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ART choice impacts antimalarial exposure and treatment outcomes in Ugandan children

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Introduction

- Malaria and HIV co-infection is prevalent in Africa and other resource limited regions with malaria disproportionately affecting young children.
- The incidence for malaria in Tororo can be > 6 episodes per person-year for HIV-uninfected children (not receiving preventative treatment)[1,2] and 1.3-2.2 for HIV-infected children [managed with TS prophylaxis and concomitant HIV antiretroviral therapy (ART)][3].
- Treatment of malaria with artemisinin combination therapies (ACT) is complicated by HIV co-infection due to significant drug-drug interactions impacting current WHO malaria treatment guidelines[4-8].
- However, little is established in terms of the optimum ACT dose in the context of ART and the maturational effects of metabolism in children; information urgently needed to inform *specific dosing guidelines for HIV infected children*.
- We sought to determine the pharmacokinetics and pharmacodynamics of the most widely used ACT, artemether-lumefantrine (AR/LR) in the setting of the most widely used ART.

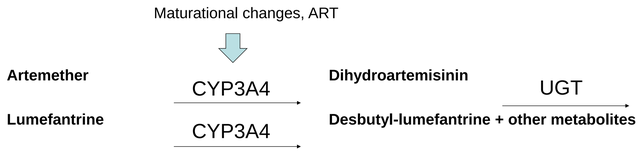


Figure 1. Pharmacology of artemether lumefantrine is complex

Study Aims

- Evaluate the pharmacokinetics of AR/LR in the context of different ART regimens, among Ugandan children
- Investigate the relationship between AR/LR exposure and treatment outcomes including risk of recurrent parasitemia and clinical malaria over day 28 and 42 day follow-up

Methods

Study Site: Tororo, Uganda, highly endemic for malaria with entomological inoculation rates in the range of 379 to 562.

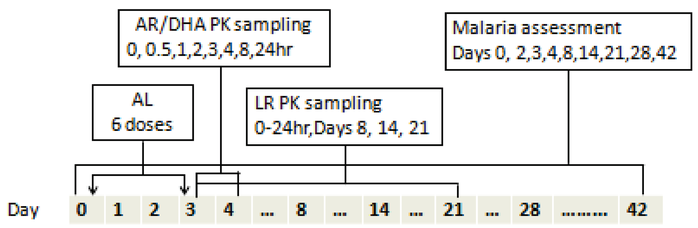
Enrollment: HIV-uninfected children (n=51 for intensive and n=134 for population PK) and HIV-infected children (n=91 for intensive and n=87 for population PK), age 1 to 8 years, with uncomplicated falciparum malaria as per positive blood smear plus fever. Treated with a standard 3-day regimen of AR/LR. HIV-infected children were stabilized on lopinavir/ritonavir (LPV/r)-, nevirapine (NVP)-, or efavirenz (EFV)-based ART.

Exclusion criteria: complicated malaria, mixed plasmodial infections and anemia (hb< 7g/dL).

Study Procedures:

- Children were treated with 6 doses over 3 days with the last dose administered in the morning of day 3.
- Intensive PK was carried out pre- and post- the 6th (final) dose.
- Samples over 24 hours were analyzed for AR, its active metabolite dihydroartemisinin (DHA) and LR.
- Additionally, samples from 48 hrs post-last dose to day 21 were analyzed for LR.
- All samples were quantitated using a sensitive LC tandem MS method (AR/DHA LOQ: 0.5 ng/ml; LR LOQ 50 ng/mL).
- Malaria treatment response was followed by blood smear microscopy on days 0, 1, 2, 3, 4, 8, 14, 21, 28, 42.
- Adverse events were followed to day 42.
- Primary outcomes were PK exposure and day 28/42 risk of recurrent malaria.

Figure 2: Intensive PK Sampling



Results

Demographic Table	
Total number of episodes in HIV-infected children	182
Total number of episodes in HIV-uninfected children	183
% episodes in HIV-infected females	59%
% episodes in HIV-uninfected females	56%
Weight in kg (median (range))	
HIV-infected	16.1 (7.7, 30)
HIV-uninfected	13.9 (10, 27)
Median total lumefantrine per dose in mg/kg (range)	
HIV-infected	12.4 (8.1, 16.3)
HIV-uninfected	10.9 (8.1, 21.4)
Age in years (median (range))	
HIV-infected	4.9 (1.4, 8.6)
HIV-uninfected	3.5 (1.1, 7.9)
Parasite density (geometric mean μL^{-1} (95% CI))	
HIV-infected	8942 (2320, 56480)
HIV-uninfected	16398 (5600, 74400)
Baseline haemoglobin (g/dL) (median(IQR))	
HIV-infected	10.5 (9.7, 11.4)
HIV-uninfected	10.8 (9.8, 11.4)

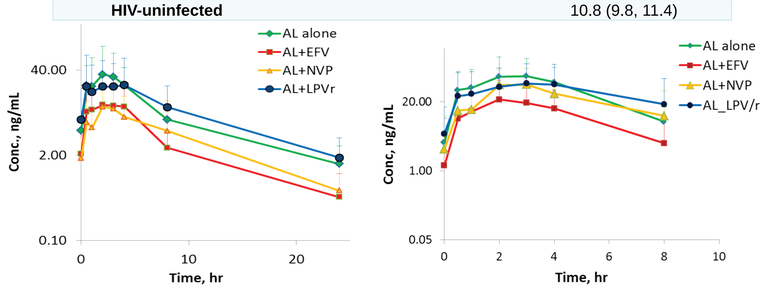


Figure 3. Mean plasma concentration versus time profile for artemether (left panel) and dihydroartemisinin (right panel) after AL administration alone (green line) and with EFV (red line), nevirapine (yellow line), or lopinavir-ritonavir (blue line). Error bar represented standard deviation (SD). Ideal PK time was used as X-axis

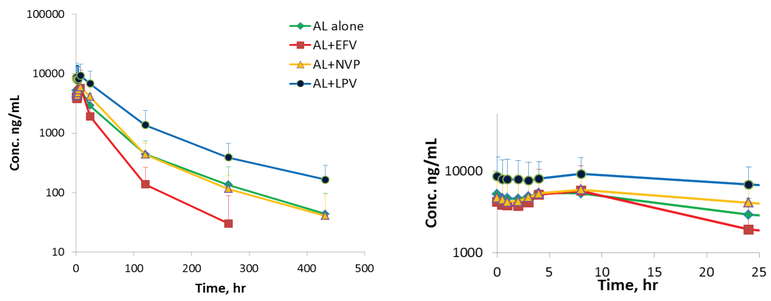


Figure 4. Mean plasma concentration versus time profile for lumefantrine after AL administration alone (green line) and with EFV (red line), nevirapine (yellow line), or lopinavir-ritonavir (blue line). Error bar represented standard deviation (SD). Ideal PK time was used as X-axis

Cumulative risk of failure in HIV-infected children on ART				
	N	**Risk of 28-day parasitologic failure (95% CI)[1]**	**HR (95% CI)**	**p-value**
EFV-based ART	50	38% (26., 53)	3.0 (1.3, 6.8)	0.01
NVP-based ART	63	30% (20, 43)	2.3 (0.96, 5.3)	0.06[2]
LPV/r-based ART	69	13% (7, 24)	Reference	N/A
LR $AUC_{0to\infty}$ below lowest quartile (hr•mg/mL)	29	35% (20, 55)	2.6 (1, 6)	0.03
LR $AUC_{0to\infty}$ above lowest quartile (hr•mg/mL)	58	16% (8, 28	Reference	N/A
LR day 7 ≤ 280 ng/mL	61	38% (27, 51)	2.3 (1.3, 4.0)	0.005
LR day 7 > 280 ng/mL	110	18% (12, 27)	Reference	N/A
	N	**Risk of 42-day recurrent malaria (95% CI) [1]**	**HR (95% CI)**	**p-value**
EFV-based ART	49	25% (15, 39)	2.3 (0.72, 7.0)	0.16[2]
NVP-based ART	62	24% (15, 37)	2.7 (0.98, 7.6)	0.06[2]
LPV/r-based ART	67	11% (5, 21)	Reference	N/A

[1] Multivariate analysis controlling for age, parasite density, and hemoglobin on day of diagnosis, as well as repeated measures in the same individual
[2] p-value significant (<0.05) in univariate analysis

The impact of LPV/r, EFV and NVP on AR, DHA, and LR PK disposition

Intensive PK (n=142)						
	AR-LR alone (C)	AR-LR+LPV/r		AR-LR+EFV		AR-LR+NVP	
	GM; 95%CI (n=51)	GM; 95%CI (n=30)	GMR, LPV/C	GM; 95%CI (n=31)	GMR, EFV/C	GM; 95%CI (n=30)	GMR, NVP/C
AR_AUC_{0-8}	120 (96.7-149)	97.1 (68.2-138)	0.809	52.8 (40.6-68.7)	0.440***	43.4 (31.7-59.0)	0.361***
DHA_AUC_{0-8}	213 (172-263)	178 (132-241)	0.836	68.4 (50.5-92.7)	0.321***	151 (119-192)	0.709*
$LR_AUC_{0-¥}$	271 (238-307)	564 (423-752)	2.08***	135 (99.6-183)	0.498***	278 (218-355)	1.030
LR Half-life	66.0 (52.0, 121)	98.6 (88.4, 119)	1.49	23.6 (21.8, 40.7)	0.358***	63.4 (46.8, 111)	0.961

GM: geometric mean; CI: confidence interval, GMR: geometric mean ratio. AR and DHA AUC_{0-8} unit is hr·ng/mL. $LR_AUC_{0-¥}$ unit is hr·µg/mL.

Intensive and population PK (n=363)						
	AR-LR alone (C)	AR-LR+LPV/r		AR-LR+EFV		AR-LR+NVP	
	Median (IQR), n=185	Median (IQR), n=68	MR, LPV/C	Median (IQR), n=48	MR, EFV/C	Median (IQR), n=62	MR, NVP/C
LR C_{7d}	345 (258, 531)	1160 (524, 2285)	3.36***	111 (63.0, 213)	0.322***	434 (285, 758)	1.26*
LR C_{14d}	86.7 (59.6, 138)	324 (167, 589)	3.74***	BLQ (BLQ, BLQ)	<1***	116 (68.3, 182)	1.34*
LR C_{21d}	BLQ (BLQ, 63.8)	158 (80.8, 280)	>1***	BLQ (BLQ, BLQ)	<1**	BLQ (BLQ, 83.4)	>1

LR C7d, C14d, and C21d are LR concentrations (ng/mL) on days 7,14 and 21 respectively ; reported as median with IQR, interquartile range.

MR, median ratio. * 0.0083<p<0.05, **0.0001<p<0.0083,***p<0.0001, significant level: p=0.0083

Number (%) of children with lumefantrine levels below threshold levels				
	LPV/r-based ART	NVP-based ART	EFV-based ART	HIV-uninfected children
Lumefantrine day 7 < 175 ng/mL	8/67 (12%)	15/63 (24%)	41/48 (85%)	57/80 (32%)
Lumefantrine day 7 < 280 ng/mL	5/67 (8%)	7/63 (11%)	34/48 (71%)	16/180 (9%)
Lumefantrine $AUC_{0to\infty}$ lowest quartile (hr•mg/mL)	3/29 (10%)	7/30 (23%)	20/30 (67%)	5/51 (10%)
Artemether AUC lowest quartile (hr•mg/mL)	7/28 (25%)	13/28 (46%)	9/29 (31%)	5/49 (10%)
Dihydroartemisinin AUC lowest quartile (hr•mg/mL)	5/28 (18%)	9/29 (31%)	14/27 (52%)	5/48 (10%)

WHO 42 day outcomes (PCR-unadjusted)			
	LPV/r-based ART N = 67 (%)	NVP-based ART N = 62 (%)	EFV-based ART N = 49 (%)
Adequate Clinical and Parasitological Response	49 (74%)	38 (61%)	26 (53%)
Late Parasitologic Failure	10 (15%)	9 (15%)	11 (23%)
Late Clinical Failure	7 (11%)	15 (24%)	12 (25%)

Discussion

- Artemether-lumefantrine is the most widely adopted ACT with millions of doses given yearly.
- Current WHO guidelines recommend LPV/r-based ART as 1st-line in children < 3 years and EFV-based ART in children >3 years of age.
- Frequent ART and ACT co-administration is common in regions with a high prevalence of co-infection, *especially in children*.
- A dramatic alteration in lumefantrine exposure was measured in the setting of concomitant ART. Children on *LPV/r-based ART* have a 3.4-fold higher exposure to lumefantrine than HIV-uninfected children. In contrast, children on EFV-based regimens have significantly reduced (GMR 0.32) exposure.
- Notably, a 10-fold reduction in lumefantrine exposure was measured in children on EFV versus children on LPV/r, underscoring the seriousness of these drug interactions.
- Importantly, differences in exposure are significantly associated with parasitologic outcomes, with a 3.0-fold HIGHER risk of failure in children on EFV-based ART as compared to those on LPV/r-based regimens.
- Findings are further supported by comparison of lumefantrine levels to previously published thresholds. Notably, 85% and 71% of children on EFV-based ART demonstrate levels below 280 and 175 ng/mL, respectively.
- PCR-corrected outcomes in all groups, including HIV-uninfected children, are being analyzed.
- Results support the need for alternative dosing of artemether-lumefantrine in the setting of EFV-based ART in children.

Acknowledgments

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