



MAKERERE UNIVERSITY

Pharmacologic considerations in the treatment of malaria in Africa

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Mahidol Oxford

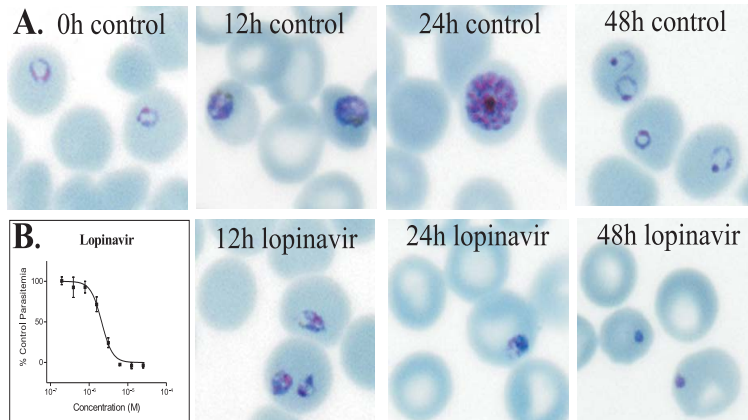


WELLCOME TRUST - MAHIDOL UNIVERSITY-OXFORD
TROPICAL MEDICINE RESEARCH PROGRAMME



University of Ibadan
Nigeria's Premier University

HIV protease inhibitors are active against malaria parasites at clinically relevant concentrations

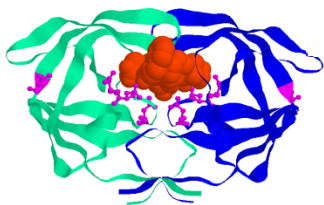


Drug	<i>P. falciparum</i> IC ₅₀ (μM)				[Serum] with standard dosing		[Serum] with boosted dosing	
	HB3	D6	Dd2	W2	C _{max}	C _{min}	C _{max}	C _{min}
Saquinavir	5.6	4.8	4.3	1.1	3.7	0.3	5.5	0.6
Ritonavir	4.7	7.9	6.9	1.2	15.5	5.1	NA	NA
Lopinavir	1.4	2.0	2.1	0.9	NA	NA	15.6	8.8
Atazanavir	6.8	11.6	7.1	2.5	3.3	0.2	8.7	1.7

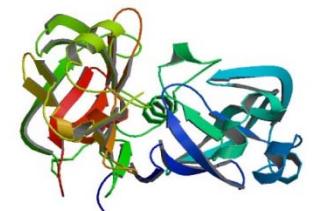
Knockouts of food vacuole plasmepsins do not affect HIV PI activity against the parasite

Drug	<i>P. falciparum</i> IC ₅₀ (μM)				
	Wild-type	PMPI KO	PMPH KO	HAP KO	PMPH/IV KO
Saquinavir	11.0	11.0	11.0	14.0	11.0
Ritonavir	10.0	11.0	11.0	14.0	11.0
Lopinavir	2.0	2.5	2.5	3.0	3.0

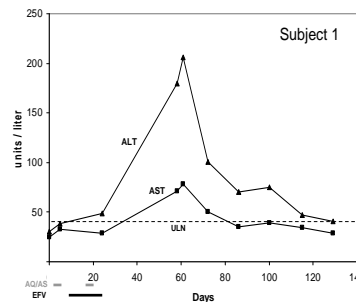
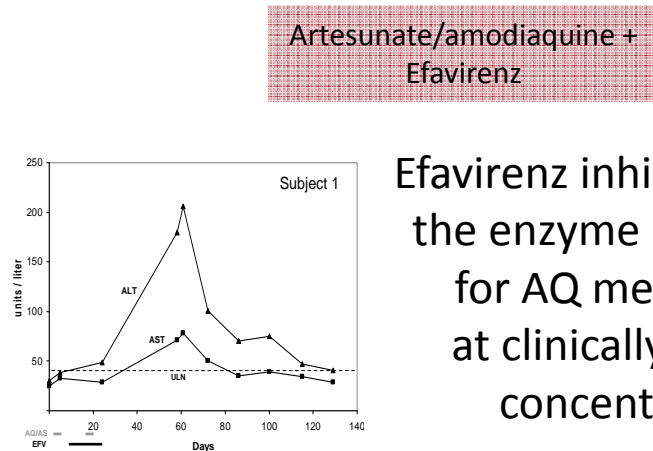
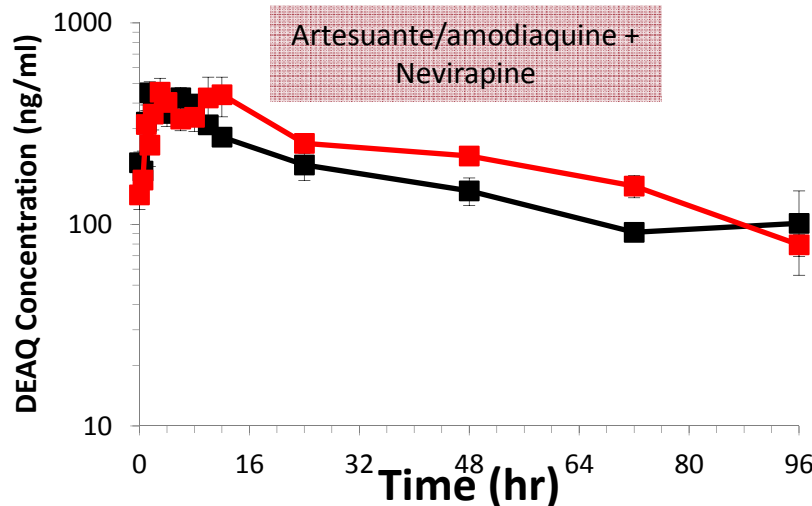
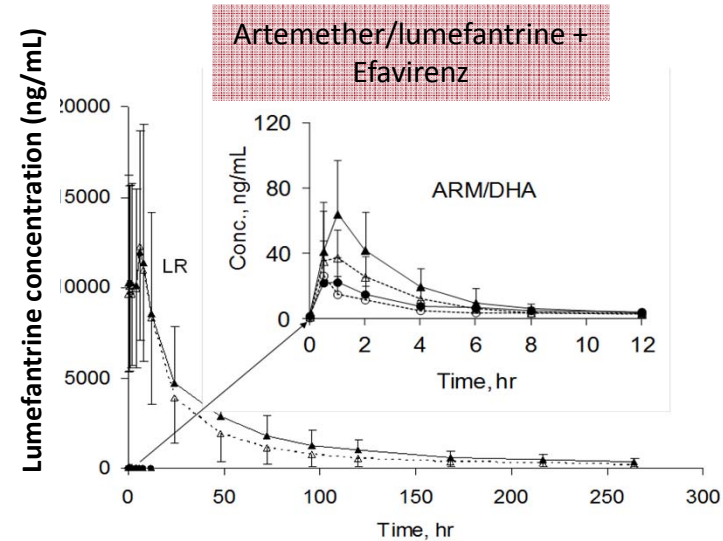
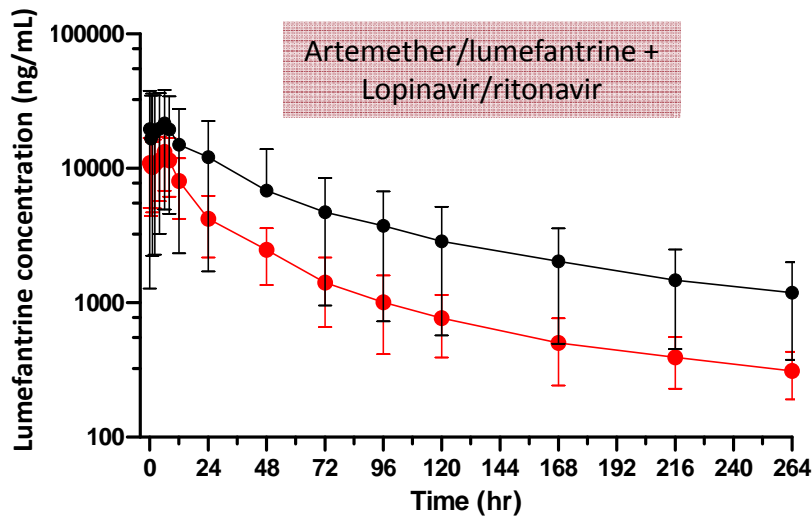
Abbreviations: PMP, plasmepsin; KO, knockout; HAP, histoispartic protease.



Parikh S, et al. AAC 2005; Parikh S, et al. AAC 2007; Nsanzabana C, et al. AAC 2012



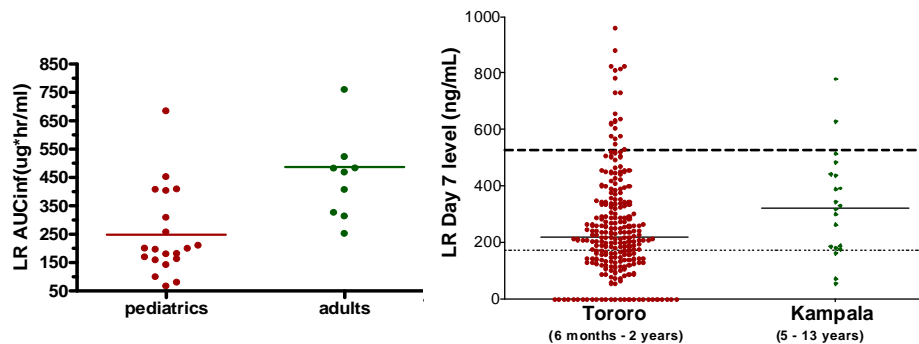
Significant interactions exist between artemisinin combination therapies (ACTs) and antiretrovirals



Efavirenz inhibits CYP2C8, the enzyme responsible for AQ metabolism, at clinically relevant concentrations

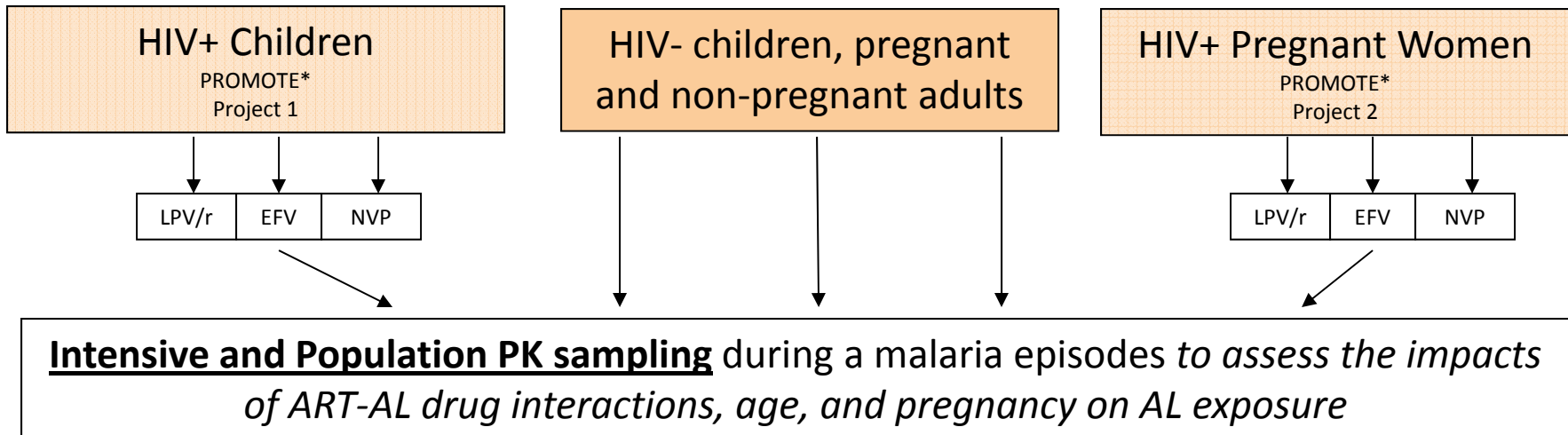
We aim to understand the PK/PD of ACTs in the most vulnerable groups: children and pregnant women

Artemether-lumefantrine



Dihydroartemisinin-piperaquine

Study Location	Age range	Day 7 level (ng/mL)	
		Capillary	Venous
Uganda	6-23 months	41.9 (median)	13.8 (median)
Burkina Faso ³	2-5 years	58.7 (median)	36.6 (median)
	5-10 years	67.5 (median)	44.1 (median)
Papua New Guinea	5-14 years		37.1 (mean)
	15-60 years		50.4 (mean)
Vietnam	17-55 years		37-118 (range)



Mwesigwa J and Parikh S, et al. AAC 2010; Tarning J, et al. Clin Pharmacol Ther 2012; NICHD R01HD068174-01 (PIs Parikh and Aweeka)

* co-enrolling subjects from (1P01HD059454) Prevention of Malaria and HIV Disease in Tororo (PROMOTE, PI Havlir)