1434

Association of lumefantrine pharmacokinetics and resistance selection following artemether-lumefantrine treatment in children with and without HIV in Uganda

Katherine Kay[1], Justin Goodwin[2], Hanna Ehrlich[2], Joyce Ou[3], Tracy Freeman[3], Kaicheng Wang[2], Fangyong Li[2], Martina Wade[2], Jonathan French[1], Liusheng Huang[4], Francesca T. Aweeka[4], Norah Mwebaza[5], Richard Kajubi[5], Matthew Riggs[1], Ana Ruiz-Garcia[1], Sunil Parikh[2]

[1]Metrum Research Group, Tariffville, CT, USA; [2]Yale Schools of Medicine and Public Health, New Haven, CT, USA; [3]Yale University, New Haven, CT, USA; [4]University of California San Francisco, CA, USA; [5]Infectious Disease Research Collaboration, Kampala, Uganda

Background

- Artemether-lumefantrine (AL) is the most widely used artemisinin-based combination therapy (ACT) in sub-Saharan Africa.
- It is essential to characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of ACTs in vulnerable populations at risk of suboptimal dosing.
- We developed a population PK/PD model using data from a previous study of AL in HIV-uninfected and HIV-infected children living in a high-transmission region of Uganda (Parikh et al, *Clin Infect Dis*, 2016).
- HIV-infected children were on either efavirenz (EFV), nevirapine (NVP), or lopinavir-ritonavir (LPV/r) based antiretroviral regimens, with daily trimethoprim-sulfamethoxazole (TS) prophylaxis.
- In this high transmission setting, reinfection was extremely common, and our wide range of lumefantrine exposure allowed us to more fully explore the relationship between recurrent parasitemia and drug exposure.
- We assessed selection for resistance in two key parasite transporters, *pfcrt* and *pfmdr1*, over a 42-day follow-up to ascertain how drug exposure impacts resistance genotype and recurrence risk.

Methods

- For the *population PK analysis*, n=277 children with n=364 malaria episodes were included (**Table 1**).
- A population PK model for lumefantrine was developed using nonlinear mixed effects modeling with a qualified installation of NONMEM®. Population and individual model parameters were estimated using the stochastic approximation expectation maximization (SAEM) method followed by Monte Carlo importance sampling (IMP).
- Drug exposure response models were developed using time-to-event (TTE) analyses with new infections captured as independent events. The exposure metric was the concentration of lumefantrine at the time of event (microscopically-detectable recurrent parasitemia) or when censored at 42 days.
- The first TTE model included all patients with a malaria infection and compared hazards in children with and without HIV (n=274 children with n=358 malaria episodes).
- The second TTE model included only patients with microscopically-detectable recurrent infections (either recrudescent or new infection) within the 42-day follow-up period for which genotyping information was available (n=176).

Table 1: Patient characteristics for population PK cohort

Parameter	HIV-uninfected children	HIV-infected children		
		EFV-based ART	LPV/r -based ART	NVP -based ART
Malaria episodes, no.				
Overall	186	48	68	62
Per child				
1	159	25	41	37
2	20	11	14	13
3	5	6	7	6
4	1	4	3	3
5+	1	2	3	3
Malaria episodes per child, median (range)	1 (1 – 5)	1 (1 – 5)	1 (1 – 8)	1 (1 – 6)
% Episodes in male children	53.2	33.3	35.3	53.2
Weight, kg, median (range)	14.1 (9.80 – 27.0)	18.0 (11.4 – 25.1)	15.4 (7.65 – 23.7)	16.0 (8.50 – 30.0)
Age, years, median (range)	3.58 (0.16 – 7.91)	6.00 (3.17 – 8.58)	4.50 (1.58 – 7.83)	4.50 (1.33 – 8.00)
Parasite density, geometric mean, parasites/μL (95% CI)	16368 (12166 / 22021)	11291 (6098.5 / 20906)	6392.8 (3523.4 / 11599)	10568 (5746.7 / 19436)

Results

Population PK of lumefantrine in the setting of antiretroviral therapy

A two-compartment population PK model with first-order absorption provided the best fit to the data and also **estimated the effect of age on bioavailability and the effect of antiretroviral therapy on lumefantrine clearance**.

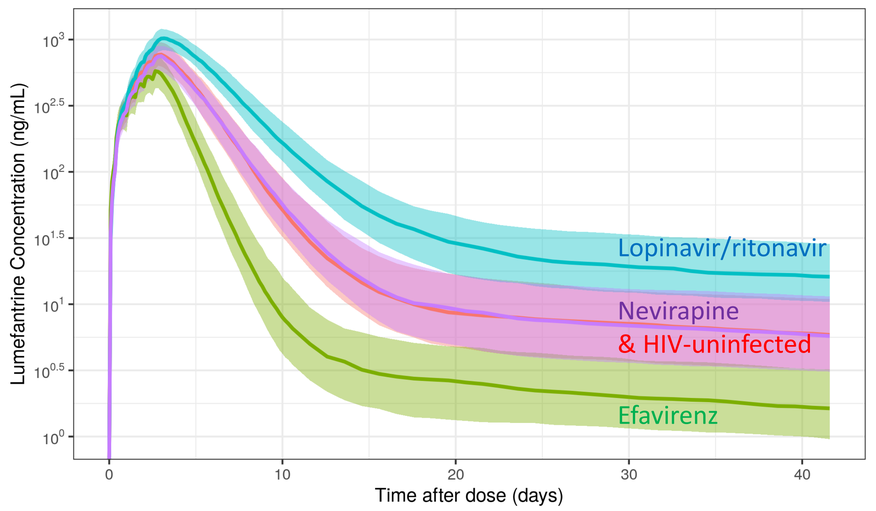

Figure 1. Lumefantrine exposure by treatment arm. Lines represent the median predicted lumefantrine concentration. Lumefantrine is metabolized by cytochrome P450 (CYP) 3A4.

- **Lopinavir/ritonavir is a potent CYP 3A4 inhibitor, which significantly increases lumefantrine exposure.**
- **Nevirapine and HIV-uninfected children have identical lumefantrine exposure.**
- **Efavirenz induces CYP 3A4, which dramatically decreases lumefantrine exposure.**

Risk of recurrence by HIV-status

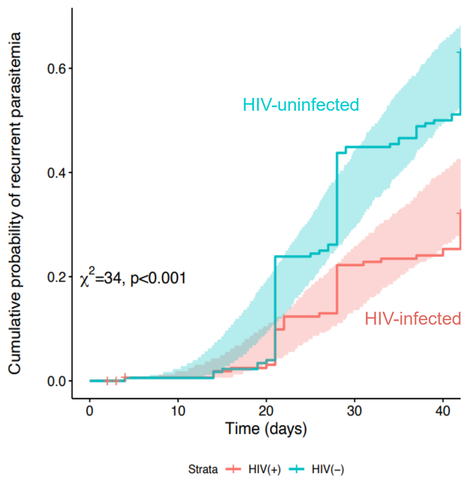

Figure 2. Cumulative probability of malaria over time in patients by HIV status. Median hazard and 95% CI.

HIV-infected children on daily TS were less likely to present with recurrent parasitemia compared to HIV-uninfected children.

Post-treatment period of chemoprophylaxis by treatment arm

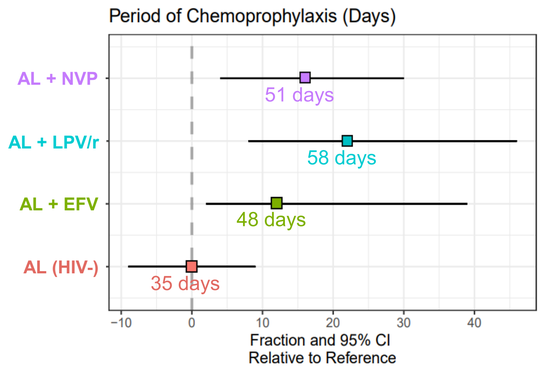

Figure 3. Period of chemoprophylaxis (PoC) in patients by antiretroviral therapy. Reference subject was an HIV-uninfected patient with a median time to recurrence of 35 days following AL.

HIV+ children on NVP had a PoC of 51 days.

HIV+ children on LPV/r had a PoC of 58 days.

HIV+ children on EFV had a PoC of 48 days.

Despite equivalent lumefantrine exposure (Fig 1), HIV-infected children on NVP plus daily TS had a PoC 16 days longer than HIV-uninfected children.

Results continued

Selection for drug resistance in recurrent infections

Table 2: Genotype selection in recurrent infections

Selection	Frequency	Percent	*p*-value
N86Y, n=170			
Change to WT	33	19.41	
Change to mutant	12	7.06	0.004
No change	125	73.53	
Y184F, n=176			
Change to WT	43	24.43	
Change to mutant	48	27.27	0.59
No change	85	48.30	
K76T, n=161			
Change to WT	70	43.48	
Change to mutant	33	20.50	< 0.001
No change	58	36.02	

- Significant selection was shown for *pfmdr1* N86 and *pfcrt* K76 wild-type parasites (less sensitive to lumefantrine).
- No evidence of selection was seen for *pfmdr1* Y184F.

Risk of recurrence by drug resistance genotype

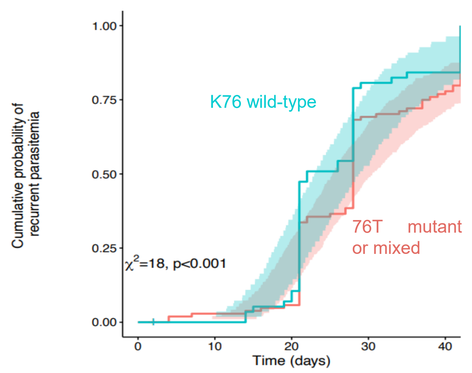

Figure 4. Cumulative probability of malaria over time in patients by *pfcrt* K76T genotype. Median hazard and 95% CI.

K76 wild-type (less sensitive) parasites were more likely to cause recurrent infection.

Lumefantrine C50 by recurrent *pfcrt* K76T genotype

C50 is defined as the concentration of lumefantrine that reduced the risk of recurrence by half on a log-scale.

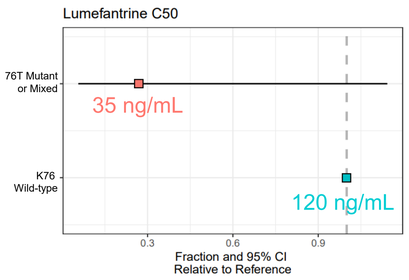

Figure 5. Lumefantrine C50 in patients by recurrent K76T genotype. Reference subject had a K76 wild-type infection with a median lumefantrine C50 of 120 ng/mL.

K76 wild-type (less sensitive) parasites were able to survive lumefantrine concentrations 3.5X higher than 76T mutant (more sensitive) parasites.

Conclusions

- TS prophylaxis provides significant protection against malaria in those with HIV; the independent effect of TS on post-treatment prophylaxis is evident through our assessments of lumefantrine PK over time.
- Significant selection was demonstrated for *pfmdr1* N86 and *pfcrt* K76 in recurrent infections, with no evidence of selection for *pfmdr1* Y184F.
- **Less sensitive parasites (*pfcrt* K76) were able to tolerate lumefantrine concentrations approximately 3.5-fold higher than more sensitive parasites (*pfcrt* 76T).**
- **This is the first population PK model of lumefantrine in HIV-infected children and demonstrates selection for reduced lumefantrine susceptibility with repeated treatments in a high transmission setting.**

Acknowledgements

We are grateful to the children and their parents/guardians who participated in the original PK/PD study, and to the IDRC study team for their support. **Funding**: This work was supported primarily by R01 HD068174, R21 HD110110, and F31 HD109060 funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Presented at ASTMH Meeting, Oct 30 – Nov 3, 2022

Published online in *Clinical Pharmacology & Therapeutics*, 19 Oct 2022