Interactions between malaria and HIV drugs in malaria endemic areas – the InterACT trial

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Introduction 1

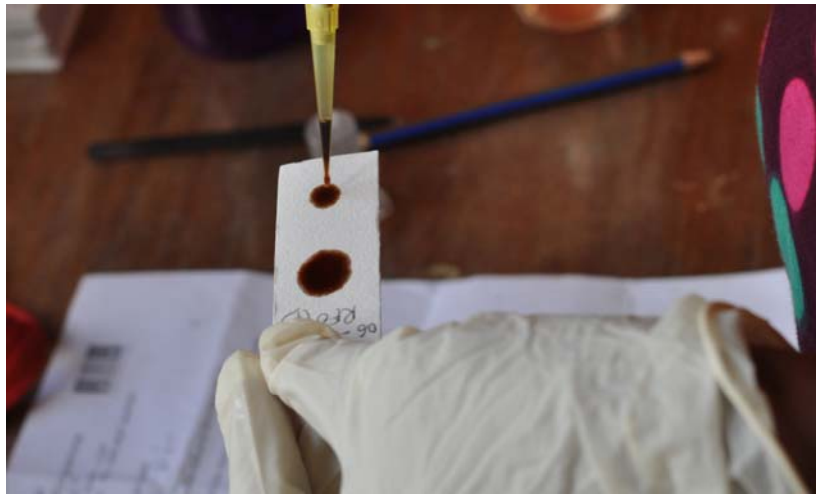
- As we all now, malaria and HIV co-infection is common in Africa.
- Fortunately, an increasing number of patients now have access to ACTs for malaria and antiretrovirals (ARVs) for HIV.
- The most commonly used ACT is artemether-lumefantrine (AL), while first-line ARVs are typically based on either nevirapine (NVP) or efavirenz (EFV).

Introduction 2

Several PK studies have demonstrated significant changes in AL concentrations when used together with NVP or EFV:

a) NVP leads to increased lumefantrine concentrations → may lead to toxicity/adverse events?

b) EFV leads to decreased lumefantrine concentrations → may lead to reduced therapeutic efficacy?



Aim and objectives of the InterACT trial

MAIN OBJECTIVE:

To inform guidelines for the treatment of malaria in patients with HIV/AIDS receiving common first-line antiretrovirals in an endemic area

KEY RESEARCH QUESTIONS:

1. What is the therapeutic efficacy of AL in patients with HIV/AIDS, including patients receiving first-line ARVs?
2. What is the safety/tolerability of AL in patients with HIV/AIDS, including patients receiving first-line ARVs?
3. What are Day 7 lumefantrine levels in nevirapine and efavirenz treated HIV patients?

InterACT study profile

- Study conducted at Muheza District Hospital, NE Tanzania
- Registered on ClinicalTrials.gov ID NCT00885287
- Included patients aged 15-60 years
- Four different groups of patients:

HIV-positive patients with malaria AL + ARV

HIV-positive patients with malaria AL only

HIV-negative patients with malaria AL only

HIV-positive patients with no malaria ARV only

InterACT study profile

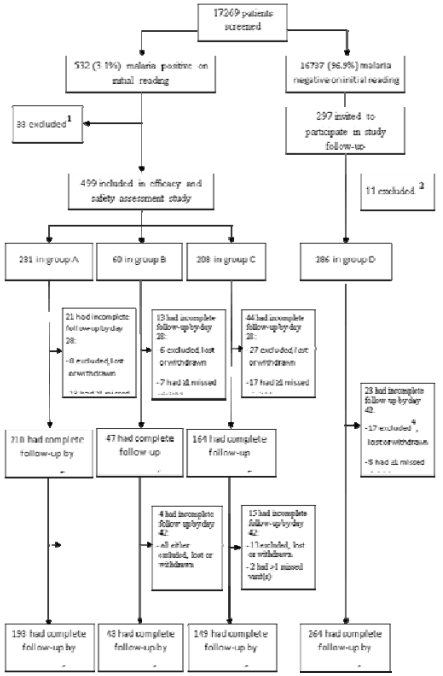
- 17,269 patients screened for malaria, July 2009-October 2012
- 785 patients met d enrolled:

  -231 HIV-positive malaria patients receiving AL + ARVs

  - 60 HIV-positive malaria patients receiving AL, no ARVs

  - 208 HIV-negative malaria patients receiving AL

  - 286 HIV-positive patients receiving ARVs, no malaria



Methods

- Standard therapeutic efficacy protocol (WHO, 2009)
- Clinical exam + blood slide on day 1, 2, 3, 7, 14, 21, 28, 35, 42
- Biochemistry and hematology analysis on day 0, 7, 14, 28, 42
- Main therapeutic efficacy results by per protocol analysis – PCR corrected treatment success at day 42
- Recording of adverse events by type (MedDRA codes) and grade in all patients enrolled
- PK analysis (University of Cape Town)

Patient characteristics 1

	HIV-positive patients with AL + ARVs (n=231)	HIV-positive patients with AL (n=60)	HIV-negative patients with AL (n=208)	HIV-positive patients with ARVs (n=286)
Age, median	42	40	27	41
Females	149 (67%)	38 (61%)	83 (43%)	235 (79%)
BMI (kg/m^2)	20.3	19.6	20.5	21.2

Patient characteristics 2

		HIV-positive patients with AL + ARVs (n=231)	HIV-positive patients with AL (n=60)	HIV-negative patients with AL (n=208)	HIV-positive patients with ARVs (n=286)
Receiving Cotrimoxazole		62 (27%)	1 (2%)	0 (0%)	109 (38%)
ARV regimen	Nevirapine-based	124 (54%)	-	-	180 (63%)
	Efavirenz-based	106 (46%)	-	-	104 (37%)

Patient characteristics 3

		HIV-positive patients with AL + ARVs (n=231)	HIV-positive patients with AL (n=60)	HIV-negative patients with AL (n=208)	HIV-positive patients with ARVs (n=286)
Parasites, geometric mean		3102	4218	4129	-
Gametocytes present		6 (3%)	1 (2%)	6 (3%)	-
CD4 cell count		336	410	644	386
Hematology	Hb	11.2	11.1	12.4	11.8
	Platelets	140	141	133	242
	WBC	3.6	4.1	4.6	4.4
	Neutrophils	2.1	1.9	2.6	2.3

Main results

1. Artemether-lumefantrine therapeutic efficacy by day 42
2. Safety data
3. Lumefantrine blood levels day 7

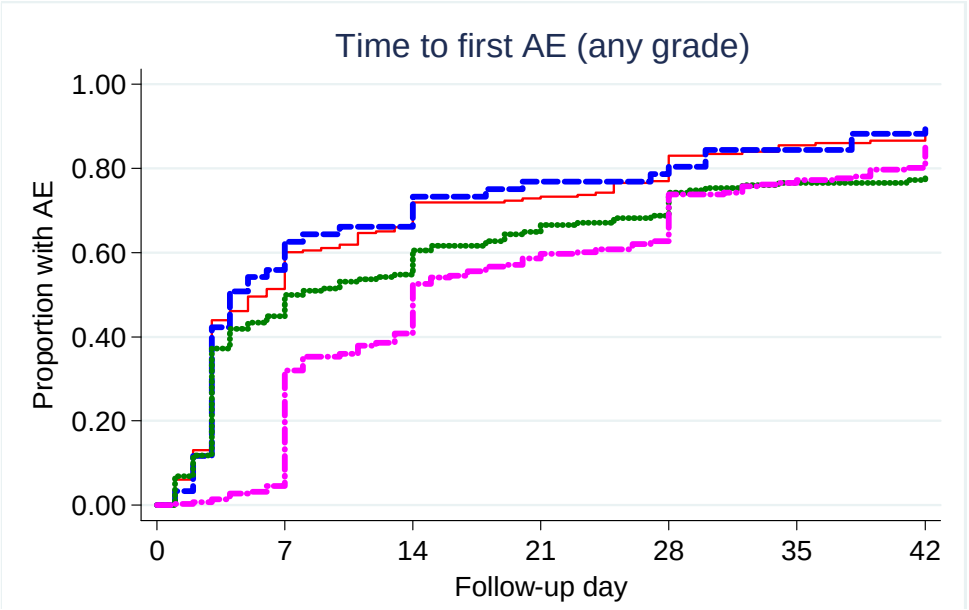
Therapeutic efficacy of artemether-lumefantrine by day 42

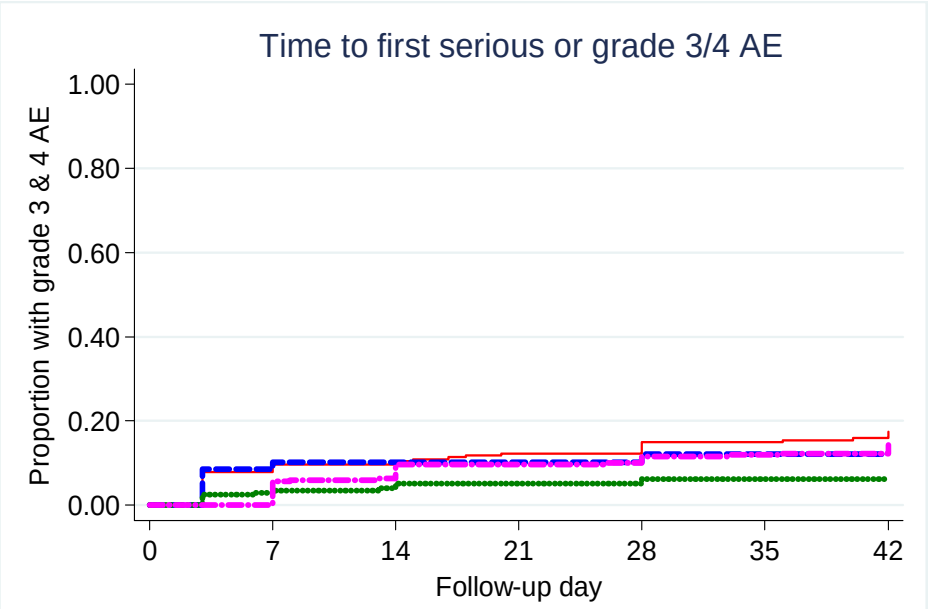
Patient group (per protocol analysis = 100% follow-up)	Adequate Clinical Parasitological Response (ACPR)	
	Without PCR-correction	With PCR-correction
HIV-positive malaria patients receiving ARV	176/193 (91.2%)	**176/177 (99.4%)**
HIV-positive malaria patients without ARVs	40/43 (93.0%)	**40/40 (100%)**
HIV-negative malaria patients	136/149 (91.3%)	**136/137 (99.2%)**

Adverse events

	HIV-positive patients with AL + ARVs (n=231)	HIV-positive patients with AL (n=60)	HIV-negative patients with AL (n=208)	HIV-positive patients with ARVs (n=286)
Patients with ≥1 adverse event of any grade	199 (86.1%)	52 (86.7%)	152 (73.1%)	31 (80.8%)
Patients with ≥1 serious AE	10 (4.3%)	4 (6.7%)	1 (0.5%)	12 (4.2%)
Patients with ≥1 serious AE or grade 3/4 AE	39 (16.9%)	7 (11.7%)	12 (5.8%)	39 (13.6%)

Time to first adverse event – initially reflects acute malaria infection





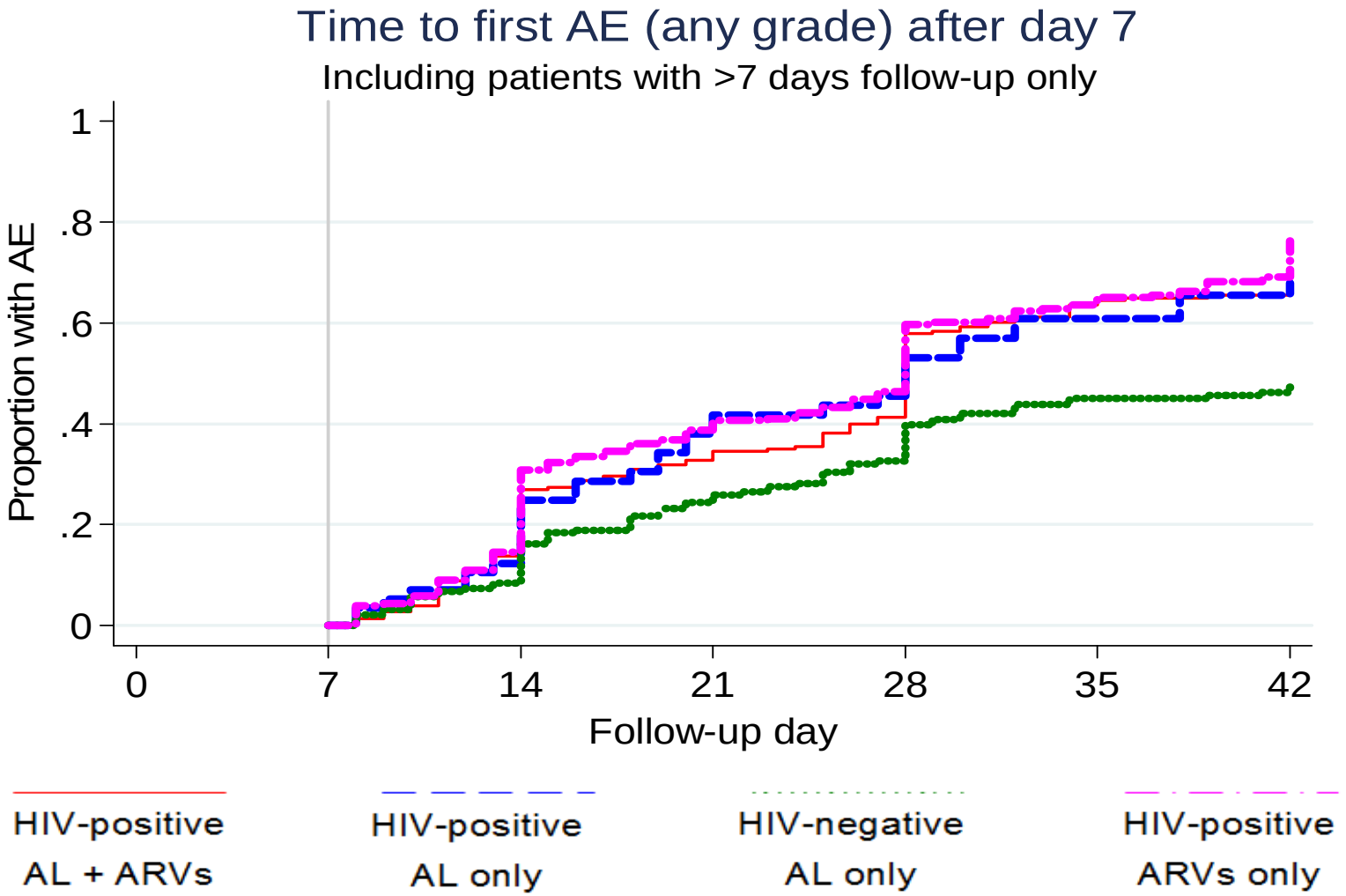
HIV-positive AL + ARVs

HIV-positive AL only

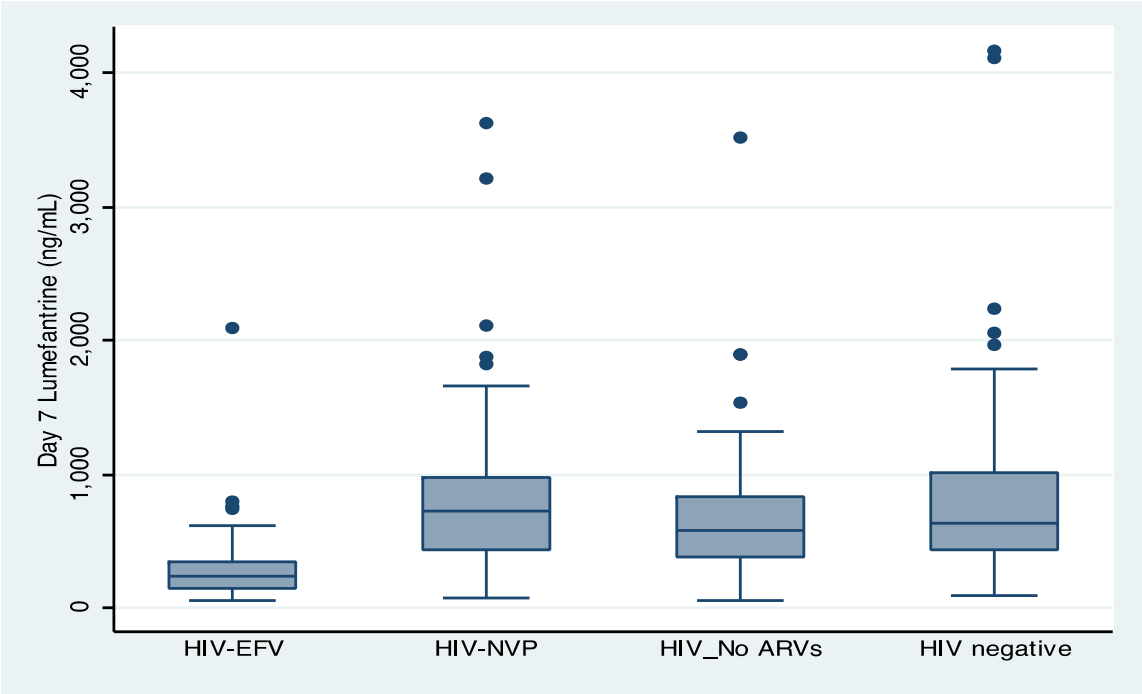
HIV-negative AL only

HIV-positive ARVs only

Time to first AE after day 7 – subsequently reflects ongoing HIV



Day 7 levels of lumefantrine



	Efavirenz-based ARVs n=93)	Nevirapine-based ARVs (n=104)	No ARVs (n=51)	HIV-negative (n=183)
Median	227	723	580	631
IQR	151-350	425 - 975	370 - 834	424 - 1010
Range	54.6 - 2090	76.5 - 3630	50.3 - 3530	87.1 - 4170

Median regression analysis of factors associated with lumefantrine levels

	Coefficient	95% Confidence Intervals	Significance
Efavirenz-based ARVs	-379	-497 to -261	<0.001
Nevirapine-based ARVs	118	1.8 to 234	0.047
HIV-infected on No ARVs	Reference		
HIV-uninfected	1.9	-105 to 109	0.973
Body Mass Index	13.3	3.8 to 22.7	0.006

FACTORS NOT ASSOCIATED WITH LUMEFANTRINE LEVELS:
HIV status, age, gender, mg/kg dose, fever / temperature, haemoglobin or baseline parasite density.

Summary of findings

1. Lumefantrine blood levels were affected by nevirapine and efavirenz – confirming results of previous studies;
2. Full therapeutic efficacy of artemether-lumefantrine in both HIV-positive and HIV-negative patients, regardless of concomitant ARV treatment;
3. Mild adverse events were commonly detected in all study groups;
4. Severe/serious adverse events seen among all HIV-positive patients, irrespective of ARV treatment.

Conclusions

1. Clinically significant drug-drug interactions between artemether-lumefantrine and nevirapine and efavirenz were not observed;
2. Our results thus support current treatment guidelines for malaria and HIV co-infection in adults;
3. However, there is a need to verify these findings in young children, who may be at higher risk of treatment failure if treated with efavirenz due to a lower level of acquired immunity.

Thank you!
More about the trial, including a video:

www.actconsortium.org/InterACT

Thank you for joining us!

Recording will be shared. Please ensure you are on our mailing list:

www.actconsortium.org/newsletter

For any questions or comments, contact

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