2167 Modeling and simulation of lumefantrine pharmacokinetics in HIV-infected and HIV-uninfected children with malaria and the role of lumefantrine exposure as a potential driver of drug resistance.

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Abstract

Treating malaria in children with and without HIV infection requires consideration of complex biological and pharmacological factors that impact artemisinin-based combination therapies (ACTs). Developmental changes in pharmacokinetics (PK) are often ignored, and concomitant anti-retroviral therapy (ART) results in drug–drug interactions (DDI) that may have significant effects. Drug exposure may also impact drug resistance selection. We have shown efavirenz (EFV) reduced exposure to both artemether (AR) and lumefantrine (LF) by 2.1- to 3.4-fold; lopinavir/ritonavir (LPV/r) increased LF exposure by 2.1-fold; and nevirapine (NVP) reduced AR exposure [1]. We developed a population PK/PD model to explore the relationship between LF exposure and resistance selection, which has not been extensively evaluated. The PK model was developed in children receiving artemether-lumefantrine (AL) alone or with an ART (EFV, LPV/r, or NVP) and parameters were estimated using nonlinear mixed effects modelling (NONMEM®). The PK model consistently predicted the observed LF profiles in pediatric patients, with and without ART, as estimated by comedication effects on LF absorption and systemic clearance. LF exposure was estimated with the PK model and used to develop a PK-PD model that associated mutation status with recurrent infections. Recurrent infections were genotyped to classify recrudescent or new infections. Drug resistance was assessed through genotyping at *pfmdr1* N86Y, *pfmdr1* Y184F and *pfcrt* K76, demonstrating that mutations associated with reduced susceptibility to LF (*pfmdr1* N86 and *pfcrt* K76) were more prevalent in recurrent infections (p=0.004 and <0.001, respectively) [2]. The DDI, affected by concomitant administration of LF with and without ART, provided an opportunity to evaluate a much broader LF exposure range than typically observed following standard LF dosing. This allowed for exploration of LF exposure in a high transmission area and the likelihood of mutation selection upon reinfection. The results presented here allow for further optimizing of AL dosing regimens and characterization of the impact of exposure on resistance selection.

Methods

The total dataset had 277 children with 364 episodes of uncomplicated malaria from a high-transmission area of eastern Uganda. All 161 HIV- children and 116 HIV+ children received AL for treatment of malaria. HIV+ children were all receiving daily ART (EFV, LPV/r, or NVP) for HIV and trimethoprim-sulfamethoxasole (TS) for prevention of opportunistic infections. The 140 children with recurrent parasitemia during 42-day follow-up (176 episodes) had their initial and recurrent infections genotyped for key mutations in drug transporters using a Luminex-based platform: the *pfcrt* K76 status was determined for 102 HIV- children (119 episodes) and 38 HIV+ children (57 episodes: n=13 EFV, n=11 LPV/r, and n=14 NVP). The full dataset was used for the PK model and the first hazard model, and the subpopulation was used in second hazard model.

Population PK model for LF

The LF population PK model was developed using nonlinear mixed effects modeling with NONMEM®. Population and individual model parameters were estimated using the stochastic approximation expectation maximization (SAEM) method followed by Monte Carlo importance sampling (IMP).

Repeated time to event model

The risk of reinfection was fitted using a repeated time to event (RTTE) model which allows the estimation of predictors (covariates) on the time-to-event (TTE) between groups (e.g. treatment arms or genotypes) and continuous, time-varying covariates (e.g. LF concentration). TTE accounts for censoring and is more powerful than logistic regression as the latter ignores the time component. While RTTE allows an event to occur several times per individual (children had up to 4 separate malaria episodes during the trial). The SAEM method was used as it is accurate for sparse data.

References

[1] Parikh, S., Kajubi, R., Huang, L., Ssebuliba, J., Kiconco, S., Gao, Q., Li, F., Were, M., Kakuru, A., Achan, J., Mwebaza, N. and Aweeka, F.T. Antiretroviral Choice for HIV Impacts Antimalarial Exposure and Treatment Outcomes in Ugandan Children. *Clin. Infect. Dis.* 63 (2016):414–422.

[2] Kajubi, R., Goodwin, J., Ehrlich, H., Ou, J., Freeman, T., Wade, M., Huang, L., Wang, K., Mwebaza, N., Li, F., Aweeka, F.T. and Parikh, S. Selection of drug-resistance markers following treatment with artemether-lumefantrine in HIV-infected and HIV-uninfected children and association with lumefantrine PK exposure. *ASTMH poster (number 1558)* (2019).

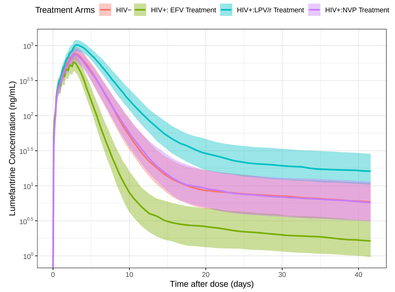
Final Results: Population PK model for lumefantrine

A two-compartment population PK model with first-order absorption provided the best fit to the data and included fixed effects of body weight on all clearance and volume terms. Fixed effects on volume used an exponent of 1 while the fixed effects on clearance used an exponent of 0.75, 0.9, 1.0 or 1.2 for children aged >60 months, >24 to ≤60 months, >3 to ≤24 months and ≤3 months, respectively. The model also **included the effect of age on bioavailability** (younger children had reduced LF bioavailability) **and the ART (i.e. EFV, LPV/r or NVP) effect on LF clearance (CL/F) and absorption (KA)**. Random effects were included to estimate the IIV in the fixed effect parameters and the residual variability of the data.

Table 1: *Lumefantrine parameter summary*

			Estimate	95% CI	Shrinkage (%)
Structural model parameters					
CL/F (L/h)	θ_1	Apparent clearance	1.20	0.952, 1.45	-
V2/F (L)	θ_2	Apparent central volume of distribution	24.1	19.0, 29.2	-
Q/F (L/h)	θ_3	Apparent intercompartmental clearance	0.380	0.258, 0.501	-
V3/F (L)	θ_4	Apparent peripheral volume of distribution	767	174, 1.36e+03	-
KA (1/h)	θ_5	Absorption rate constant	0.0215	0.0197, 0.0234	-
Covariate effect parameters					
AGE_F	θ_6	Age effect on bioavailability (F)	0.204	-0.0586, 0.467	-
$EFV_{CL/F}$	θ_7	EFV effect on CL/F	0.982	0.163, 1.80	-
$LPV/r_{CL/F}$	θ_8	LPV/r effect on CL/F	-0.514	-0.696, -0.332	-
$NVP_{CL/F}$	θ_9	NVP effect on CL/F	0.0191	-0.324, 0.362	-
EFV_{KA}	θ_{10}	EFV effect on KA	0.484	0.282, 0.685	-
LPV/r_{KA}	θ_{11}	LPV/r effect on KA	-0.212	-0.305, -0.120	-
NVP_{KA}	θ_{12}	NVP effect on KA	-0.0589	-0.207, 0.0891	-
Interindividual variance parameters					
IIV-CL/F	$\Omega_{[1,1]}$	Variance of CL/F	0.735 [CV%=104]	0.526, 0.945	5.86
IIV-V2/F	$\Omega_{[2,2]}$	Variance of V2/F	0.813 [CV%=112]	0.504, 1.12	32.6
IIV-Q/F	$\Omega_{[3,3]}$	Variance of Q/F	0.0250 [CV%=15.9]	0.0250, 0.0250	67.5
IIV-V3/F	$\Omega_{[4,4]}$	Variance of V3/F	0.956 [CV%=127]	0.590, 1.32	36.4
IIV-KA	$\Omega_{[5,5]}$	Variance of KA	0.0280 [CV%=16.9]	0.00705, 0.0490	58.2
Residual variance					
Proportional	$\Sigma_{[1,1]}$	Variance	0.200 [CV%=44.7]	0.173, 0.226	-

Abbreviations: CI = confidence intervals; SE = standard error, EFV = efavirenz, LPV/r = lopinavir/ ritonavir, NVP = nevirapine. Confidence intervals = estimate ± 1.96 * SE, CV% of omegas = sqrt(exp(estimate) - 1) * 100, CV% of sigma = sqrt(estimate) * 100



Source code: PK_simulation.R
Source graphic: ./deliv/figure/VPC/207/Simulation.pdf

Figure 1: *LF exposure by treatment arm.*

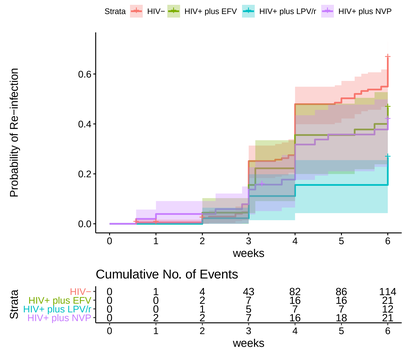
The PK model consistently predicted the observed LF profiles in pediatric patients, with and without ART (*Figure 1*).

We have previously shown DDIs between LF + EFV reduced LF exposure and LF + LPV/r increased LF exposure [1]. Here we expand that to specifically quantify the effect of age on LF bioavailability and comedication effects on LF absorption and clearance (*Table 1*).

Conclusions

- The final population PK model was able to predict the LF exposure for all children, with and without HIV, and explicitly characterize (i) how bioavailabilty changed with age and (ii) how exposure changed with ACT/ART DDIs. i.e. DDIs between LF + EFV reduced LF exposure and LF + LPV/r increased LF exposure.
- The RTTE analysis (all patients) showed HIV status and LF concentration were important factors determining the time to re-infection.
- HIV-infected children had a lower risk of recurrent parasitemia than HIV-uninfected children, likely due in part to the protective effects of trimethoprim-sulfamethoxazole against malaria and to effective control of HIV with ART.
- The risk of reinfection with genotypes associated with reduced susceptibility to LF (i.e. WT *pfcrt* K76T) appears to be 6.6% higher than the risk of reinfection with genotypes associated with LF sensitivity (mutant) during the first 42 days post-treatment.
- Compared to the time of treatment, recurrent infection genotypes were more likely to occur with *pfmdr1* N86Y genotypes less sensitive to LF (p=0.004). However, RTTE analysis looked only at recurrent genotypes which, for the WT (less sensitive) *pfmdr1* N86Y was almost at fixation, and so *pfmdr1* N86Y was not informative to the RTTE model.

Preliminary Results: Repeated time to event (RTTE) model



Source code: PLOTS.R
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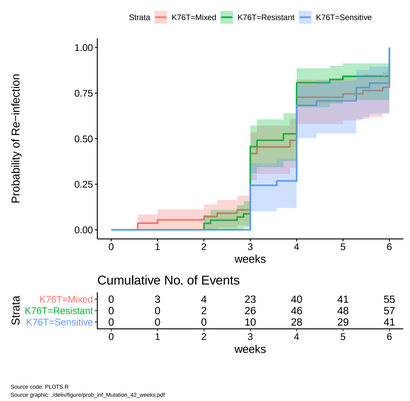
Figure 2: *Probability of re-infection by HIV status and ART treamtment.*



Source code: PLOTS.R
Source graphic: ./deliv/figure/prob_inf_Mutation_42_weeks.pdf

Figure 3: *Probability of re-infection with different pfcrt K76T genotypes.*

Note that sensitive infections had the "mutant" status (blue) while infections with reduced LF sensitivity (or resistance) had the "wild-type" status (green).

- RTTE analysis: included all patients and the variables affecting the hazard included HIV status (+ or -) and LF concentration.
- **The probability of reinfection was higher in HIV- children compared to HIV+ children on ART & TS (*Figure 2*).**
- Higher LF exposure reduced the risk of re-infection. **For HIV+ patients, the risk of re-infection was highest in those receiving EFV-based ART (with lowest LF exposure) and lowest in those receiving LPV/r-based ART (with highest LF exposure).**

- RTTE analysis: included patients with recurrent infections and the variables affecting the hazard included *pfcrt* K76T status, HIV status (+ or -) and LF concentration.
- For *pfcrt* K76T, infections were determined to be the wild-type (WT), mutant, or mixed at both the initial infection and at the time parasitemia was 1st detected by microscopy during follow-up.
- For *pfcrt* K76T, the probability of being re-infected with less LF sensitive parasites (i.e. *pfcrt* K76T = WT or mixed) increased earlier and faster than reinfection with sensitive parasites (*Figure 3*).
- This preliminary RTTE analysis showed **the risk of reinfection with resistant parasites (i.e. WT status for *pfcrt* K76T) within 42 days increased 6.6% compared to reinfection with sensitive (mutant) parasites** while a re-infection with a mixed infection decreased 2.0% relative to sensitive infections.
- The risk of re-infection in HIV-infected patients decreased by 64% relative to HIV-uninfected patients.

pfmdr1 N86Y was genotyped, and we have previously demonstrated that mutations associated with reduced susceptibility to LF were more prevalent in recurrent infections (p=0.004). However, RTTE analysis looks only at recurrent genotypes and for *pfmdr1* N86Y almost all recurrent infection genotypes were WT (less sensitive); *pfmdr1* N86Y was not informative in an RTTE analysis.

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