Abstract
Treating malaria in children with and without HIV infection requires consideration of complex biological and pharmacological factors that impact antimicrobial combination therapies (ACTs). Developmental changes in pharmacokinetics (PK) are often ignored, and concurrent 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 (ART) and lumefantrine (LF) by 2.1- to 3.4-fold; loxapine/tiorperazine (LPV/r) increased LF exposure by 2.1-fold; and nevirapine (NVP) reduced ART exposure [1]. We developed a population PK model to explore the relationship between ART and ART resistance, which has not been extensively evaluated.

The 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 modeling (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-DDI model that associated mutation status with recurrent infections. Recurrent genotypes were grouped based on drug susceptibility analysis to classify resistant or new infections. Drug resistance was assessed using genotyping at pfmdr1 (K76T) and pfcrt (N86Y) and pfcrt K76T, demonstrating that combinations associated with reduced susceptibility to LF (pfcrt K76T) were more prevalent in recurrent infections (p = 0.004 and < 0.001, respectively) [2]. The DDI, affected by concurrent administration of ART 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 also allow for further optimizing of AL dosing regimens and characterization of the impact of exposure on resistance selection.

Methods
The total dataset consisted of 277 children with 364 episodes of uncomplicated malaria from a high-transmission area of eastern Uganda. All 161 HIV-infected and 116 HIV-uninfected children received AL for treatment of malaria. HIV+ children were all receiving daily ART (EFV, LPV/r, or NVP) for HIV and trimethoprim-sulfamethoxazole (TS) for prevention of opportunistic infections. The 140 children with recurrent malaria episodes during 42 days following the initial infection and recurrent infections grouped for key mutations in drug transporters using a Linex-based platform: the pfcrt K76T status was determined for 102 HIV children (119 episodes) and 38 HIV children (37 episodes; n = 13 FPI; n = 11 LPV/r; 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 (BMP). The risk of reinfection was fitted using a repeated time to event (RTTE) model which allows the 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.

Conclusions

• The final population PK model was able to predict the LF exposure for all children, with and without HIV infection and explicitly characterize how bioavailability changed with age and (ii) exposure change with ART. DDI effects. i.e. DDIs between LF and EFV reduced LF exposure and LF + LPV/r increased LF exposure [1].

• For pfcrt K76T genotypes, the probability of being re-infected with less LF sensitive parasites (i.e. pfcrt K76T) was more prevalent in recurrent infections (p = 0.004 and < 0.001, respectively) [2]. The DDI, affected by concurrent administration of ART 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 also allow for further optimizing of AL dosing regimens and characterization of the impact of exposure on resistance selection.

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• RTTE analysis: included patients with recurrent infections and the variables affecting the hazard included ART DDIs. i.e. DDIs between LF and EFV reduced LF exposure and LF + LPV/r increased LF exposure [1].

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References


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