# In-vivo efficacy and safety of AL *Vs* DP for treatment of uncomplicated falciparum malaria and assessment of parasite genetic factors associated with parasite clearance or treatment failure

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# Introduction

- Artemisinin combination therapies (ACTs), are recommended antimalarial for treatment of uncomplicated falciparum malaria and have contributed to the recent reduction in malaria burden

- Common combinations are artemether-lumefantrine (AL), artesunate-amodiaquine (AS+AQ), artesunate-mefloquine (AS+MQ), and dihydroartemisinin-piperaquine (DP)

- Due to high level of resistance to SP, Tanzania introduced AL in 2006 and implementation started in January 2007

- AL has been used in Tanzania since 2007 and DP has been recently recommended as an alternative drug for treatment of uncomplicated falciparum malaria

# Introduction

- Efficacy studies are recommended by WHO to monitor the efficacy of ACTs and possibly detect evolution/emergence of tolerance/resistance to these drugs.

- However, implementation of the WHO recommendation has not been fully done by most malaria endemic countries

- More studies are also needed to assess the efficacy and safety of DP which has been introduced in Tanzania for treatment of uncomplicated falciparum malaria.

- With reports of resistance to artemisinins in South East Asia, intensive surveillance is needed to determine parasite genetic/genomic factors and mutations that might be associated with treatment outcome among patients with uncomplicated malaria

# Objectives

- **Main objective:**
  - to assess the efficacy and safety of AL and DP for treatment of uncomplicated malaria, and to investigate parasite genetic factors which might affect anti-malarial drug treatment outcome among patients treated with ACTs

- **Specific objectives:**
  - To assess *in-vivo* efficacy of AL and DP for treatment of uncomplicated malaria
  - To determine incidence of AEs among patients treated with AL or DP
  - To screen for parasite genomic factors possibly associated with tolerance/resistance to ACTs

# Methods

# Study sites
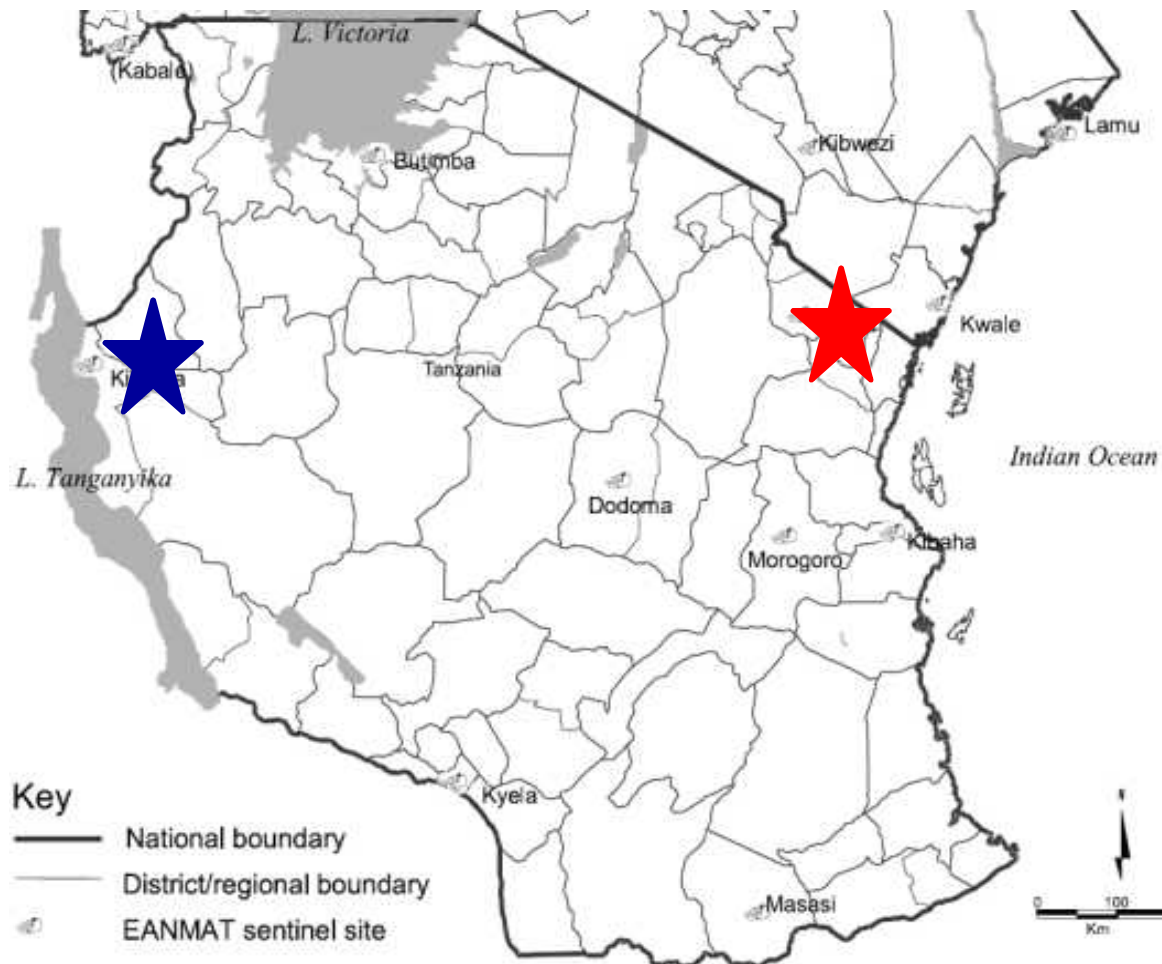


Muheza District Hospital – Tanga (RED) and  Ujiji Health Centre – Kigoma (BLUE)

# Study design

- Design: open-label, randomized and non-inferiority trial to compare the efficacy and safety of DP with AL for treatment of uncomplicated falciparum malaria

- Sample size: 150 children per arm

- Inclusion criteria (as per WHO protocol of 2009):
  - Age: 6 months to 10 years
  - Parasite density: 250 – 200,000 asexual parasites/µl
  - Suspected malaria: axillary temperature $\geq 37.5^{\circ}$C or a history of fever within the past 24 hours

- Exclusion criteria:
  - Severe malaria/chronic illnesses
  - severe anaemia (Hb < 5 g/dL) and
  - mixed or mono-infection with species other the *P. falciparum*

# Follow-up and Outcomes

- **Follow-up:**
  - Day 28 and extended to D42 for AL
  - D42 and extended follow up to D63 for DP

- **Primary outcomes:**
  - parasitological cure on days 28 and 42 for AL
  - parasitological cure on days 42 and 63 for DP.

- **Secondary outcomes:**
  - Parasite clearance – up to 72hrs post treatment
  - Hb recovery during follow-up
  - Genomic profile *P. falciparum*
  - Reduction in gametocyte carriage at D14 and D28 Vs day 0
  - occurrence and severity of adverse events

# Results

# Enrolment and follow-up

| Item | AL | DP | Total |
|---|---|---|---|
| **Muheza(target = 150 patients in each arm)** | | | |
| Number of patients enrolled | 96(64.0%) | 96(64.0%) | 192(64.0%) |
| Completed follow-up (D42/63) | 85(88.5%) | 85(88.5%) | 170(88.5%) |
| Lost to follow-up | 1(1.0%) | 3(3.1%) | 4(2.1%) |
| Withdrawn | 10(10.4%) | 8(8.3%) | 18(9.4%) |
| **Ujiji (target = 150 patients in each arm)** | | | |
| Number of patients enrolled | 160(106.7%) | 157(104.7%) | 317(105.7%) |
| Completed follow-up (D42/63) | 144(90.0) | 136(86.6%) | 280(88.3%) |
| Lost to follow-up | 6(3.8%) | 9(5.7) | 15(4.7%) |
| Withdrawn | 10(6.3%) | 12(7.6%) | 22(6.9) |

# Baseline characteristics

| Variable | AL | DP | Overall |
|---|---|---|---|
| **Muheza** | | | |
| Number of patients enrolled (n) | 96 | 96 | 192 |
| Age in years***, mean(SD) | 3.3(2.2) | 3.1(2.0) | 3.2(2.1) |
| Weight (kg),mean(SD) | 13.4(4.4) | 13.1(4.4) | 13.2(4.4) |
| Sex (male)*, n (%) | 59(61.5) | 57(59.4) | 116(60.4) |
| Body temperature in ° C, mean(SD) | 38.6 (1.1) | 38.7(1.1) | 38.6(1.1) |
| Geometric mean parasite density (asexual parasite /ul), 95% CI*** | 29,857 (23,175-38,465) | 36,478 (29,595-44,961) | 33,001 (28,027-38,859) |
| Haemoglobin g/dL, mean(SD)*** | 8.9(1.6) | 8.9(1.6) | 8.9(1.6) |
| **Ujiji** | | | |
| Number of patients enrolled (n) | 160 | 157 | 317 |
| Age in years***, mean(SD) | 4.1(2.4) | 4.2(2.6) | 4.1(2.5) |
| Weight (kg),mean(SD) | 13.9(4.4) | 13.9(4.3) | 13.9(4.3) |
| Sex (male)*, n (%) | 83(51.9) | 77(49.0) | 160(50.3) |
| Body temperature in ° C, mean(SD) | 38.1(1.3) | 38.0(1.4) | 38.1(1.3) |
| Geometric mean parasite density (asexual parasite /ul), 95% CI*** | 61,0715 (49,510-76,929) | 52,700 (42,079-66,002) | 57,087 (48,800-66,781) |
| Haemoglobin g/dL, mean(SD)*** | 9.5(1.7) | 9.6(1.6) | 9.2(1.6) |

# Treatment outcome

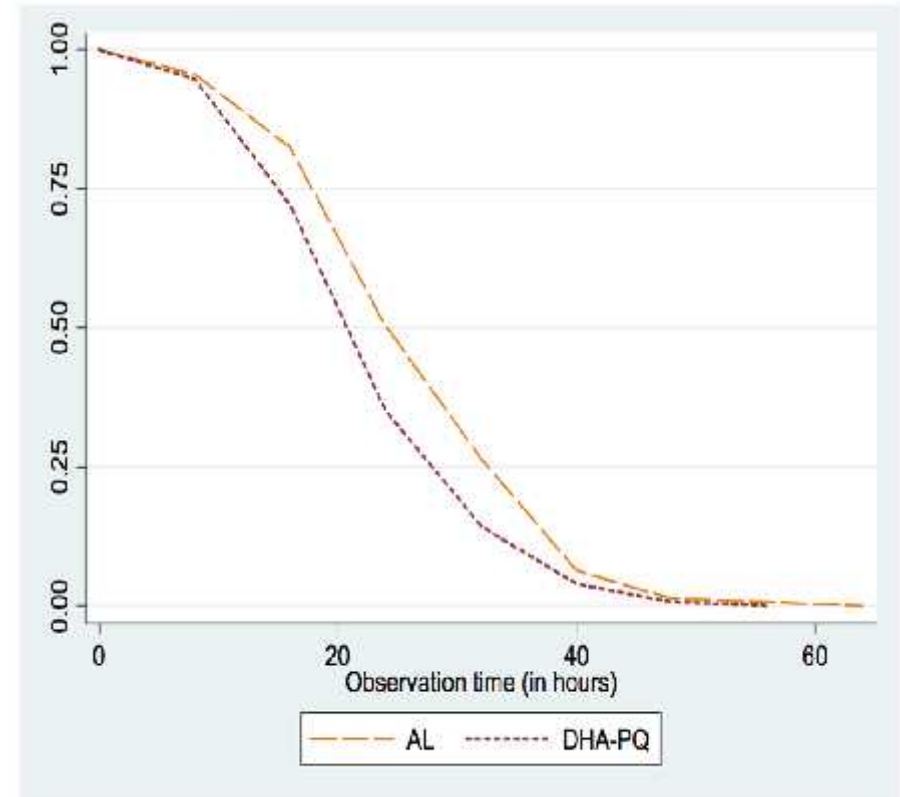| Outcome | AL | | DP | |
|---|---|---|---|---|
| **Outcome** | **AL** | | **DP** | |
| **Muheza** | **D28(n=88)** | **D42(n=85)** | **D42(n=88)** | **D63(n=85)** |
| ETF | 0 | 0 | 0 | 0 |
| LCF | 14(15.9%) | 33(38.8%) | 15(17.0%) | 29(34.1%) |
| LPF | 9(10.2%) | 2(1.2%) | 4(4.6%) | 3(3.5%) |
| ACPR | 65(73.9%) | 51(60.0%) | 69(78.4) | 53(62.4%) |
| | | | | |
| **Ujiji** | **D28(n=150)** | **D42(n= 144 )** | **D42(n=149)** | **D63(n= 136 )** |
| ETF | 0 | 0 | 0 | 0 |
| LCF | 17(11.3%) | 55(38.2%) | 16(10.7%) | 66(48.5%) |
| LPF | 25(16.7%) | 17(11.8%) | 19(12.8%) | 6(4.4%) |
| ACPR | 108(72%) | 72(50.0%) | 114(76.5%) | 64(47.1%) |

# Parasite Clearance
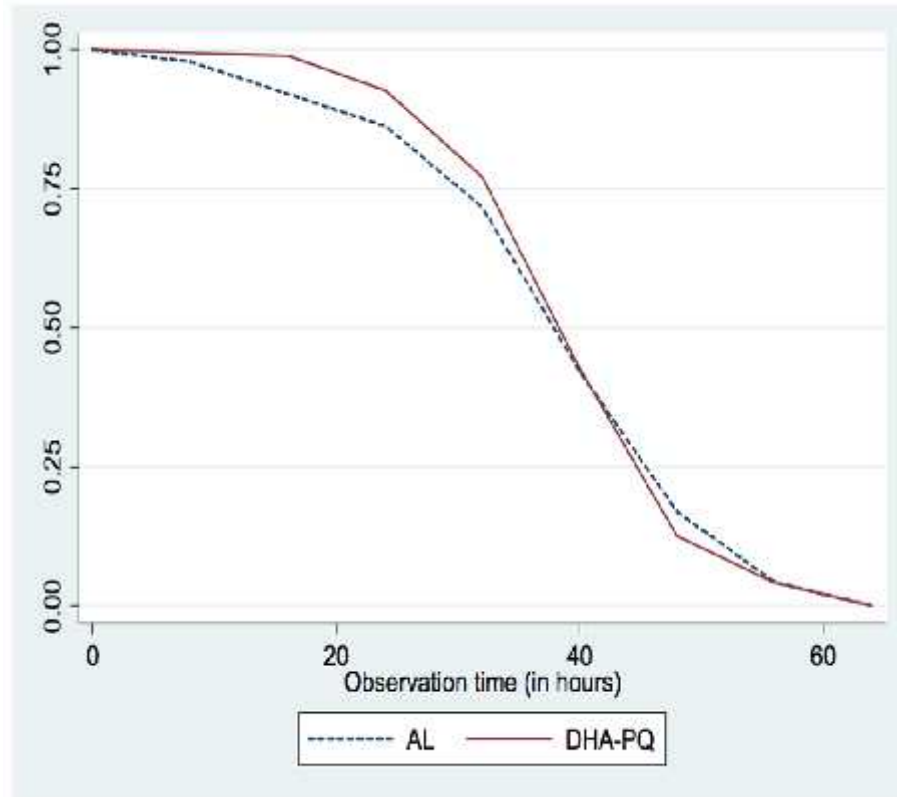
## Muheza

## Ujiji



No patient had parasites after 72hrs,  but majority at Muheza had parasites up to 36hrs

# Discussion and Conclusion

- At Muheza, the target sample size could not be reached due to limited funding; extension of the study beyond 6 months was not possible

- Ujiji had higher number of cases compared to Muheza, due to higher burden of malaria (THMIS, 2012)

- Both AL and DP had similar clinical efficacy before PCR correction

- The efficacy of the two drugs was similar at both sites during day 28 and 42 for AL and DP, respectively

- Low clinical efficacy during extended follow-up at Ujiji could be due to high malaria transmission

- No patients had parasites on Day 3 although the clearance was slower at Muheza compared to Ujiji

# Challenges

- Insufficient funds for field and lab work

- Low malaria transmission in Muheza

- Lack of funds to pay local staff at the HFs

# Ongoing work/perspective

- DNA extraction for genomic analysis (to be done at Sanger Institute, UK) and other molecular analyses to be done in Tanga
- PCR genotyping to distinguish recrudescent from new infections
- Completing data analysis for:
  - Trends of Hb during follow-up Vs day 0
  - Gametocyte carriage at D14 and D28 Vs day 0
  - Occurrence and severity of AEs
- Prepare final report and manuscripts

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- Co- Investigators: Samuel Gesase[1], Janneth Mghamba[2], Esther Ngadaya[3], Peter Mmbuji[2], Sigsbert Mkude[4], Renata Mandike[4], Ritha Njau[5],  Ally Mohamed[4] and Martha Lemnge[1]
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