Population pharmacokinetics of lumefantrine in the presence of nevirapine in HIV infected children

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ABSTRACT

Background: The geographical overlap of malaria and HIV in sub-Saharan Africa poses a major public health challenge, which is further worsened by the potential interactions between antimalarial and antiretroviral drugs when co-administered.

Objective: This study aimed to determine the population pharmacokinetic parameters of lumefantrine in the presence of nevirapine in HIV infected children.

Methods: A sparse pharmacokinetic study of lumefantrine was conducted in children living with HIV and being treated with nevirapine-based antiretroviral drug combination and were also being treated for malaria using artemether/lumefantrine (AL) combination. Blood sampling was performed at baseline (pre-dose, day 0) and at three additional time points selected from days 1, 3, 7, 14, 21, or 28. The pharmacokinetic modeling of lumefantrine was performed using a population approach with a non-linear mixed effect model (NLMEM) using a software program MonolixSuite® 2019 version R2, Lixoft, Antony, France, (http://www.lixoft.com).

Results: Lumefantrine pharmacokinetics were best described by a three-compartment disposition model with transit-compartment absorption and additive residual error. The mean transit time was 1.16 h, and apparent elimination clearance was estimated at 0.84, with low between-subject variability. Concomitant nevirapine use was associated with a modest, non-significant 6% increase in apparent lumefantrine clearance ($P > 0.05$). Allometric weight-based models did not significantly improve model performance. Diagnostic plots and visual predictive checks confirmed adequate model fit and predictive performance.

Conclusion: Nevirapine-based antiretroviral therapy did not result in clinically meaningful alteration of lumefantrine pharmacokinetics in children. These findings support continued use of standard weight-based artemether-lumefantrine dosing in HIV-infected paediatric populations receiving nevirapine.

Keywords: Population pharmacokinetics, Drug interaction, Artemether-lumefantrine, Malaria, Children.

Pharmacocinétique de population de la luméfantrine en présence de la névirapine chez les enfants infectés par le VIH

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RÉSUMÉ

Contexte: La superposition géographique du paludisme et du VIH en Afrique subsaharienne constitue un défi majeur de santé publique, qui est encore aggravé par les interactions potentielles entre les médicaments antipaludiques et antirétroviraux lorsqu'ils sont administrés conjointement.

Objectif: Cette étude visait à déterminer les paramètres pharmacocinétiques de population de la luméfantrine en présence de névirapine chez les enfants infectés par le VIH.

Méthodes: Une étude pharmacocinétique à échantillonnage clairsemé de luméfantrine a été menée chez des enfants vivant avec le VIH, traités par une combinaison de médicaments antirétroviraux à base de névirapine, et qui étaient également traités contre le paludisme à l'aide d'une combinaison artéméther/luméfantrine (AL). Des prélèvements sanguins ont été effectués au début de l'étdue (avant administration, jour 0) et à trois autres moments choisis parmi les jours 1, 3, 7, 14, 21 ou 28. La modélisation pharmacocinétique de la luméfantrine a été réalisée selon une approche populationnelle avec un modèle non linéaire à effets mixtes (NLMEM) à l'aide du logiciel MonolixSuite® 2019 version R2 (Lixoft , Antony, France, http://www.lixoft.com).

Résultats: La pharmacocinétique de la luméfantrine était mieux décrite par un modèle de distribution à trois compartiments avec absorption par compartiment de transit et erreur résiduelle additive. Le temps de transit moyen était de 1.16 h et la clairance d'élimination apparente était estimée à 0.84, avec une faible variabilité interindividuelle. L'administration concomitante de névirapine était associée à une augmentation modeste, non significative, de 6 % de la clairance apparente de la luméfantrine ($p > 0.05$). Les modèles allométriques basés sur le poids n'ont pas amélioré de manière significative les performances du modèle. Les graphiques de diagnostic et les vérifications visuelles prédictives ont confirmé l'adéquation du modèle et ses performances prédictives.

Conclusion: Le traitement antirétroviral à base de névirapine n'a pas entraîné de modification cliniquement significative de la pharmacocinétique de la luméfantrine chez l'enfant. Ces résultats confirment la pertinence du maintien de la posologie standard d'artéméther-luméfantrine, adaptée au poids, chez les populations pédiatriques infectées par le VIH et recevant de la névirapine.

Mots-clés: pharmacocinétique de population, interaction médicamenteuse, artéméther-luméfantrine, paludisme, enfants.

INTRODUCTION

Malaria and human immunodeficiency virus (HIV) infection continue to impose a significant dual burden of disease across sub-Saharan Africa, especially among children who often need concurrent antimalarial and antiretroviral therapy (ART).[1] In paediatric populations, developmental changes in drug metabolism further complicate treatment management, increasing the risk of clinically important drug-drug interactions that may compromise efficacy or safety.

Artemether-lumefantrine (AL) remains the most widely implemented artemisinin-based combination therapy for uncomplicated *Plasmodium falciparum* malaria in endemic settings.[1] The partner drug lumefantrine, characterised by slow absorption and extensive distribution, is primarily metabolised via cytochrome P450 3A4 (CYP3A4) and influenced by drug transport processes, notably P-glycoprotein-mediated transport.[2,3] Exposure to lumefantrine, particularly day-7 plasma concentrations, is a well-established pharmacokinetic predictor of therapeutic success and the risk of recrudescence.[4]

HIV treatment regimens in children often include non-nucleoside reverse transcriptase inhibitors (NNRTIs), such as nevirapine, which induce CYP3A4 and thereby have the potential to alter lumefantrine disposition. Population pharmacokinetic analyses in adults have demonstrated that co-administration of ARTs can substantially modify lumefantrine exposure: efavirenz-based ART has been associated with large decreases in lumefantrine exposure, while lopinavir/ritonavir markedly increases exposure; nevirapine's effect on lumefantrine exposure has been smaller and inconsistent across studies.[5,6] In pooled individual participant data from ten studies (n = 793), lumefantrine exposure increased 3.4-fold with lopinavir-ritonavir but was decreased by 47 % with efavirenz-based regimens. Whereas nevirapine- and dolutegravir-based ART did not show a statistically significant effect on lumefantrine exposure in adults.[6] This meta-analysis underscores the importance of considering ART choice in managing malaria treatment outcomes in coinfected populations.

In paediatric settings, specific pharmacokinetic interactions with nevirapine remain a critical concern. Prospective analyses in African children receiving nevirapine-based ART report a significant increase in lumefantrine exposure, with concurrent trends toward reduced artemether and dihydroartemisinin concentrations, findings that may differ from those in adult populations and suggest age-specific pharmacokinetic responses.[7] Additionally, population pharmacokinetic data in Ugandan children treated for uncomplicated malaria confirm that age and weight are significant determinants of lumefantrine bioavailability and exposure, with implications for therapeutic outcomes.[8] Though direct paediatric population pharmacokinetic modelling in HIV-infected children on nevirapine remains limited, these data collectively indicate a plausible interaction that may warrant dosing consideration and optimisation.

Use of non-linear mixed-effects modeling facilitates robust characterisation of sparse concentration versus time data - a common constraint in paediatric studies - and enables precise quantification of inter-individual variability and clinically relevant covariates affecting drug exposure. Given the high prevalence of malaria-HIV co-infection in African paediatric populations and the emerging evidence of ART-driven modification of antimalarial pharmacokinetics, it is essential to elucidate the population pharmacokinetics of lumefantrine in children receiving nevirapine-based ART to inform dosing strategies that optimise safety and efficacy.

Accordingly, this study aimed to characterise the population pharmacokinetics of lumefantrine in HIV-infected children undergoing nevirapine-based antiretroviral therapy and to assess the influence of concomitant nevirapine on lumefantrine disposition.

METHODS

Study area and patients

This prospective PK/PD study of artemether-lumefantrine for the treatment of uncomplicated malaria in HIV-infected children and HIV-uninfected children was conducted between March 2017 and December 2018. This study was carried out at three HIV treatment facilities located and managed within the hospital. Ikorodu General Hospital, Ijede General Hospital, Massey Street Children's Hospital, and the outpatient departments of the hospitals, all in Lagos State. The three hospitals were Lagos State-owned secondary healthcare facilities. The Lagos State Health Service Commission manages the study hospitals. Patients were enrolled in the study only when they met the inclusion criteria which included: age 2 to 12 years; microscopic confirmation of Plasmodium falciparum; body weight ≥ 6 kg; absence of severe malnutrition; haemoglobin concentration ≥ 7 g/dL; no history of associated comorbidity such tuberculosis, liver or renal failure; no history of recent use of any drug that

impacts CYP450 enzymes; no prior malaria treatment in ≤ 28 days, no signs of complicated malaria such as multiple or repeated convulsions, hyper/hypo glycaemia, macro-haemoglobinuria, extreme prostration and hyperpyrexia. HIV-infected children were typically on standard weight-based-dosed lamivudine and zidovudine with nevirapine (NVP).

Clinical management

The study enrolled children diagnosed with *P. falciparum* malaria via microscopy, with the intent to treat. Standard 6-dose treatment of weight-based artemether-lumefantrine (Coartem Dispersible 20 mg/120 mg, Novartis Pharma AG, Basel, Switzerland) was administered with milk in the clinic (initial dose) and at home (continued treatment), to enhance and control for lumefantrine absorption.[9] Active follow-up was instituted from day 0 (diagnosis) through day 28. Recurrent malaria episodes were genotyped to distinguish recrudescent from new infections. The details of recruitment and dosing were stated in our previous publication.[10]

Blood sampling and drug analysis

Sparse blood sampling was performed at baseline (pre-dose, day 0) and at three additional time points selected from days 1, 3, 7, 14, 21, or 28. Venous blood was collected into vacutainer (Lithium-heparin) bottles, centrifuged and stored at -80 ºC until analysis.

The concentration of lumefantrine was determined using a High-Performance Liquid Chromatography (HPLC) machine attached to a column, Zorbax C18 150 X 4.6mm, 5 µm, at a flow rate of 0.5 mL/minute, a wavelength of 335 nm, coupled with an Ultraviolet (UV) detector. The calibration range was 50-8000 ng/mL, LLOQ was 50 ng/mL, and CV % was < 5 %.

Pharmacokinetic methods and statistical analysis

The pharmacokinetic modelling of lumefantrine was performed using a population approach with non-linear mixed effect modelling using a software program MonolixSuite® 2019 version R2, Lixoft, Antony, France, http://www.lixoft.com/). This software program combines the stochastic expectation maximisation algorithm (SEAM) and Markov Chain Monte Carlo (MCMC) procedure for likelihood maximization.[11-13] Model diagnostics were performed using goodness-of-fit plots and a visual predictive check (VPC). The Objective Function Value (OFV), which is proportional to -2 multiplied by the log-likelihood of the data, was used in model discrimination.[13] The OFV is considered χ^2 distributed, and a decrease in value of at least 3.84 or 6.64 was deemed significant at 0.05 and 0.01 significant levels, respectively, of 1 degree of freedom, i.e., when one parameter is added to the nested model. Models were further selected based on the precision of parameter estimates and a decrease in Bayesian information criteria (BIC). The robustness and accuracy of the model were evaluated using the resampling statistical method of bootstrapping.

The Lognormal distribution model of the equation described interindividual variability.

$$\theta_i = \theta_p \times e^{\eta} \quad (1)$$

where θ_i in equation (1), is the estimate of the PK parameter of the individual patient, θ_p is the typical population PK parameter value, and η is the between-subject variability, which is a random variable from a normal distribution with a mean of zero and variance ω^2.

Residual variability was described by an additive error model with the equation;

$$C_{it} = P_{it} + \varepsilon \quad (2)$$

Where C_{it} and Pit in equation (2) are the observed and predicted concentrations of lumefantrine for the *i*th patient at time t, respectively, while t represents the error.

Concentration data below the limit of quantification were treated as missing data since they were less than 10 % of the total observed data. Disposition parameters of the model were venous whole blood clearance/bioavailability *(CL/F)*, central volume of distribution /F *(Vc/F)*, intercompartmental clearance */F (Q_1/F and Q_2/F)*, and peripheral volume of distribution*/F (Vp_1/F and Vp_2/F)*. One, two, and three-compartment distribution models were tested with different absorption models, including first-order absorption, first-order absorption with lag time, Zero-order absorption, and transit compartment absorption model with a linear elimination model. Allometric scaling (weight-normalised model and weight-normalised) was included unconditionally in all models, including the base model.

Concomitant administration of NVP was added as a categorical covariate. The covariate was evaluated on the relative bioavailability of lumefantrine and its elimination clearance. Other covariates tested include body weight in kg, variants of CYP3A4, age, and sex. Each covariate was

added in a stepwise manner with a forward criterion of P < 0.05 and a backward criterion of P < 0.001. R v 4.0.1 (the R Foundation for Statistical Computing, Vienna, Austria) was inter-phased with Monolix by Rsmlx (R Speaks Monolix; http://www.rsmlx.webpopix.org) to generate a 95 % confidence interval of the parameter estimates using the bootstrap statistical technique.[14] Population pharmacokinetic parameters were expressed as means with relative standard error (RSE). A two-tailed P-value of < 0.05 was considered to be statistically significant.

Ethical considerations

The Health Research Ethics Committee of the Lagos University Teaching Hospital approved the protocol of this study and assigned it an approval number (ADM/DCST/HREC/1437). Permission for informed consent was sought from the legally authorised representative for all the children. In addition to this, children above 7 years were asked for their assent.

RESULTS

Study population and baseline characteristics

A total of 1,032 children were screened for Plasmodium falciparum malaria, of whom 72 (7.0 %) met the eligibility criteria and were enrolled into the study. Following attrition due to withdrawal of consent and loss to follow-up, 52 children were included in the final population pharmacokinetic analysis, comprising 20 HIV-infected children receiving nevirapine-based antiretroviral therapy and 32 HIV-uninfected children serving as controls.

Baseline demographic and clinical characteristics of the study participants are summarised in Table 1. The mean age of children in the nevirapine group was significantly lower than that of the control group (7.00 ± 2.83 vs 8.81 ± 1.98 years; P = 0.008). Body weight did not differ significantly between groups, supporting the appropriateness of weight-based dosing of artemether-lumefantrine across the study population. Sex distribution was comparable between groups, and baseline parasite densities were similar, indicating comparable disease severity at enrolment.

Baseline plasma concentrations of artemether and lumefantrine did not differ significantly between the nevirapine and control groups, suggesting similar initial antimalarial exposure prior to pharmacokinetic modeling. Among HIV-infected children, median CD4 cell counts indicated preserved immune status, consistent with stable antiretroviral therapy (Table 1).

Table 1: Baseline characteristics of the participants' demographics and plasma antimalarial drug concentrations

Baseline Characteristics	Control (n=32)	Nevirapine +AL (n=20)	*P*
Demographics			
[a]Age (yr)	8.81 ±1.98	7.00 ±2.83	0.008[b]
[a]Weight (kg)	24.19±6.12	25.6 ±4.64	0.381[b]
Gender, No. (%)			
Female	16 (50.00)	12 (60.00)	0.573[c]
Male	16 (50.00)	8 (40.00)	
Parasite Density	21478 (7774-310080)	20907 (8378-41512)	0.915[d]
CD4 count (cells/uL)	N/A	456 (320-750)	
[a]Plasma level of AL			
Artemether (mg)	285.00 ±73.09	288.00±60.31	0.879[b]
Lumefantrine (mg)	1710±438.53	1728±361.89	0.879[b]

[a]Values are Mean ±SD or Median (Interquartile range)
[b]Reported P values calculated using the Unpaired T-test for continuous variable
[c]Reported P values calculated using the Chi-squared test for categorical variable
[d]Reported P values calculated using the Mann-Whitney test for continuous variable

Population pharmacokinetic model development

Sparse lumefantrine concentration-time data obtained from days 0 to 28 were pooled and analysed using a non-linear mixed-effects modeling approach. Among the structural models evaluated, a three-compartment disposition model provided a superior fit compared with one- and two-compartment models, as evidenced by a lower objective function value and improved diagnostic plots.

The absorption phase was best described using a transit-compartment model with a fixed number of transit compartments, outperforming first-order, lag-time, and zero-order absorption models. This finding reflects the delayed and variable absorption characteristics of lumefantrine and is consistent with its known dependence on gastrointestinal conditions and fat co-administration.

Interindividual variability was adequately captured using a log-normal distribution for key pharmacokinetic parameters, while residual unexplained variability was best described by an additive error model. Inclusion of allometric scaling based on body weight did not significantly improve model performance and therefore, was not retained in the final model.

Population pharmacokinetic parameter estimates

The final population pharmacokinetic parameter estimates are presented in Table 2. The mean transit time for lumefantrine absorption was estimated at 1.16 hours, with moderate between-subject variability, reflecting interindividual differences in absorption kinetics. The apparent elimination clearance (CL/F) was estimated at 0.84, with relatively low variability, indicating consistent elimination across the population.

The apparent volume of distribution of the central compartment (Vc/F) was estimated at 0.16, with moderate between-subject variability, consistent with the extensive tissue distribution characteristic of lumefantrine. Peripheral distribution parameters further supported a multi-compartment disposition profile.

Concomitant administration of nevirapine was associated with a 6 % increase in apparent lumefantrine clearance; however, this effect did not reach statistical significance ($P > 0.05$). The relative standard errors for key pharmacokinetic parameters were generally below 50 %, indicating acceptable parameter precision. η-shrinkage values were within acceptable limits (≤ 30 %) for all major parameters, supporting the reliability of individual parameter estimates.

Table 2: Parameter estimates describing population pharmacokinetics of lumefantrine

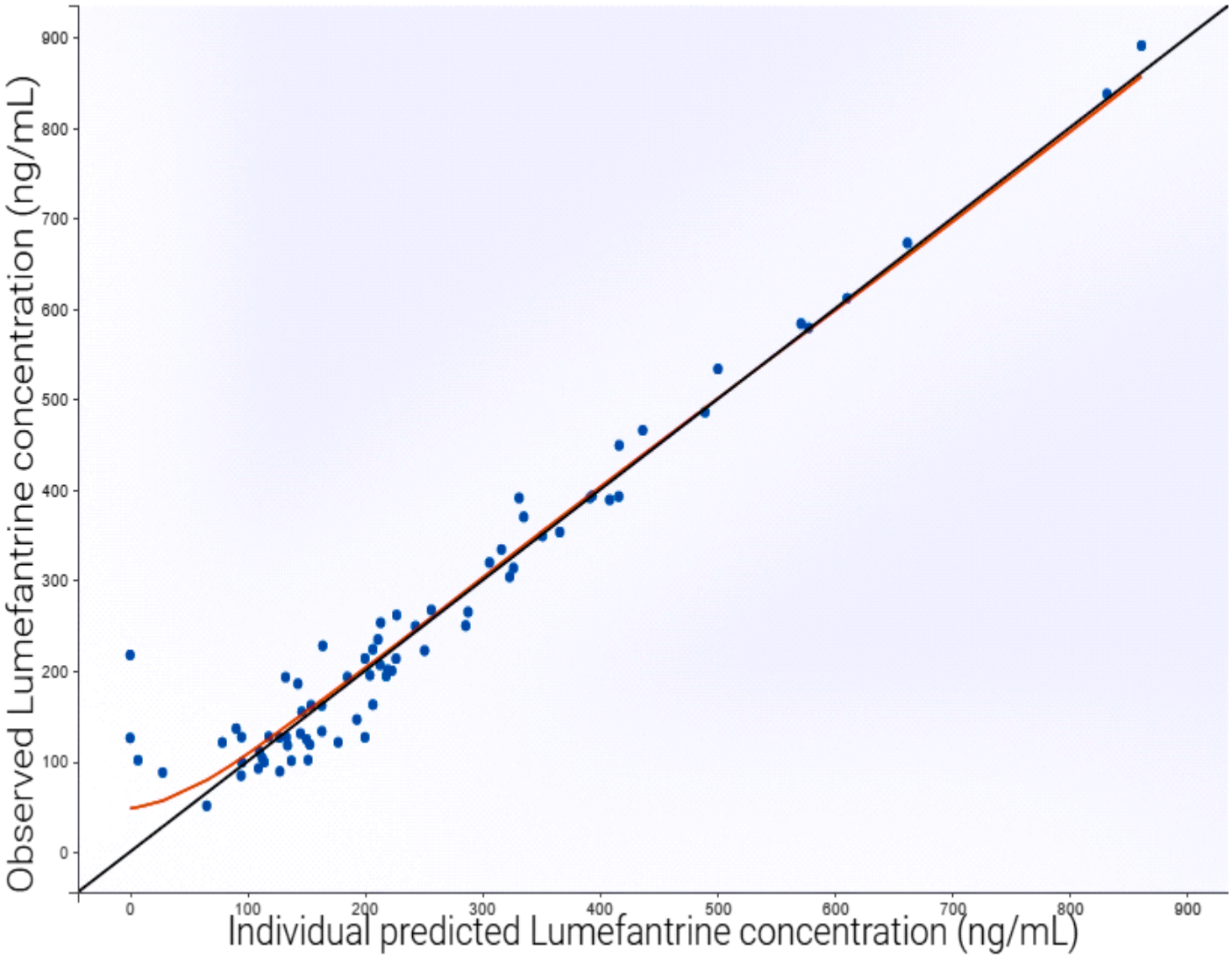
Parameters	Population estimates [RSE%]	95% CI	BSV [RSE %]	95% CI	Shrinkage (%)
K_{tr}	2.74 [17]	1.40, 7.14	0.18 [13]	0.15 - 0.45	5.7
Mtt (h)	1.16 [8.3]	0.64, 2.95	0.19 [213]	0.07- 0.66	5.29
K_a (h^{-1})	0.201 [6.7]	0.19, 4.52	0.13 [59]	0.06 - 0.46	15
Cl/F	0.84 {3.5]	0.25, 1.73	0.07 [21]	0.03 - 0.54	2.45
$NVP_{Cl/F}$	0.060 [20]	-0.18, 0.38	0.2 [23.3]	-	-
V_c/F	0.16 [42.3]	0.14, 0.43	0.32 [76.4]	0.07 - 0.54	-15.5
Q_1/F	0.014 [48.8]	0.01, 0.03	1.5 [22.3]	0.04 - 0.33	-10.7
V_{p1}/F	2.4 [18.1]	1.72, 3.19	0.19 [105]	0.02 - 0.31	6.48
Q_2/F	0.00070 [52.4]	-	0.09 [204]	0.01 - 5.82	-12.4
V_{p2}/F	0.37 [86.2]	-	0.12 [145]	0.08 - 3.59	7.22
RUV	52.3 [13.7]	18.43, 63.16	-	-	-

CL/F is the apparent elimination clearance. *Vc/F* is the apparent volume of distribution of the central compartment. Q_1/F and Q_2/F are the inter-compartment clearance between the central and the peripheral compartments 1 and 2 respectively. V_{P1}/F and V_{P2}/F are the apparent volume of distribution of the peripheral compartments 1 and 2, respectively. MTT is the mean transit time of the absorption. RUV is the variance of the unexplained residual variability. BSV is the between-subject variability or interindividual variability. RSE is the relative standard error, $NVP_{CL/F}$ is the effect on elimination, the 2.5 to 97.5 percentiles of bootstrap estimates as generated through R. *Based on the population mean values from Monolix.

Goodness-of-Fit and Model Diagnostics

Goodness-of-fit diagnostics demonstrated that the final model adequately described the observed lumefantrine concentration-time data. Plots of observed versus individual predicted concentrations showed close agreement, with data points symmetrically distributed around the line of identity (Figure 1). The locally weighted regression line closely followed the identity line, indicating minimal systematic bias.

Conditional weighted residuals plotted against time after dose revealed no major trends, although mild bias was observed at early time points, likely reflecting variability in the absorption phase (Figure 2). Overall, residuals were randomly distributed, supporting the adequacy of the structural and error models.



Observations plotted against the individual predicted concentration. The black line is the identity line and the red-coloured line is the locally weighted least square regression line. The concentrations are presented on a logarithmic (base 10) axis.

Figure 1: Basic goodness-of-fit plot for the final lumefantrine model.

The dashed line is the identity line, and the yellow-coloured line is the locally weighted least square regression line.

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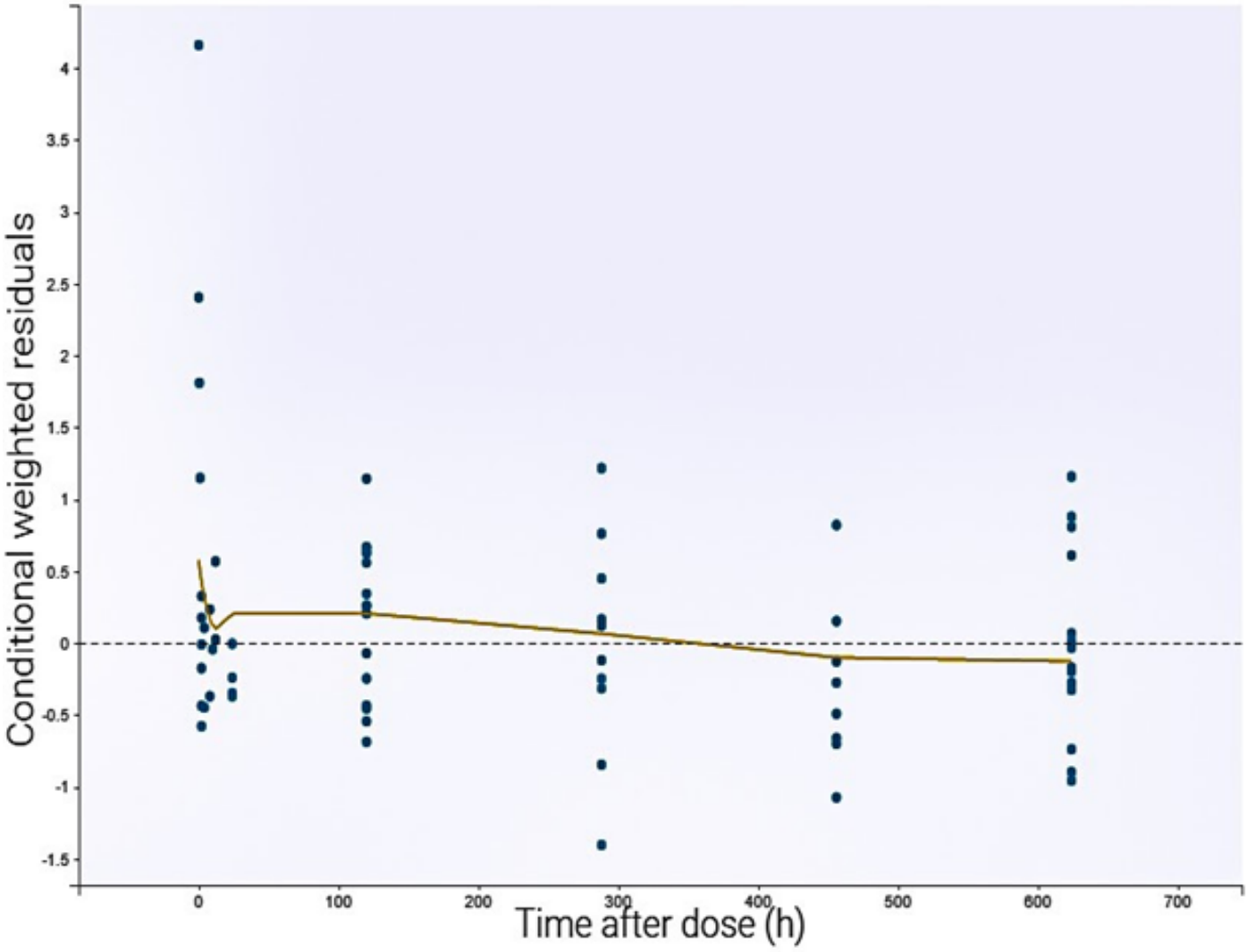


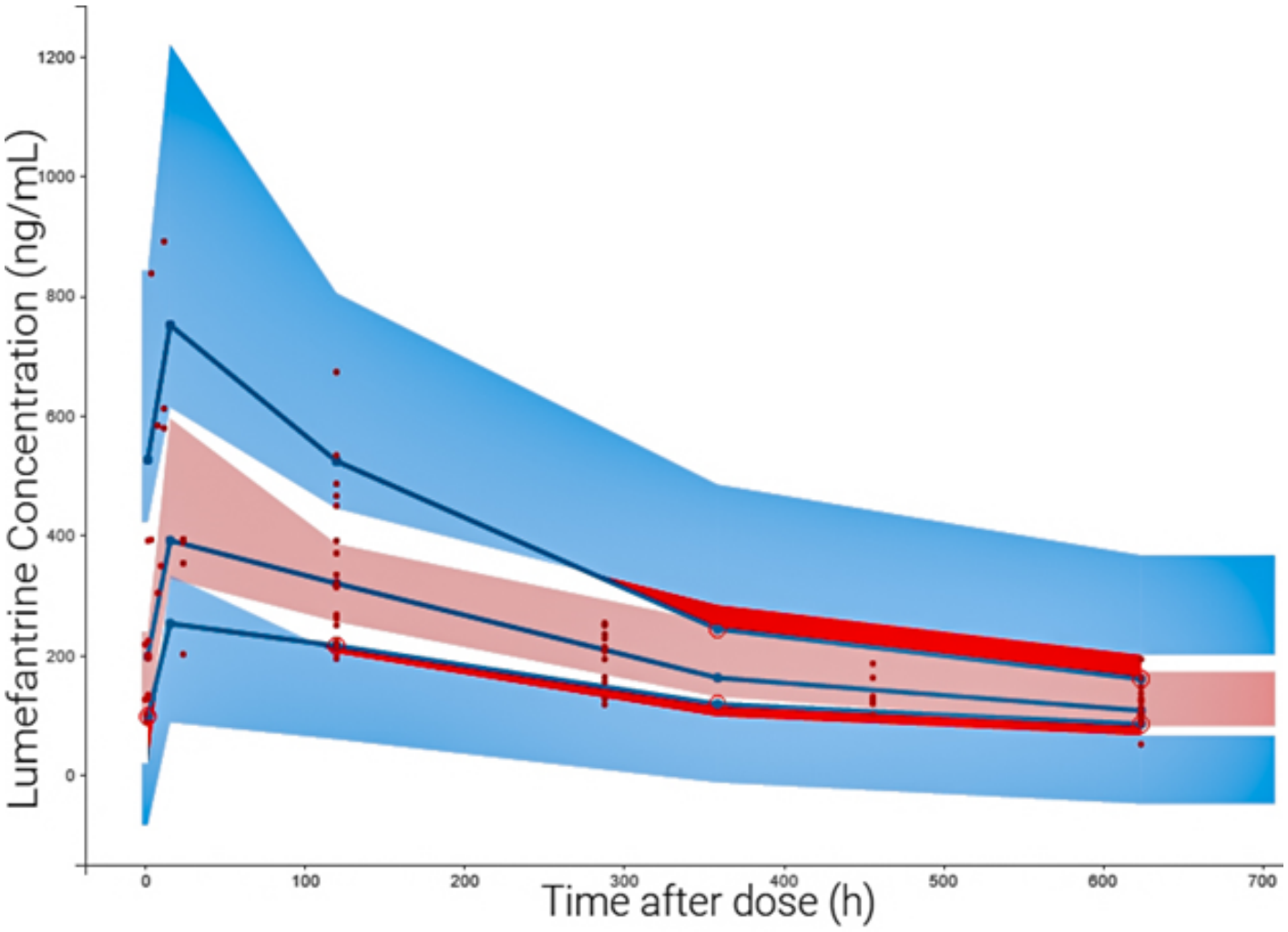
The dashed line is the identity line, and the yellow-coloured line is the locally weighted least square regression line.

Figure 2: Conditional weighted residuals plotted against time after dose.

Visual predictive check

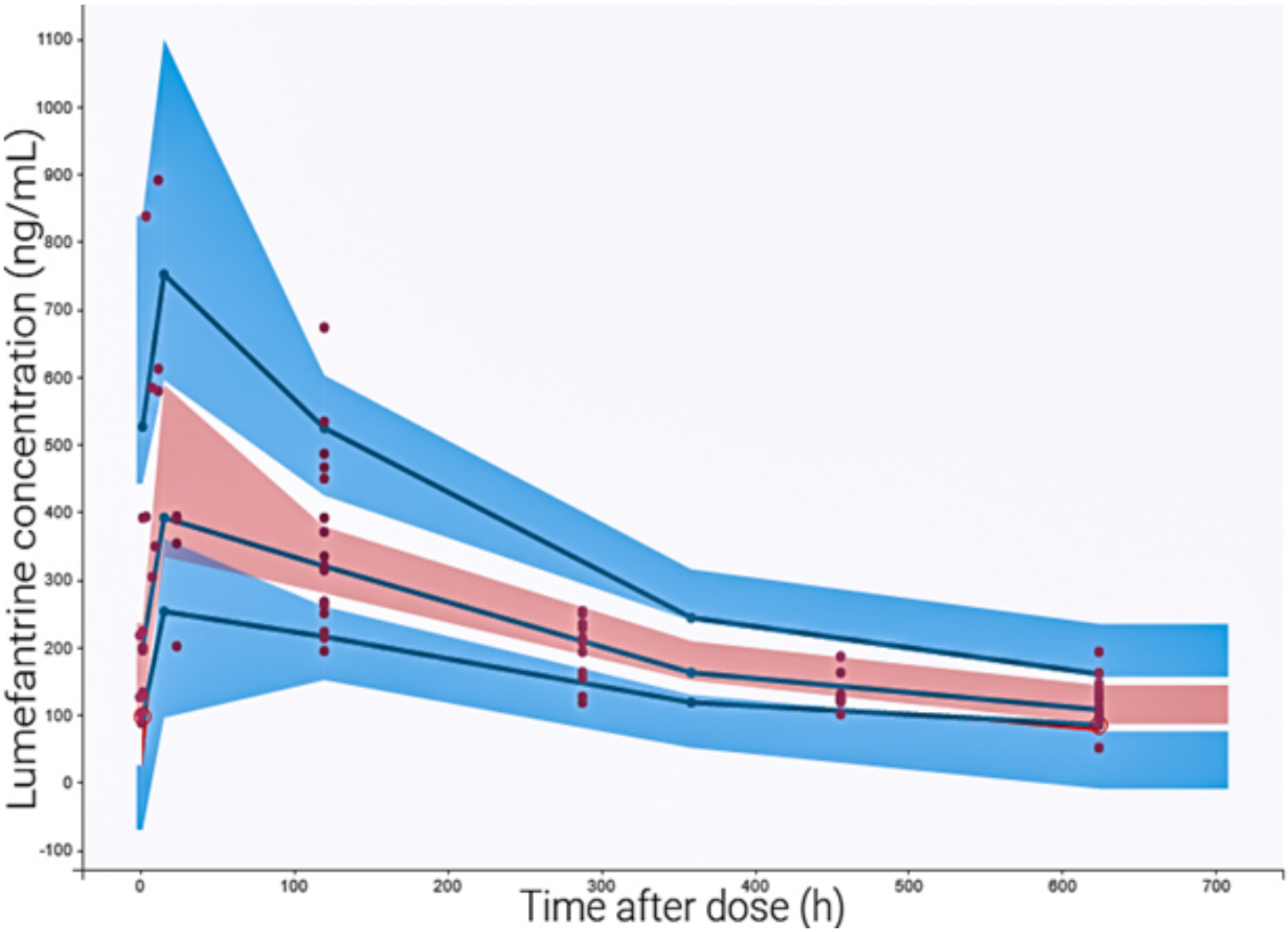
Visual predictive checks further confirmed the predictive performance of the final pharmacokinetic model. The base model demonstrated instability, with a substantial proportion of observed concentrations falling outside the simulated prediction intervals (Figure 3). In contrast, the final model showed good predictive accuracy, with fewer than 10 % of observed concentrations lying outside the 10th and 90th percentiles of the simulated data (Figure 4).

The final prediction-corrected concentration-time plot illustrated close alignment between observed data points and simulated median profiles, with appropriate coverage of variability across the dosing interval (Figure 5). These results indicate that the final model reliably captures both the central tendency and variability of lumefantrine pharmacokinetics in the study population.



Circles represent the observations and solid lines represent the 5 th, 50 th and 95 th percentiles of the observed data. The shaded areas represent the 95 % confidence intervals around the simulated 5 th, 50th, and 95 th percentiles. The concentrations are presented on a logarithmic (base 10) axis.

Figure 3: Visual predictive checks of the Base model for lumefantrine.

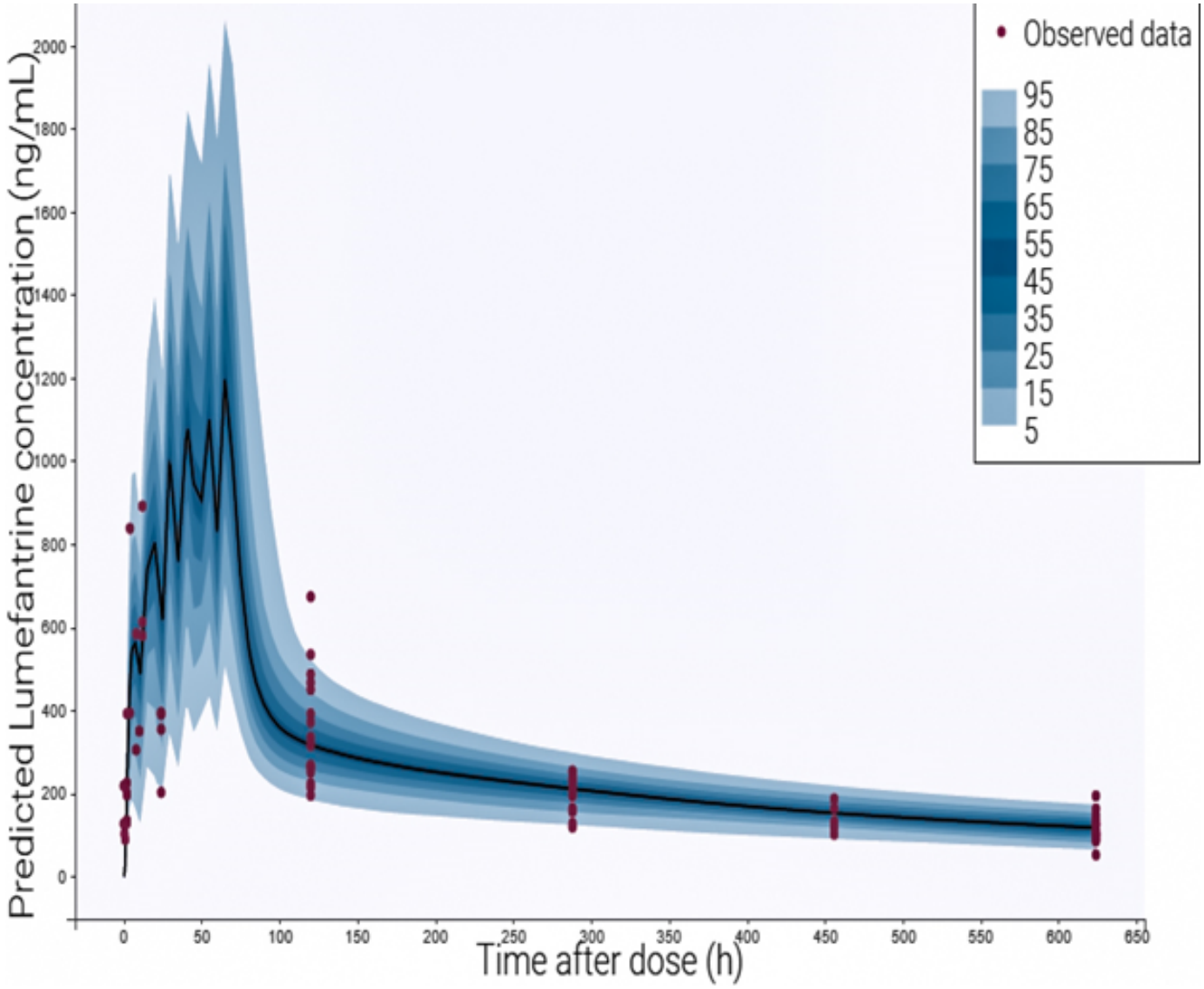


Circles represent the observations and solid lines represent the 5 th, 50 th and 95 th percentiles of the observed data. The shaded areas represent the 95 % confidence intervals around the simulated 5 th, 50 th, and 95 th percentiles. The concentrations are presented on a logarithmic (base 10) axis.

The solid line at the centre represents the median, while the prediction intervals are indicated by the depth of shading between the 5 th and 95 th percentile as shown on the scale to the right.

The solid line at the centre represents the median, while the prediction intervals are indicated by the depth of shading between the 5 th and 95 th percentile.

Figure 4: Visual predictive checks of the final models for lumefantrine



The solid line at the centre represents the median, while the prediction intervals are indicated by the depth of shading between the 5 th and 95 th percentile as shown on the scale to the right.

Figure 5: Prediction of lumefantrine concentration distribution plotted against time for the final model superimposed on the observed data points.

DISCUSSION

This study characterised the population pharmacokinetics of lumefantrine in HIV-infected children receiving nevirapine-based antiretroviral therapy using a non-linear mixed-effects modelling approach. A three-compartment disposition model with transit-compartment absorption and linear elimination best described the sparse lumefantrine concentration-time data. Importantly, concomitant administration of nevirapine was associated with a modest, non-significant increase in apparent lumefantrine clearance, resulting in a 6 % reduction in exposure. Although not statistically significant, this finding has potential clinical relevance given the exposure-response relationship established for lumefantrine.

The pharmacokinetic behaviour of lumefantrine observed in this study is consistent with its known physicochemical and metabolic characteristics. Lumefantrine is a highly lipophilic compound with slow and variable absorption, extensive tissue distribution, and elimination primarily mediated by CYP3A4, with contributory roles of intestinal transporters such as *P-glycoprotein*.[2,3] These features contribute to substantial interindividual variability, particularly in paediatric populations, where developmental physiology further influences drug disposition.

The three-compartment structural model identified in

this study aligns with previous paediatric population pharmacokinetic analyses. Salman *et al*, similarly, reported a three-compartment disposition model for lumefantrine in children,[15] contrasting with the predominantly two-compartment models reported in adult and pregnant populations.[2,16,17] This discrepancy likely reflects age-dependent differences in distribution kinetics and sampling design, as paediatric studies often rely on sparse sampling strategies that benefit from more flexible structural models. Goodness-of-fit diagnostics, acceptable η-shrinkage, and robust visual predictive checks supported the adequacy of the final model in the present study.

The observed increase in apparent lumefantrine clearance in children receiving nevirapine is biologically plausible. Nevirapine is a known inducer of CYP3A4 and has been shown to influence the expression of drug-metabolising enzymes and transporters, including intestinal *P-glycoprotein*.[5] Induction of these pathways could enhance first-pass metabolism or systemic clearance of lumefantrine, thereby reducing overall exposure. Although the effect size observed in this study was modest and did not reach statistical significance, even small reductions in lumefantrine exposure may be clinically meaningful in children, particularly in settings with high parasite burden or emerging antimalarial resistance.

The findings of this study are broadly consistent with recent pooled and meta-analytic evidence examining antiretroviral-lumefantrine interactions. An individual participant data meta-analysis by Francis *et al*, demonstrated that efavirenz-based antiretroviral therapy substantially reduces lumefantrine exposure.[6] In contrast, nevirapine-based regimens exert a smaller and more variable effect, often not reaching statistical significance. Importantly, these analyses were dominated by adult data, highlighting the relevance of paediatric-specific studies such as the present work. The absence of a statistically significant interaction in this study supports the current clinical practice of co-administering artemether-lumefantrine with nevirapine-based antiretroviral therapy in children, provided that appropriate weight-based dosing and adherence are ensured.

Despite the lack of statistical significance, the direction of the observed effect warrants careful consideration. Lumefantrine exposure, particularly day-7 concentrations, has been repeatedly associated with malaria treatment outcomes, with lower exposures linked to an increased risk of recrudescence.[4] In high-transmission settings, even marginal reductions in exposure could contribute to suboptimal parasite clearance at the population level. These findings therefore reinforce the importance of ensuring adequate dosing, optimising fat co-administration, and maintaining adherence in paediatric patients receiving concomitant antiretroviral therapy.

This study contributes valuable population pharmacokinetic data on lumefantrine in HIV-infected children, a population that remains under-represented in pharmacometrics research. The use of a population modelling approach allowed efficient characterisation of lumefantrine disposition under real-world clinical conditions and provides a quantitative basis for evaluating drug-drug interaction risk in this vulnerable group.

From a clinical perspective, the findings of this population pharmacokinetic study support the continued use of standard weight-based artemether-lumefantrine dosing in HIV-infected children receiving nevirapine-based antiretroviral therapy. Although a modest increase in lumefantrine clearance was observed, this did not translate into a clinically meaningful reduction in exposure. This pharmacokinetic observation is corroborated by our previously published clinical outcome study, which demonstrated that nevirapine-based antiretroviral therapy did not significantly impair malaria treatment outcomes, including parasitological and clinical cure rates, in HIV-infected children treated with artemether-lumefantrine.[10] Taken together, these complementary pharmacokinetic and clinical data indicate that nevirapine does not compromise the effectiveness of artemether-lumefantrine when appropriately dosed, thereby reinforcing current treatment practices in malaria-HIV co-infected paediatric populations in endemic settings.

Several limitations of this study should be acknowledged. First, the use of sparse pharmacokinetic sampling, while ethically appropriate for paediatric populations, limits the precision with which certain distribution parameters can be estimated. Although population modelling mitigates this constraint, some parameters-particularly those associated with deep peripheral compartments-were estimated with relatively wide confidence intervals.

Second, the sample size was modest, which may have limited the statistical power to detect small but clinically relevant effects of nevirapine on lumefantrine pharmacokinetics. As such, the absence of statistical significance should not be interpreted as definitive evidence of no interaction.

Third, pharmacogenetic data were not comprehensively incorporated into the final model. Genetic variability in CYP3A4, CYP3A5, and transporter genes may contribute to interindividual variability in lumefantrine exposure and could partially explain the observed heterogeneity in clearance.

Although this study focused primarily on pharmacokinetic endpoints and did not formally integrate exposure-response analyses within the present modelling framework, the clinical relevance of the findings is strengthened by complementary outcome data from our previously published work. In that study, nevirapine-based antiretroviral therapy was not associated with reduced malaria treatment efficacy or increased risk of therapeutic failure in HIV-infected children treated with artemether-lumefantrine.[10] This alignment between pharmacokinetic and clinical outcome data supports the translational validity of the present findings and mitigates concerns that the modest pharmacokinetic changes observed would adversely affect treatment success.

CONCLUSION

This study demonstrates that a three-compartment population pharmacokinetic model with transit-compartment absorption best describes lumefantrine pharmacokinetics in HIV-infected children receiving nevirapine-based antiretroviral therapy. Concomitant nevirapine administration was associated with a modest, non-significant increase in apparent lumefantrine clearance, suggesting no major impairment of lumefantrine exposure under standard dosing conditions. These findings support the continued use of artemether-lumefantrine in children receiving nevirapine-based antiretroviral therapy, while underscoring the importance of strict adherence to weight-based dosing and appropriate fat co-administration to ensure optimal drug exposure. The study adds important paediatric-specific evidence to the growing body of literature on antimalarial-antiretroviral drug interactions and highlights the value of population pharmacokinetic modelling in informing rational dosing strategies for vulnerable populations.

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