Influence of nevirapine and ritonavir/lopinavir based antiretroviral therapy on Lumefantrine exposure in HIV-1 infected patients

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Background and Objectives

- Artemether-lumefantrine is the most widely recommended first-line treatment for uncomplicated falciparum malaria globally.
- Considering the substantial geographic overlap of **HIV** and **malaria** disease burdens, it is important to understand any potential **drug-drug** interactions.
- **Lumefantrine** and many of the antiretroviral agents are metabolized by CYP3A4 isoenzyme.
- Absorption of lumefantrine is enhanced by food particularly by fat.
- Nevirapine is an inducer whereas ritonavir is a potent inhibitor of CYP3A4, which can lead to potential drug interactions.

Objectives:

- To characterize the population pharmacokinetics of **lumefantrine**.
- To explore the impact of **nevirapine**- and **lopinavir/ritonavir**- based antiretroviral therapy (ART) on lumefantrine exposure.

Methods

Data:

- The pharmacokinetic data from SEACAT 2.4.1 & SEACAT 2.4.2 studies were used for the present analysis. The participants were HIV positive but did not have malaria. (1,2)
- No. of Patients – 55 adults
- Total No. of samples – 1908
- Adult Dose - 480 mg twice daily for three days
- Sampling schedule – 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 14, 24, 30, 36, 42, 48, 54, 60, 61.5, 62, 63, 64, 65, 66, 68, 70, 72, 96, 120, 144, 168, 336 and 504 h post-first AL dose

Table-1: Study group details

Study groups	No. of patients (No. of samples)
Arm 1 (Artemether+Lumefantrine)	18 (567)
Arm 2 (AL + Nevirapine based ART)	18 (449)
Arm 3 (AL + Lopinavir based ART) Phase 1 –Single dose of AL Phase 2 – Multiple doses of AL	 19 (380) 15 (512)

Model building:

- NONMEM 7.3 (FOCE-I)
- Pirana
- PSN
- Xpose

Table-2: Characteristics of patients

Covariate	Median	Range
Age (yrs)	32.3	19.6 - 60.9
Weight (kg)	60	45.5 – 88
Gender (male/female)	10/45	
Fat free mass (kg)	41.2	31.3-59.6

Results

- A three compartment model with transit absorption described the data well.
- Allometric body weight was used to scale Clearance and Volume of distribution parameters

Figure 1: Structure of the model

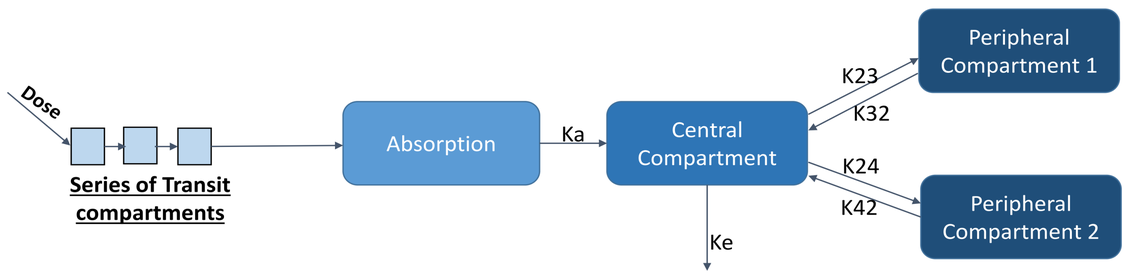


Table-3: Final parameter estimates (5th and 95th percentile)*

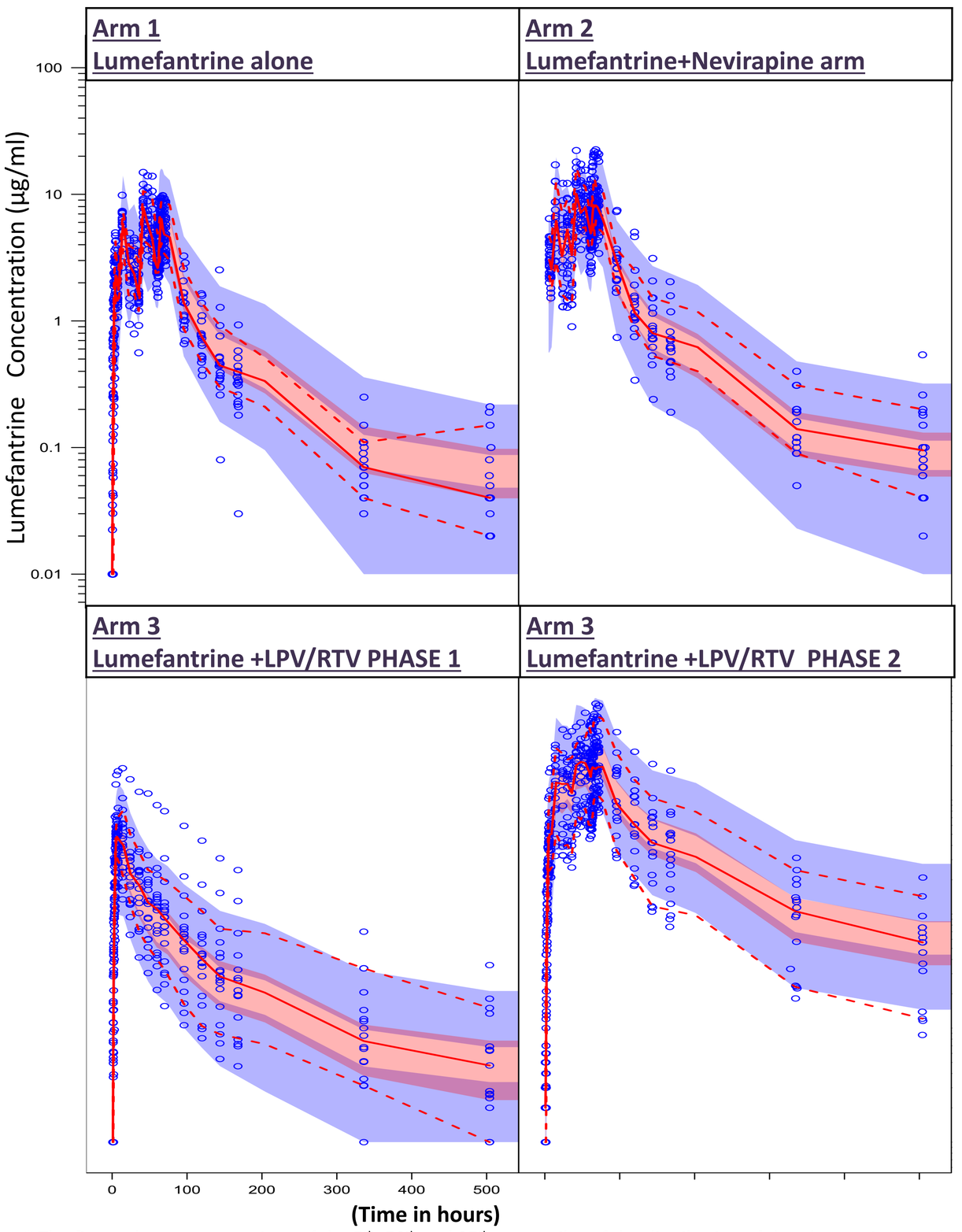
Parameter	Typical value	BSV	BOV
CL/F (L/h)	**11.9** (9.788 – 13.307)	**29.5%** (24.624 - 33.269)	-
V/F (L)	**205** (172.523 – 227.710)	-	-
BIO	1 FIX	**23.4%** (17.327 – 29.994)	**53.3%** (47.307 – 58.681)
MTT(h)	**2.76** (2.450 – 2.958)	-	32.2% (27.947 – 34.467)
Ka (1/h)	**0.733** (0.549 – 0.909)	-	51.4% (39.363– 65.859)
V3 (L)	859 (553.190 – 967.291)	-	-
Q (L/h)	2.04 (1.711 – 2.234)	19.4% (12.652 – 25.967)	-
NN	**8.27** (6.864 – 9.945)	-	-
V4(L)	177 (144.688 – 193.298)	-	-
Q2(L/h)	7.15 (5.761 – 8.168)	-	-
Add Error (mg/L)	0.0235 (0.017 – 0.033)	-	-
Prop Error	15.3% (13.7%– 16.9%)	-	-

*Percentiles from nonparametric bootstrap (n=100) of the final model
CL and V parameters reported for patient with bodyweight of 60 kg

Table-4: Effect of ARVs on Lumefantrine exposure

Parameter	Effect
Effect of Nevirapine on Lumefantrine	
BIOAVAILABILITY	↑ 36.4% (25.971 – 74.538)
Effect of LPV/RTV on Lumefantrine	
CLEARANCE	↓ 45.6 % (35.506 - 53.535)
BIOAVAILABILITY	↑187% (123.650 – 235.514)
ABSORPTION RATE	↓ 58.9% (47.536 – 67.416)
Difference in morning and evening doses	
BIOAVAILABILITY (evening doses)	↑ 173% (149.246 – 195.059)

Figure 2: Visual predictive check (log scale)*



* The figure shows a comparison of the 5th, 50th and 95th percentiles of the distribution of the observations (red lines) and confidence bands around the percentiles for simulated predictions.

Conclusions

- The clearance of lumefantrine was **45.6%** less when co-administered with LPV/RTV.
- The bioavailability was increased by **36.4%** and **187%** with Nevirapine and LPV/RTV co-administration.
- Increase in the lumefantrine exposure when co-administered with ARVs.
- Bioavailability varied between morning & evening doses (Diurnal/Food effects): **173%** higher with evening doses compared to morning doses

Next step: Pooled analysis to refine the findings and to determine effects of malaria disease and other ARVs.

References

1) Kredo T, Mauff K, Workman L, Van der Walt JS, Wiesner L, Smith PJ, Maartens G, Cohen K, Barnes KI. The interaction between artemether-lumefantrine and lopinavir/ritonavir-based antiretroviral therapy in HIV-1 infected patients. BMC Infect Dis. 2016;27;16:30.
2) Kredo T, Mauff K, Van der Walt JS, Wiesner L, Maartens G, Cohen K, Smith P, Barnes KI. Interaction between artemether-lumefantrine and nevirapine-based antiretroviral therapy in HIV-1-infected patients. Antimicrob Agents Chemother. 2011;55:5616-23.
3) Savic RM, Jonker DM, Kerbusch T, Karlsson MO. Implementation of a transit compartment model for describing drug absorption in pharmacokinetic studies. J Pharmacokinet Pharmacodyn. 2007;34:711-26.
4) Borrmann S, Sallas WM, Machevo S, González R, Björkman A, Mårtensson A, Hamel M, Juma E, Peshu J, Ogutu B, Djimdé A, D'Alessandro U, Marrast AC, Lefèvre G, Kern SE. The effect of food consumption on lumefantrine bioavailability in African children receiving artemether-lumefantrine crushed or dispersible tablets (Coartem) for acute uncomplicated Plasmodium falciparum malaria. Trop Med Int Health. 2010;15:434-41.