures of nutritional status could explain the variability in ARV apparent bioavailability (F1), oral clearance (CL/F) and volume of distribution (V/F) between the RRC and Ugandan children and within the cohort of the Ugandan children. This covariate search was performed using a stepwise covariate model-building procedure, described elsewhere.[49–52]

Analyses were performed using Nonlinear mixed-effects modeling (NONMEM VI, Globomaxx LLC, Hanover, MD, USA). Concentrations below the LLOQ were excluded from the first PK analyses. The estimation of the final PK-models was repeated including LLOQ data, with LLOQ values set at the value of ½ LLOQ.

Virologic outcome analysis

The observed PK variability between EFV, NVP and LPV and contrasting changes in exposure between Ugandan and RRC children suggests differences in virologic outcomes may occur. Thus, we sought to investigate distinctions in virologic outcomes for each treatment group (LPV, EFV, NVP). The primary outcome for this analysis was confirmed virologic failure (CVF), defined as having 2 sequential plasma HIV RNA levels of > 400 c/ml after at least 24 weeks of ARV as previously described within the first 96 weeks of follow up.[37] Multivariate COX regression models of CVF were developed, adjusting for age, baseline CD4 and baseline HIV RNA levels. As the number of ARV-naïve and -experienced children differed between treatment arms, outcomes were compared first between ARV-naïve and -experienced children. Then stratified Cox regression was performed with ARV-naïve *versus* experienced as a stratification factor. Comparisons were performed between NVP, LPV and EFV treated patients (subgroup analysis). To evaluate whether baseline nutritional status was an important predictor of CVF, we utilized the same models, but added, individually, baseline WAZ, HAZ, BAZ or “malnutrition”. In order to explore the relationship between PK of ARVs and CFV, we compared outcomes between patients without and with one or more concentrations below LLOQ and explored the correlation between exposure (estimated using individual AUC values) and CVF. Statistical analyses were performed using SPSS version 20.0 (IBM, Armonk, NY).

Results

Concentrations of EFV, LPV or NVP for 330 DBS from 163 Ugandan children were combined with concentrations for 1189 plasma samples from 204 RRC children. Ten percent of the concentrations for Ugandan children were below LLOQ. Overall, 14% of children with any value below LLOQ were malnourished while 7% of patients with all concentrations above LLOQ were malnourished (P=0.694). The median age of Ugandan children at the time of sampling was 4.0 yrs (range 0.7–7.2 years, Table 1), while children from RRC were slightly older with a median age of 5.8 yrs (range 0.5–12). While 22% of

Ugandan children were underweight, only 8% of children from RRC were deemed underweight. 48% of Ugandan children were malnourished (underweight, thin and/or stunted). Most Ugandan children experienced moderate or severe household food insecurity (96%) and 40% experienced moderate to severe household hunger.

Population PK model

Using the historical RRC datasets and literature-based models for EFV, LPV and NVP.[31,35,36] PK-parameters CL/F and V/F were estimated. No correlation between CL/F and nutritional status was seen for EFV, LPV nor NVP in RRC children. The prediction corrected VPCs indicate that the observed EFV and LPV concentrations in Ugandan children were in agreement with the simulated concentrations expected in these children based on the RRC population models (figure 1). In contrast, the observed NVP concentrations in Ugandan children were consistently above the median of the simulated concentrations expected in these children. Comparison of PK parameters between RRC models and joint base models showed that inclusion of Ugandan children in the model resulted in an increase in CL/F by 9% and 11% for EFV and LPV and a decrease in CL/F by 11% for NVP (Table 2). V/F was similarly altered (+4% for EFV, +6% for LPV, and −10% for NVP). As CL/F and V/F were both altered in the joint model, an altered F1 in Ugandan children was estimated. Compared to RRC children, F1 of EFV and LPV were reduced by 11% (P=0.045) and 18% (P=0.008) and F1 of NVP was 46% (P < 0.001) higher in Ugandan children. The introduction of apparent bioavailability (F1) explained 4%, 2% and 6% of the inter-individual variability in EFV, LPV and NVP exposures respectively (Table 2). Although not significant, the introduction of F1 resulted in a large decrease in objective function value in comparison with estimating altered CL/F (P=0.655, P=0.403, P=0.371 for NVP, EFV and LPV respectively).

We compared ARV F1 between non-malnourished and malnourished Ugandan children and other measures of nutritional status. No significant difference in EFV F1 between non-malnourished and malnourished Ugandan children was observed. There was a trend toward lower LPV (P=0.114) exposures and higher NVP exposures (P=0.046) in malnourished in comparison to the non-malnourished Ugandan children (Table 2). In the Ugandan children the measures of HFIA and HHS were not predictive of ARV PK (data not shown).

As it is possible that children with concentrations below LLOQ were severely malnourished and had severe malabsorption, the estimation of the final PK-models was repeated after including LLOQ data. The inclusion of LLOQ data only affected the estimation of the volume of distribution of the drug and did not influence clearance. Including the LLOQ data did not affect any correlation between malnutrition and ARV PK (data not shown).

In order to assess the scope of potential problems using WHO dosing guidelines, minimum concentrations (C_{trough}) in children from Uganda and RRCs, were predicted using the final PK model for EFV, LPV and NVP and the WHO dosing guidelines.[38] Simulated EFV C_{trough} fell below the minimum recommended C_{trough} of 1 mg/L[38,53] in 23% of Ugandan and RCC children (Table 3). For LPV, simulations suggest that weight based dosing will result in appropriate C_{trough}[38,53] concentrations in 97% Ugandan children. For NVP, C_{trough}

concentrations exceeded the minimum recommended C_{trough} of 3 mg/L[38,53] in 98% of Ugandan children (Table 3).

Virologic outcome analyses

Based on the relatively low bioavailability of EFV and LPV and high bioavailability of NVP in the Ugandan children compared to RRC, we hypothesized that there would be differences in virologic outcomes between the ARV treatment groups. All patients used in the PK-analysis were included in the outcome analysis. One patient was lost to follow up after three weeks of treatment and 1 patient did not reach 1 year follow up. All other patients reached at least 1 year follow up.

In adjusted multivariate models of CVF, no differences in CVF were noted between patients who were ARV-naïve or ARV-suppressed for the whole group or per treatment arm, Table 4). After stratification, no differences in CVF were noted between children receiving EFV, LPV or NVP (P= 0.773, P= 0.428, P= 0.729 respectively). Two children discontinued from NVP due to adverse reactions (Stevens-Johnson Syndrome and hepatitis), but EFV or LPV/r treatments were never changed due to concern for adverse reactions.[39] Patients with one or more concentrations below LLOQ showed a higher chance of treatment failure in the whole group and specifically in the LPV treated patients (HR=2.08 and P=0.080, HR=4.09 and P=0.012 respectively). CVF was not explained by the exposure to ARVs (data not shown).

Based on the PK variability due to malnutrition, we hypothesized that poor nutrition may predict failure among the LPV and EFV, or conversely be protective against failure in NVP. None of the parameters of malnutrition were predictive of CVF (WAZ P=0.389, HAZ P= 0.587, BAZ P= 0.566, Malnutrition P=0.204, Table 4), even when restricting to ARV naïve (data not shown). In subgroup analyze, among children receiving LPV or EFV, baseline nutritional measures were not predictive of CVF (Table 4), but in the NVP arm, low WAZ and low HAZ were each at least marginally significantly associated with lower risk of CVF (WAZ HR= 1.54, P= 0.068, HAZ HR=1.48 P=0.034, Table 4).

Discussion

This study showed that EFV and LPV exposures were reduced by 11% and 18% among HIV-infected Ugandan children compared to children residing in resource-rich settings. Conversely, NVP exposures were 46% higher among Ugandan children. Notably, 23% of children on EFV exhibited trough concentrations less than the target level of 1 mg/L. Overall findings are attributed to distinctions in ARV bioavailability and nutritional detriments in our Ugandan cohort. Reduced exposure especially EFV may be clinically relevant for these children.[54] Despite altered ARV bioavailability and a significant proportion of children from our cohort exhibiting CVF, there were no differences in virologic outcomes between the LPV/r, EFV or NVP treatment arms; findings that differ from the results of P1060, where children (< 3 years) randomized to LPV/r *versus* NVP had superior virologic outcomes.[55] Although exposures and CVF malnutrition were not directly predictive of CVF in our study, malnourished Ugandan children (compared to non-malnourished Ugandan children) showed a lower risk of CVF plus higher NVP exposure. Two children in the NVP group experienced significant adverse events which raise concerns

over excessive NVP exposure. Individual virologic outcomes reflect an integral of drug exposure over a long period time resulting in a steady recovery of height and weight for the PROMOTE-PEDS trial children.[56] Therefore, drug exposures and nutritional status which were captured only at specific points in time in our study may not adequately have captured differences in drug exposure throughout treatment.

The RRC and Ugandan cohorts emanate from different populations, variable in age, ethnicity and genetic background, pretreatment, drug dosing, lack of randomization, use of antimalarials and differences in adherence. In the analyses some variables could not fully be accounted for. As mutation frequency was unknown in our cohort, a literature based assumption was made that mutation frequency in the Ugandan children[48] and RRC children[35,57] were similar. Time of dosing was recorded by the patient and not observed by clinic staff. Guardians of 83% of children reported 100% adherence which suggests overly optimistic reporting. The fact that 13% of patients showed one or more concentrations below LLOQ suggests that these patients had missed full doses of LPV, despite adherence reporting suggesting otherwise. Patients with concentrations below LLOQ showed a higher CVF risk, suggesting that low ARV exposures due to non-adherence may lead to treatment failure. Previous studies show that food insecurity decreases adherence to ART,[6] and poor adherence is associated with ART PK variability.[58–60] Savic et al. showed that adherence, assessed using Medication Event Monitoring System (MEMS), explained much of the variability in atazanavir pharmacokinetics 35 European HIV infected adults.[61] Future dedicated PK-studies using denser sampling techniques at specific times throughout treatment, (pre-existing) drug mutations and incorporating objective biomarkers of ARV adherence, would increase the understanding of PK variability and virologic outcomes due to malnourishment.

This is the first study which is specifically designed to study malnutrition in children. Nutritional status lowers bioavailability of EFV and LPV and increases bioavailability of NVP in Ugandan children. EFV and LPV was also previously studied by our group in Ugandan women from the PROMOTE-Pregnant women trial with food insecurity and these changes in PK are consistent with that study.[46] Earlier PK-studies in malnourished children do not clearly show a correlation between malnutrition and ARV exposures. In a study of 41 HIV-infected Ugandan children receiving EFV, no relationship between WAZ or HAZ and EFV exposures was observed.[34] Pollock *et al.* showed no independent effect of malnutrition on NVP exposures in 43 Malawian children.[29] Ellis *et al.* showed reduced NVP concentrations in stunted children, but increased exposures in wasted children.[26]

Mechanistically, malnutrition may reduce albumin or α-acid glycoprotein concentrations,[62,63] thereby increasing the free fraction of highly protein bound drugs such as LPV and EFV thus enhancing drug metabolism and elimination. High NVP exposures may also be explained by diminished auto-induction of NVP metabolism[64,65] due to malnutrition.[4,6] The lack of nutrition and/or a diet low in fat may also affect ARV absorption,[66–70] or ARV cellular transport, especially of protease inhibitors.[59,60,71,72] Future studies into the mechanisms by which malnourishment contributes to altered ARV-specific bioavailability will show whether the findings are generalizable to other malnourished children and may guide optimal ARV treatment in malnourished children.

In summary, the current study shows that altered ARV exposure in a cohort of Ugandan children with high rates of malnutrition and food insecurity results in modestly reduced bioavailability of EFV and LPV and increased bioavailability of NVP. In spite of previous findings, no difference in CVF was seen between treatment groups. Further studies to assess the impact of malnutrition on ARV pharmacokinetics, drug adherence and clinical outcomes in children residing in resource-limited settings are warranted.

Acknowledgments

The authors would like to thank the children and their parents who have participated in the PROMOTE-PEDS trial and to acknowledge the dedicated PROMOTE-PEDS study team, members of the Makerere University-University of California San Francisco Research Collaboration, and the midwives at Tororo District Hospital. In addition, we would like to thank Dr. Capparelli, Dr. Scherpbier, Dr. Huitema, Dr ter Heine and Dr. Julien for their generous contributions to the data set and analysis and Dr. Keizer for his help in the analysis. In addition we would like to acknowledge the Center for AIDS Research Pharmacology Core Laboratory and the Infectious Disease Research Center and the UCSF Center for AIDS Research; 5 P30 AI022763; NIH/NIAID. The primary sponsor of the PROMOTE-Pregnant Women and Infants trial is the National Institute for Child Health and Human Development P01 HD059454 (Havlir). Dr Young is supported by K01 MH098902-01 from the National Institute of Mental Health. Abbvie provided Lopinavir/ritonavir for the parent trial. Dr Ruel received support from the NIH(K236045901A2). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

1. [accessed May 2013] UNAIDS report on the global AIDS Epidemic. 2012. http//www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/gr2012/20121120_UNAIDS_Global_Report_2012_en.pdf
2. Bowen A, Palasanthiran P, Sohn AH. Global challenges in the development and delivery of paediatric antiretrovirals. Drug Discov Today. 2008; 13:530–535. [PubMed: 18549980]
3. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, KR. Developmental pharmacology--drug disposition, action, and therapy in infants and children. N Engl J Med. Sep 18.2003 349:1157–1167. [PubMed: 13679531]
4. Boullata JI. Drug disposition in obesity and protein-energy malnutrition. Proc Nutr Soc. 2010; 69:543–550. [PubMed: 20696092]
5. Krishnaswamy K. Drug metabolism and pharmacokinetics in malnourished children. Clin Pharmacokinet. 1989; 17 (Suppl 1):68–88. [PubMed: 2692941]
6. Raiten DJ. Nutrition and pharmacology: general principles and implications for HIV. Am J Clin Nutr. 2011; 94:1697S–1702S. [PubMed: 22089445]
7. Koethe JR, Heimburger DC. Nutritional aspects of HIV-associated wasting in sub-Saharan Africa. Am J Clin Nutr. 2010; 91:1138S–1142S. [PubMed: 20147470]
8. Anema A, Vogenthaler N, Frongillo EA, Kadiyala S, Weiser SD. Food insecurity and HIV/AIDS: current knowledge, gaps, and research priorities. Curr HIV AIDS Rep. 2009; 6:224–231.
9. SYAWAM, SW. A review of the role of food insecurity in adherence to care and treatment among adult and pediatric populations living with HIV and AIDS. AIDS Care. 2013 In Press.
10. de Gonzalez RD, et al. Correlation between lopinavir plasma levels and lipid abnormalities in patients taking lopinavir/ritonavir. AIDS Patient Care STDS. 2003; 17:443–445. [PubMed: 14588081]
11. Gutierrez F, et al. Lopinavir plasma concentrations and changes in lipid levels during salvage therapy with lopinavir/ritonavir-containing regimens. J Acquir Immune Defic Syndr. 2003; 33:594–600. [PubMed: 12902803]
12. Wateba MI, Billaud E, Dailly E, Jolliet P, Raffi F. Low initial trough plasma concentrations of lopinavir are associated with an impairment of virologic response in an unselected cohort of HIV-1-infected patients. HIV Med. 2006; 7:197–199. [PubMed: 16494635]

13. Ananworanich J, et al. Pharmacokinetics and 24-week efficacy/safety of dual boosted saquinavir/lopinavir/ritonavir in nucleoside-pretreated children. Pediatr Infect Dis J. 2005; 24:874–879. [PubMed: 16220084]
14. Leth FV, et al. Pharmacokinetic parameters of nevirapine and efavirenz in relation to antiretroviral efficacy. AIDS Res Hum Retroviruses. 2006; 22:232–239. [PubMed: 16545009]
15. Stahle L, Moberg L, Svensson JO, Sonnerborg A. Efavirenz plasma concentrations in HIV-infected patients: inter- and intraindividual variability and clinical effects. Ther Drug Monit. 2004; 26:267–270. [PubMed: 15167626]
16. Hsu A, et al. Pharmacokinetic-pharmacodynamic analysis of lopinavir-ritonavir in combination with efavirenz and two nucleoside reverse transcriptase inhibitors in extensively pretreated human immunodeficiency virus-infected patients. Antimicrob Agents Chemother. 2003; 47:350–359. [PubMed: 12499212]
17. Casado JL, et al. A clinical study of the combination of 100 mg ritonavir plus 800 mg indinavir as salvage therapy: influence of increased plasma drug levels in the rate of response. HIV Clin Trials. 2000; 1:13–19. [PubMed: 11590485]
18. Marzolini C, et al. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. AIDS. 2001; 15:71–75. [PubMed: 11192870]
19. Ciccarelli N, et al. Efavirenz associated with cognitive disorders in otherwise asymptomatic HIV-infected patients. Neurology. 2011; 76:1403–1409. [PubMed: 21502598]
20. Gutierrez F, et al. Prediction of neuropsychiatric adverse events associated with long-term efavirenz therapy, using plasma drug level monitoring. Clin Infect Dis. 2005; 41:1648–1653. [PubMed: 16267739]
21. Abrams B, Duncan D, Hertz-Picciotto I. A prospective study of dietary intake and acquired immune deficiency syndrome in HIV-seropositive homosexual men. J Acquir Immune Defic Syndr. 1993; 6:949–958. [PubMed: 8100273]
22. Baum MK, Shor-Posner G. Nutritional status and survival in HIV-1 disease. AIDS. 1997; 11:689–690. [PubMed: 9108956]
23. Koethe JR, et al. Association between weight gain and clinical outcomes among malnourished adults initiating antiretroviral therapy in Lusaka, Zambia. J Acquir Immune Defic Syndr. 2010; 53:507–513. [PubMed: 19730111]
24. Weiser SD, et al. The association between food insecurity and mortality among HIV-infected individuals on HAART. J Acquir Immune Defic Syndr. 2009; 52:342–349. [PubMed: 19675463]
25. Weiser SD, et al. Food insecurity is associated with morbidity and patterns of healthcare utilization among HIV-infected individuals in a resource-poor setting. AIDS. 2012; 26:67–75. [PubMed: 21904186]
26. Ellis JC, et al. Nevirapine concentrations in HIV-infected children treated with divided fixed-dose combination antiretroviral tablets in Malawi and Zambia. Antivir Ther. 2007; 12:253–260. [PubMed: 17503667]
27. Hirt D, et al. Is the recommended dose of efavirenz optimal in young West African human immunodeficiency virus-infected children? Antimicrob Agents Chemother. 2009; 53:4407–4413. [PubMed: 19635964]
28. L'homme RF, et al. Nevirapine, stavudine and lamivudine pharmacokinetics in African children on paediatric fixed-dose combination tablets. AIDS. 2008; 22:557–565. [PubMed: 18316996]
29. Pollock L, et al. Pharmacokinetics of nevirapine in HIV-infected children with and without malnutrition receiving divided adult fixed-dose combination tablets. J Antimicrob Chemother. 2009; 64:1251–1259. [PubMed: 19812065]
30. Ren Y, et al. High prevalence of subtherapeutic plasma concentrations of efavirenz in children. J Acquir Immune Defic Syndr. 2007; 45:133–136. [PubMed: 17417100]
31. ter RH, et al. A pharmacokinetic and pharmacogenetic study of efavirenz in children: dosing guidelines can result in subtherapeutic concentrations. Antivir Ther. 2008; 13:779–787. [PubMed: 18839779]
32. Verweel G, et al. Plasma concentrations of the HIV-protease inhibitor lopinavir are suboptimal in children aged 2 years and below. Antivir Ther. 2007; 12:453–458. [PubMed: 17668553]

33. von NH, et al. Need for therapeutic drug monitoring in HIV-1 infected children receiving efavirenz doses according to international guidelines. Eur J Med Res. 2006; 11:377–380. [PubMed: 17101460]
34. Fillekes Q, et al. Pediatric underdosing of efavirenz: a pharmacokinetic study in Uganda. J Acquir Immune Defic Syndr. 2011; 58:392–398. [PubMed: 21926634]
35. Nikanjam M, et al. Nevirapine exposure with WHO pediatric weight band dosing: enhanced therapeutic concentrations predicted based on extensive international pharmacokinetic experience. Antimicrob Agents Chemother. 2012; 56:5374–5380. [PubMed: 22869579]
36. Jullien V, et al. Population analysis of weight-, age-, and sex-related differences in the pharmacokinetics of lopinavir in children from birth to 18 years. Antimicrob Agents Chemother. 2006; 50:3548–3555. [PubMed: 16940058]
37. Achan J, et al. Antiretroviral agents and prevention of malaria in HIV-infected Ugandan children. N Engl J Med. 2012; 367:2110–2118. [PubMed: 23190222]
38. Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection 2006. 2006.
39. Ruel T, et al. Virologic and immunologic outcomes of HIV-infected Ugandan children randomized to lopinavir-ritonavir or nonnucleoside-reverse-transcriptase-inhibitor therapy. J Acquir Immune Defic Syndr. 2013
40. Centers for Disease Control and Prevention. Growth charts. 2000. http://www.cdc.gov/growthcharts/percentile_data_files.htmat <http://www.cdc.gov/growthcharts/percentile_data_files.htm>
41. WHO expert committee. Physical status: the use and interpretation of anthropometry, chapter 5 Infant and children. 1995:161–255.
42. Duggan MB. Anthropometry as a tool for measuring malnutrition: impact of the new WHO growth standards and reference. Ann Trop Paediatr. 2010; 30:1–17. [PubMed: 20196929]
43. Swindale JCA, Bilinsky P. Household food insecurity access scale (HFIAS) for measurement of food access: Indicator guide. Washingt DC Food Nutr Tech Assist Proj. 2007:1–31.
44. MDTBAS, JC. Introducing a simple mesure of household hunger for cross-cultural use. Tech Note, FANTA2. Feb.2011 :1–13.
45. Kromdijk W, et al. Use of dried blood spots for the determination of plasma concentrations of nevirapine and efavirenz. J Antimicrob Chemother. 2012; 67:1211–1216. [PubMed: 22302563]
46. Bartelink IH, et al. Pharmacokinetics of lopinavir/ritonavir and efavirenz in food insecure HIV-infected pregnant and breastfeeding women in tororo, uganda. J Clin Pharmacol. 201310.1002/jcph.167
47. Floren LC, et al. Nelfinavir pharmacokinetics in stable human immunodeficiency virus-positive children: Pediatric AIDS Clinical Trials Group Protocol 377. Pediatrics. 2003; 112:e220–e227. [PubMed: 12949316]
48. Mukonzo JK, et al. A novel polymorphism in ABCB1 gene, CYP2B6*6 and sex predict single-dose efavirenz population pharmacokinetics in Ugandans. Br J Clin Pharmacol. 2009; 68:690–699. [PubMed: 19916993]
49. De Cock RF, et al. The role of population PK-PD modelling in paediatric clinical research. Eur J Clin Pharmacol. 2011; 67 (Suppl 1):5–16. [PubMed: 20340012]
50. Sheiner LB, Ludden TM. Population pharmacokinetics/dynamics. Annu Rev Pharmacol Toxicol. 1992; 32:185–209. [PubMed: 1605567]
51. Karlsson MO, Savic RM. Diagnosing model diagnostics. Clin Pharmacol Ther. 2007; 82:17–20. [PubMed: 17571070]
52. Lindbom L, Pihlgren P, Jonsson EN. PsN-Toolkit--a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. Comput Programs Biomed. 2005; 79:241–257.
53. Aarnoutse RE, Schapiro JM, Boucher CA, Hekster YA, Burger DM. Therapeutic drug monitoring: an aid to optimising response to antiretroviral drugs? Drugs. 2003; 63:741–753. [PubMed: 12662123]
54. HHS Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children-A Working Group of the Office of AIDS Research Advisory Council (OARAC). HHS Panel on

Antiretroviral Therapy and Medical Management of HIV-Infected Children-A Working Group of. AIDS info: Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. 2013. at http://aidsinfo.nih.gov/guidelines

55. Violari A, et al. Nevirapine versus ritonavir-boosted lopinavir for HIV-infected children. N Engl J Med. 2012; 366:2380–2389. [PubMed: 22716976]
56. Ruel, T., et al. Growth recovery among HIV-infected children randomized to lopinavir/ritonavir or NNRTI-based therapy. CROI 2014, poster; 14AD.
57. ter HR, et al. Clinical evaluation of the determination of plasma concentrations of darunavir, etravirine, raltegravir and ritonavir in dried blood spot samples. Bioanalysis. 2011; 3:1093–1097. [PubMed: 21585304]
58. Ferraris RP, Carey HV. Intestinal transport during fasting and malnutrition. Annu Rev Nutr. 2000; 20:195–219. [PubMed: 10940332]
59. Winter TA, Lemmer ER, O'Keefe SJ, Ogden JM. The effect of severe undernutrition, and subsequent refeeding on digestive function in human patients. Eur J Gastroenterol Hepatol. 2000; 12:191–196. [PubMed: 10741934]
60. Winter TA. The effects of undernutrition and refeeding on metabolism and digestive function. Curr Opin Clin Nutr Metab Care. 2006; 9:596–602. [PubMed: 16912556]
61. Savic RM, et al. Effect of adherence as measured by MEMS, ritonavir boosting, and CYP3A5 genotype on atazanavir pharmacokinetics in treatment-naive HIV-infected patients. Clin Pharmacol Ther. 2012; 92:575–583. [PubMed: 23033116]
62. Ashton JM, Bolme P, Zerihun G. Protein binding of salicylic and salicyluric acid in serum from malnourished children: the influence of albumin, competitive binding and non-esterified fatty acids. J Pharm Pharmacol. 1989; 41:474–480. [PubMed: 2570853]
63. Krishnaswamy K, Ushasri V, Naidu NA. The effect of malnutrition on the pharmacokinetics of phenylbutazone. Clin Pharmacokinet. 1981; 6:152–159. [PubMed: 7214778]
64. Mirochnick M, Clarke DF, Dorenbaum A. Nevirapine: pharmacokinetic considerations in children and pregnant women. Clin Pharmacokinet. 2000; 39:281–293. [PubMed: 11069214]
65. Riska P, et al. Disposition and biotransformation of the antiretroviral drug nevirapine in humans. Drug Metab Dispos. 1999; 27:895–901. [PubMed: 10421616]
66. Lamorde M, et al. Effect of Food on the Steady-State Pharmacokinetics of Tenofovir and Emtricitabine plus Efavirenz in Ugandan Adults. AIDS Res Treat. 2012; 2012:105980. [PubMed: 22454762]
67. Lamorde M, et al. Steady-state pharmacokinetics of lopinavir plus ritonavir when administered under different meal conditions in HIV-infected Ugandan adults. J Acquir Immune Defic Syndr. 2012; 60:295–298. [PubMed: 22481601]
68. Ibarra M, et al. Impact of food administration on lopinavir-ritonavir bioequivalence studies. Eur J Pharm Sci. 2012; 46:516–521. [PubMed: 22522225]
69. Klein CE, et al. The tablet formulation of lopinavir/ritonavir provides similar bioavailability to the soft-gelatin capsule formulation with less pharmacokinetic variability and diminished food effect. J Acquir Immune Defic Syndr. 2007; 44:401–410. [PubMed: 17224848]
70. Kaul S, et al. Bioavailability in healthy adults of efavirenz capsule contents mixed with a small amount of food. Am J Health Syst Pharm. 2010; 67:217–222. [PubMed: 20101064]
71. Gracey M, Cullity GJ, Suharjono, Sunoto. The stomach in malnutrition. Arch Dis Child. 1977; 52:325–327. [PubMed: 871218]
72. Griffin L, Annaert P, Brouwer KL. Influence of drug transport proteins on the pharmacokinetics and drug interactions of HIV protease inhibitors. J Pharm Sci. 2011; 100:3636–3654. [PubMed: 21698598]

Figure 1a

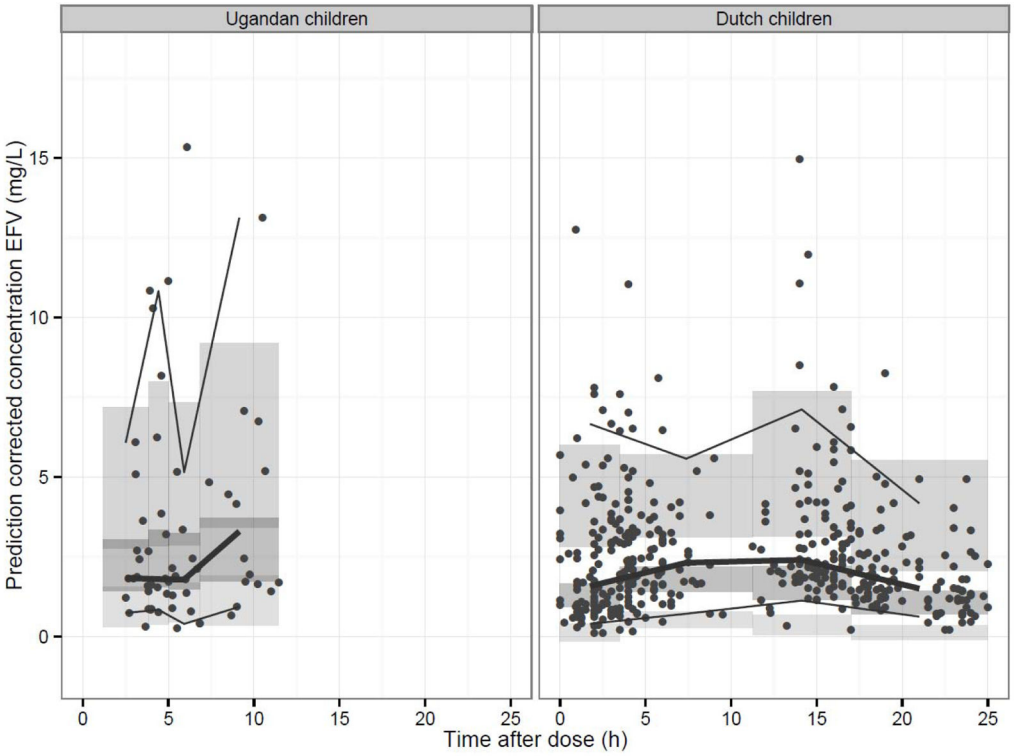

Figure 1b

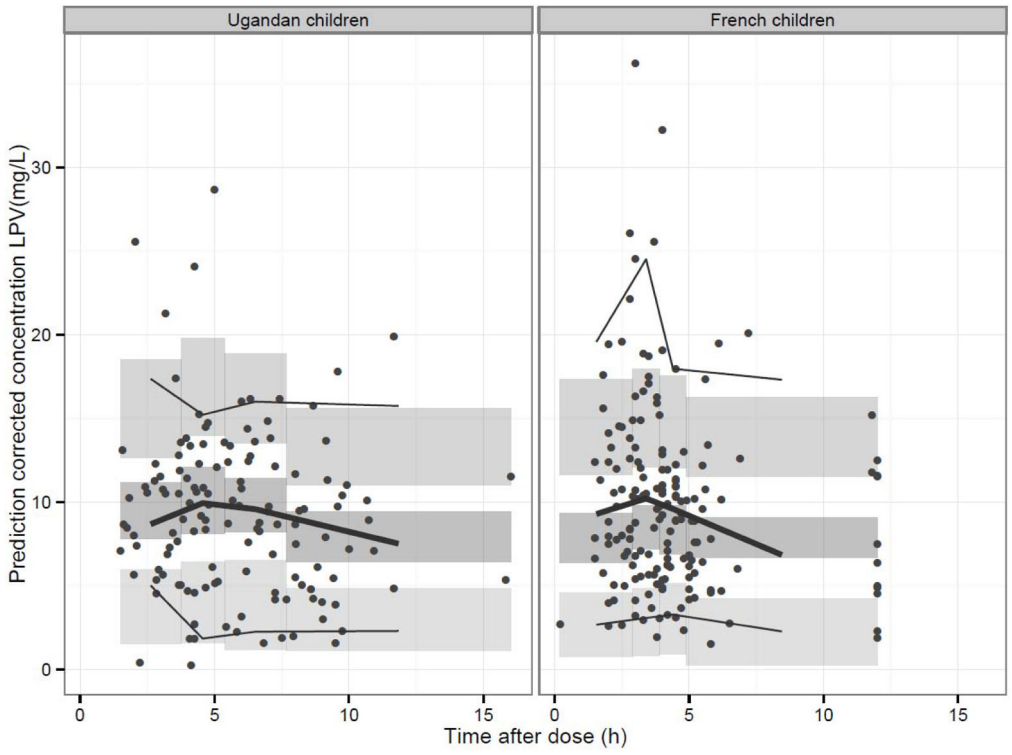

Figure 1c

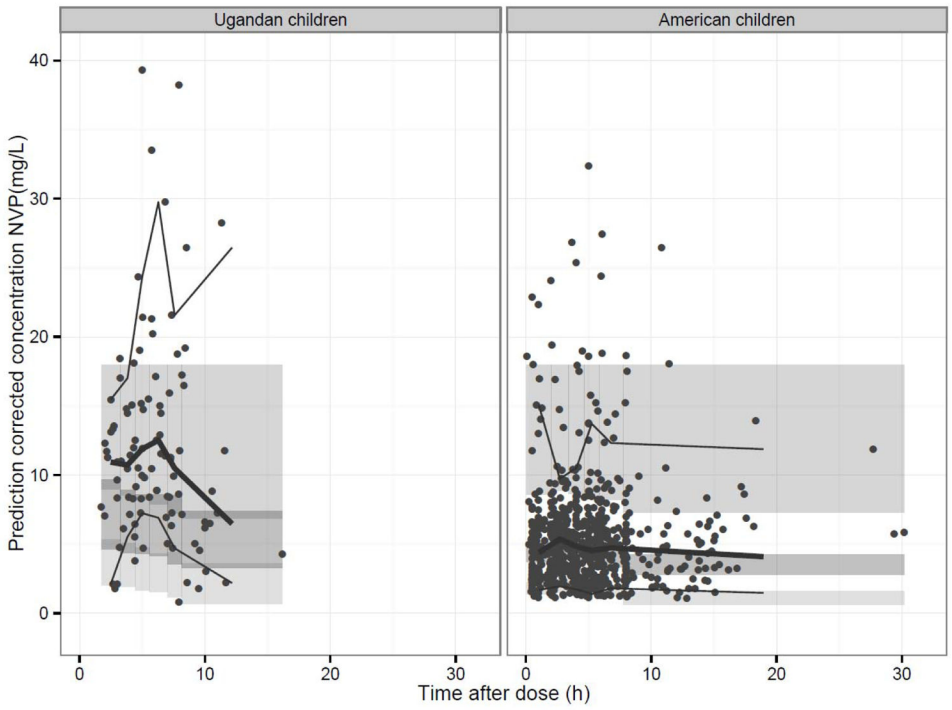

Figure 1.

Simulated concentration-time profiles* in children from the RRC datasets (right) and Ugandan children (left) using a) EFV, b) LPV, c) NVP.

* Simulations were performed using prediction corrected visual predictive checks. Concentrations were predicted validated literate-based models for EFV, LPV and NVP. A visual predictive check compares the observations and simulated predictions and can be used to assess ability of the validated PK-models to reproduce the central tendency and the variability in the observed Ugandan data. correction is performed by normalizing the observed and simulated dependent variable within a single bin (clustered data) based on the typical population prediction for the median independent variable (eg. The individual clearance for a patient of 18 kg, is normalized to the population predicted clearance of a patient of that weight). The solid lines represent the 5^{th} percentile, median and 95^{th} percentile of the prediction corrected observed plasma concentrations. The semitransparent dark grey field represents a simulation-based 95% confidence interval for the median and the semitransparent light grey fields show the 95% confidence intervals of the simulated data.

EFV: efavirenz, LPV: lopinavir, NVP: nevirapine,

Pediatr Infect Dis J. Author manuscript; available in PMC 2016 March 01.

Table 1

Characteristics of children from Uganda (left) and resource-rich countries (right) The median (range) of values are presented, unless specified otherwise.

Study	**Uganda**			**Netherlands**	**France**	**USA**
Drug	EFV	LPV	NVP	EFV	LPV	NVP
No. of patients	32	83	48	52	56	96
ART-naïve/ART-suppressed patient	26/6	59/24	28/20			
No. of samples	62	165	103	394	184	611
No. of samples below LLOQ	0	38	3	52	0	0
Max no sampling occassions	4	4	4	20	7	9
Age (years)	5.1 (2.4 – 7.0)	3.9 (1.0 – 7.2)	3.9 (0.7 – 6.9)	6.2 (0.9 – 11)	2.7 (0.5 – 7.9)	5.9 (0.5 – 12)
Weight (kg)	15.0 (8.3 – 25)	14.5 (6.0 – 24)	14.0 (5.2 – 22)	20.0 (11 – 48)	13.0 (6.0 – 32)	20.8 (5.5 – 74)
Drug dose (mg/m2)[1]			168 (133 – 278)			117 (77 – 124)
Drug dose (mg/kg) [2]						
>7.5–≤15kg	17.4 (13.8 – 20.5)	15.4(8.9–22.2)		19.7 (13–17.6)	13.3 (8.9 – 26.0)	
>15–≤20kg	16.7 (11.1 – 20)	12.9(7.6 – 16.7)		14.8 (13.9 – 15.6)	13.9 (8.6 – 22.2)	
>20–≤25kg	12.5 (7.0– 19.5)	12.2 (8.5 – 12.5)		14.6 (13.0 – 16.7)	12 (10.3 – 13.3)	
>25kg				13.3 (11.0 – 16.2)	7.6 (6.9 – 9.6)	
WAZ[3]	−1.13 (−4.9 – 1.7)	−1.23 (−4.0 – 0.9)	−1.5 (−5.8 – 0.91)	0.28 (−3.1 – 2.1)	−0.37 (−3.7 – 3.1)	−0.085 (−2.8 – 2.8)
HAZ[3]	−1.5 (−5.2 – 3.6)	−1.7 (−5.1 – 1.1)	−1.9 (−8.3 – 1.9)			
BAZ[3]	−0.27(−2.5 – 2.0)	−0.31 (−2.7 – 3.1)	−0.23 (−2.5 – 1.4)			0.41 (−2.2 – 3.3)
Underweight (%)[4]	25	18	27	10	14	4
Stunted (%)[5]	42	44	46			11
Thin (%)[6]	6	7	6			2
Malnourished (%)[7]	44	47	50			14
Food insecurity category (%)[8]						
No/Mild/Moderate/Severe	3, 3, 26, 68	3, 3, 24, 71	0, 0, 35, 65			
Household hunger (%)[9]						
Limited/Moderate/Severe	48, 52, 0	65, 29, 6	59, 36, 5			
Adherence (%)[10]						

Study	Uganda			Netherlands	France	USA
≥85–95%, ≥95%–<100%, 100%	6, 9, 84	1, 13, 86	4, 17, 79			

[1] Uganda: NVP suspension was dosed 10mg/ml (Aurobindo®, India) or as a 200mg tablet (Hetero® India) 160–200mg/m2. For the first 14 days of treatment, NVP was administered only once daily. After the first 14 days, NVP was administered every 12 hours. The NVP dose could be increased as long as there were no clinical concerns and Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) were normal.

RCC: NVP maintenance dose of 120mg/m^2 was used in all patients (liquid or tablet formulation, Table 1)

[2] Uganda: EFV was dosed as a suspension (Stocrin®30mg/ml solution Merck Sharp & Dohme, Netherlands) 19.5 mg/kg/dose or as a 200mg tablet (Strides, India) 15mg/kg/dose once daily, with a maximum of 600mg/dose.

RRC: EFV dose in this trial ranged from 27mg/kg in young children to 10 mg/kg in children older than 5 years of age, and was administered as syrup, capsule or tablets. [31]
Uganda: Ritonavir boosted LPV suspension (Kaletra ®, 80/20mg solution Abbvie, Germany) was dosed according weight, < 7kg: 16/4mg/kg/dose, 7 to <15 kg: 12/3mg/kg/dose, 15 to 40 kg: 10/2.5mg/kg/dose, > 40 kg: 400/100 mg/dose, or as a 100/25mg tablet (Aluvia ® Abbvie, Germany): 15–25 kg: 200/50mg/dose >25–35 kg: 300/75 mg/dose >35 kg: 400/100 mg tabs)/dose twice daily.

RRC: The LPV dosage ranged from 8.9 – 26.0 mg/kg twice daily.[36]

[3] Z-scores for weight, height and body mass index (BMI) were computed using WHO growth standards (2007).[40]

[4] Underweight: <−2SD WAZ,

[5] Stunted <−2SD HAZ[41]

[6] Thin: <−2SD BAZ[42]

[7] Malnourished was classified as: underweight, stunted, and/or thinness.

[8] Food insecurity was measured using the Household Food Insecurity Access Scale (HFIAS).[43] Children were classified as living in households that were food secure, mild, moderately or severely food insecure.

[9] Household hunger was classified using the Household Hunger Scale (HHS).[44] Children were classified as living in households that were categorized as having little to no household hunger, moderate household hunger or severe household hunger.

[10] Adherence in the Ugandan children was based on patient or parent/guardian report using a 3-day adherence recall and a visual analog scale. For the RRC studies, EFV adherence was monitored by telephone and at each follow-up visit, while LPV and NVP adherence was not specifically monitored.

EFV: efavirenz, LPV: lopinavir, NVP: nevirapine, WAZ: weight-for-age Z-score, BAZ: Body Mass Index for age Z-score. HAZ: height-for-age Z-score

Table 2

Comparison of the population pharmacokinetic parameter estimates clearance and volume of distribution of the original models of children of resource-rich countries (RRC).

	Drug		Estimate in a typical patient of 15 kg(RSE, shrinkage)			
		P	F1 % RRC, Uganda	CL/F (L/h)	V/F (L)	IIV CL/F (%, RSE, shrinkage)
RRC model	EFV		100,-	3.83 (17)	96 (11)	55 (16,3), 12.0 (76,58)
Joint base model			100100	**4.17**(11)	100 (11)	92 (12,6), **12.0** (67, 66)
Joint final model		0.045	100, **89** (17)	3.61 (10)	98(12)	91 (12,6), **11.2** (84,69)
Split Uganda non/malnourished		0.998	100, 86 (21), 94 (27)	3.89 (10)	98(12)	91 (13,6), **11.2** (77,69)
RRC model	LPV		100,-	1.87 (13)	11.5 (11)	44 (12, 15)
Joint base model			100100	**2.08**(4.5)	12.2 (8.9)	**41** (10,18)
Joint final model		0.008	100, **82** (7)	1.86 (12)	11.5 (10)	**40** (10,19)
Split Uganda non/malnourished		0.114	100, 87.1 (9), 74.6 (13)	1.86 (12)	11.5 (10)	40 (10,19)
RRC model	NVP		100,-	1.36 (5)	99.9 (48)	53 (8.4,6)
Joint base model			100, 100	**1.21** (5)	90 (43)	**57** (8,7)
Joint final model		<0.001	100, **146** (11)	1.36 (5)	86 (40)	**53** (8,9)
Split Uganda non/malnourished		0.046	100, 126 (14), 173 (13)	1.36 (5)	77 (39)	53 (8,8)

In RRC we used the validated literate-based models and pediatric data for EFV, LPV and NVP, to calculate all PK-parameters.

In the Joint base model, the RRC data and Ugandan data were joined. The literature-based models were refitted to the RRC and Ugandan datasets and all PK-parameters were re-estimated (joint base model).

In the joint final model differences in exposures between Ugandan and RRC children were corrected for using an apparent F1. In the split Uganda model, ARV F1 was compared between non-malnourished and malnourished Ugandan children and other measures of nutritional status.

F1=apparent bioavailability, CL=clearance V= volume of distribution RRC= resource rich countries

Table 3

Percentage of C_{trough}- values below the miminum target concentration of EFV, LPV and NVP, using the current pediatric guidelines in children from Uganda versus resource rich countries (RRC)

Drug	EFV		LPV		NVP	
	Dose (mg/day)	C_{trough} <1mg/L	Dose (mg/kg)	C_{trough} <1mg/L	Dose (mg/m^2)	C_{trough} <1mg/L
Ugandan children						
>5–≤7.5kg	150		16	3%	200	1%
>7.5–≤15kg	200	23%	12	3%	200	1%
>15–≤20kg	250	25%	10	4%	200	2%
>20–≤25kg	300	30%	10	3%	200	2%
RRC children						
>5–≤57.5kg	150		16	2%	200	6%
>7.5–≤15kg	200	22%	12	3%	200	5%
>15–≤20kg	250	23%	10	2%	200	5%
>20–≤25kg	300	21%	10	2%	200	5%

C_{trough} = minimum concentration, EFV: efavirenz, LPV: lopinavir, NVP: nevirapine

Table 4

Predictors of confirmed virologic failure*

	All patients			subgroup analysis								
	CVF 20%			EFV, CVF 18%			LPV, CVF 20%			NVP, CVF 22%		
	HR	**CI95%**	**P**	**HR**	**CI95%**	**P**	**HR**	**CI95%**	**P**	**HR**	**CI95%**	**P**
ARV-naïve vs suppressed	0.98	0.19–5.23	0.985	1.68	0.06–43.8	0.754	1.01	0.07–13.7	0.992	18.47	0.01–36000	0.451
Stratified for naïve/suppressed												
NVP	reference		0.729									
EFV	0.84	0.26–2.71	0.773									
LPV	0.73	0.34–1.57	0.428									
LLOQ (no/yes)	**2.08**	0.92–4.73	**0.080**				**4.09**	1.36–12.3	**0.012**	0.31	0.04–2.76	0.294
WAZ	1.13	0.85–1.50	0.389	0.86	0.28–2.66	0.796	1.03	0.70–1.52	0.869	1.54	0.97–2.45	0.068
HAZ	1.06	0.85–1.33	0.587	1.01	0.51–1.99	0.976	0.86	0.59–1.23	0.399	**1.48**	1.03–2.13	**0.034**
BAZ	1.08	0.84–1.39	0.566	0.60	0.14–2.67	0.508	1.15	0.84–1.57	0.378	1.20	0.65–2.21	0.561
Malnutrition (no/yes)**	0.61	0.29–1.30	0.204	0.29	0.02–4.24	0.364	1.10	0.32–3.80	0.875	**0.36**	0.11–1.20	0.096

EFV: efavirenz, LPV: lopinavir, NVP: nevirapine, CVF=confirmed virologic failure HR= hazard ratio, WAZ: weight-for-age Z-score, BAZ: Body Mass Index for age Z-score. HAZ: height-forage Z-score

*Multivariate COX regression models of virologic failure, included age and baseline CD4 and HIV RNA levels. In the subgroup analyses, the analyses were split between the three treatment arms. Significant predictors shown in bold.

**'non-malnourished children were chosen as reference group'.