Artemether-lumefantrine versus dihydroartemisinin-piperaquine for treatment of uncomplicated falciparum malaria in Uganda:

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Introduction

- In Uganda, artemether-lumefantrine is the recommended first-line treatment for uncomplicated malaria. Concerns about the following issues:
  - Cost and availability
  - Twice a day dosing
  - High reinfection rates in high endemic areas

Objectives

• Compare the efficacy and safety of artemether-lumefantrine (AL) and dihydroartemisinin-piperaquine (DP) for the treatment of uncomplicated malaria at a high transmission site in Uganda.

Study Methodology

- Randomized, single blinded, clinical trial with 42 days follow up.
- Study site:
  - Aduku HC Apac District
  - Site has perennial holoendemic malaria
  - EIR of 1564
- Genotyping was done to distinguish recrudescence from new infections
- Primary outcomes risk of recurrent parasitemia at days 28 and 42 unadjusted and adjusted by genotyping

Study Methodology

- Inclusion criteria:
  - Age 6 months – 10 years
  - Fever or history of fever in past 24 hours
  - *P. falciparum* mono-infection
  - Parasite density 2000/µl – 200,000/µl
  - No severe disease or other febrile illness

Study Methodology

- Treatment.
  - AL: 6 dose regimen (20 mg artemether/120 mg lumefantrine tablets),
  - DP: 3 dose regimen. (40 mg dihydroartemisinin/320 mg piperaquine tablets, total dose of 6.4 and 51.2 mg/kg of dihydroartemisinin and piperaquine, respectively).
  - Treatment was given with a fatty meal and directly observed.
- All patients given ITN at enrollment

Assessment of Treatment Efficacy

- Outcomes classified according to 2003 WHO guidelines
  - Early treatment failure (ETF)
  - Late clinical failure (LCF)
  - Late parasitological failure (LPF)
  - Adequate clinical and parasitological response (ACPR)

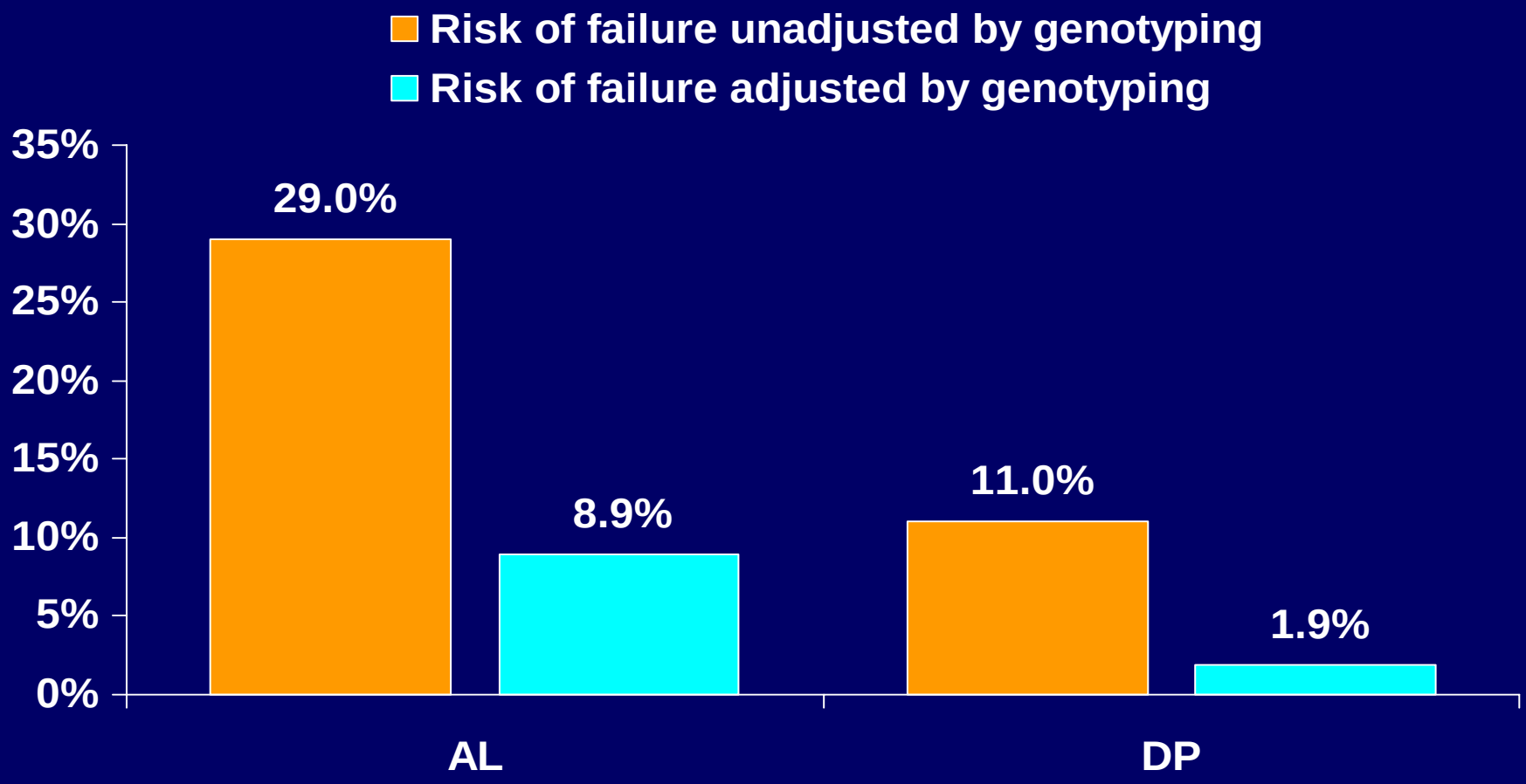
- Risk of recurrent parasitemia (unadjusted by genotyping)
  - Proportion of patients with ETF, LCF or LPF

- Risk of recrudescence (adjusted by genotyping)
  - Proportion of patients with ETF or LCF/LPF due to recrudescent parasites using Kaplan-Meier product limit formula (new infections censored)

Baseline Characteristics

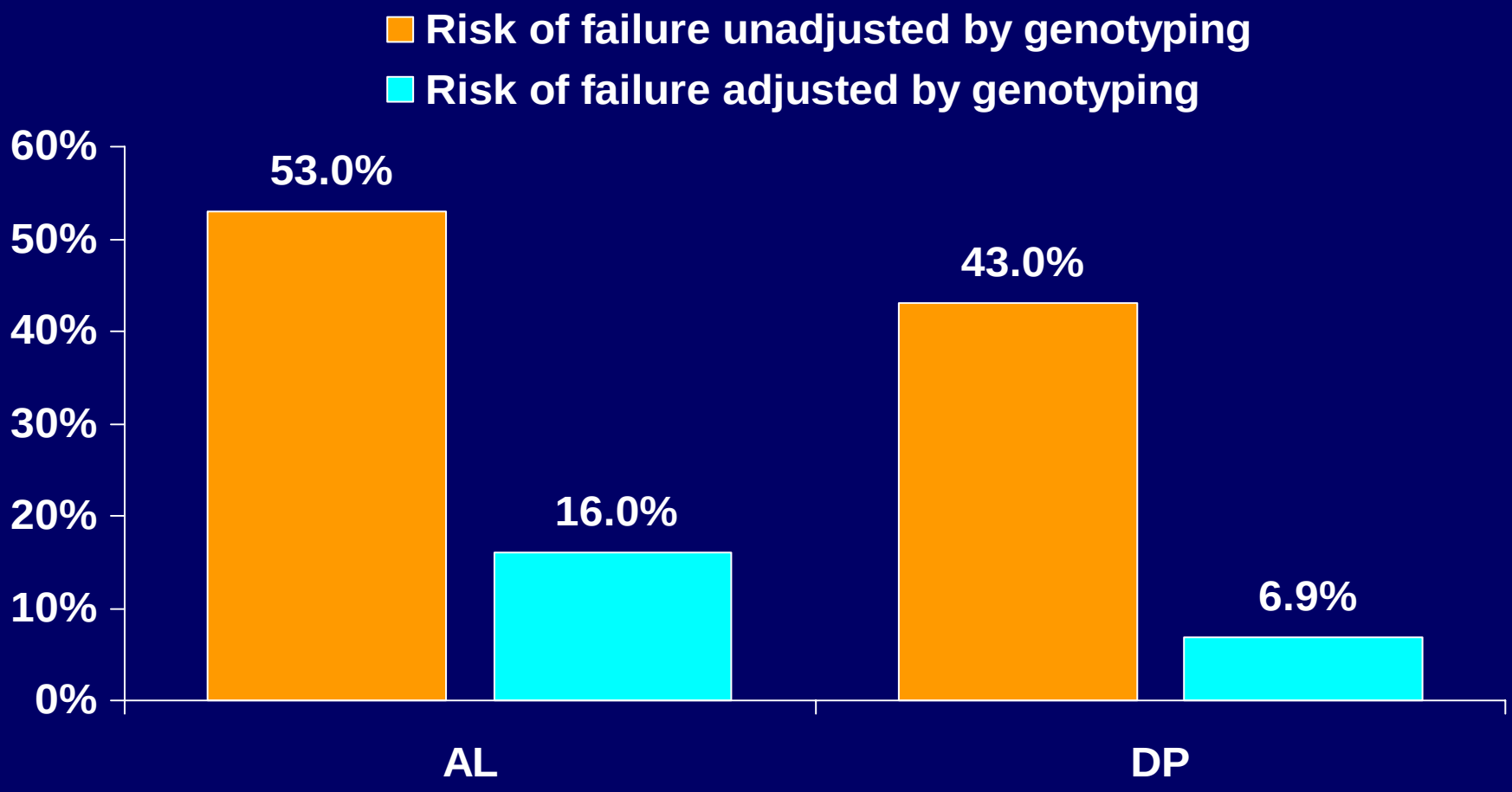
Characteristic	Treatment group	
	AL (n=210)	**DP (n=211)**
Completed (%)	208 (99%)	209 (99%)
Age in years, median (IQR)	1.8 (1.0-2-7)	1.5 (0.8-2.5)
Age less than 5 years (%)	195 (93%)	200 (95%)
Temperature ºC, mean (SD)	37.7 (1.0)	37.7 (1.1)
Geometric mean parasite density	23394	22789
Hemoglobin gm/dL, mean (SD)	9.7 (1.8)	9.5 (1.9)
Recent antimalarial use (%)	40 (19%)	33 (16%)

28 day Comparative Results



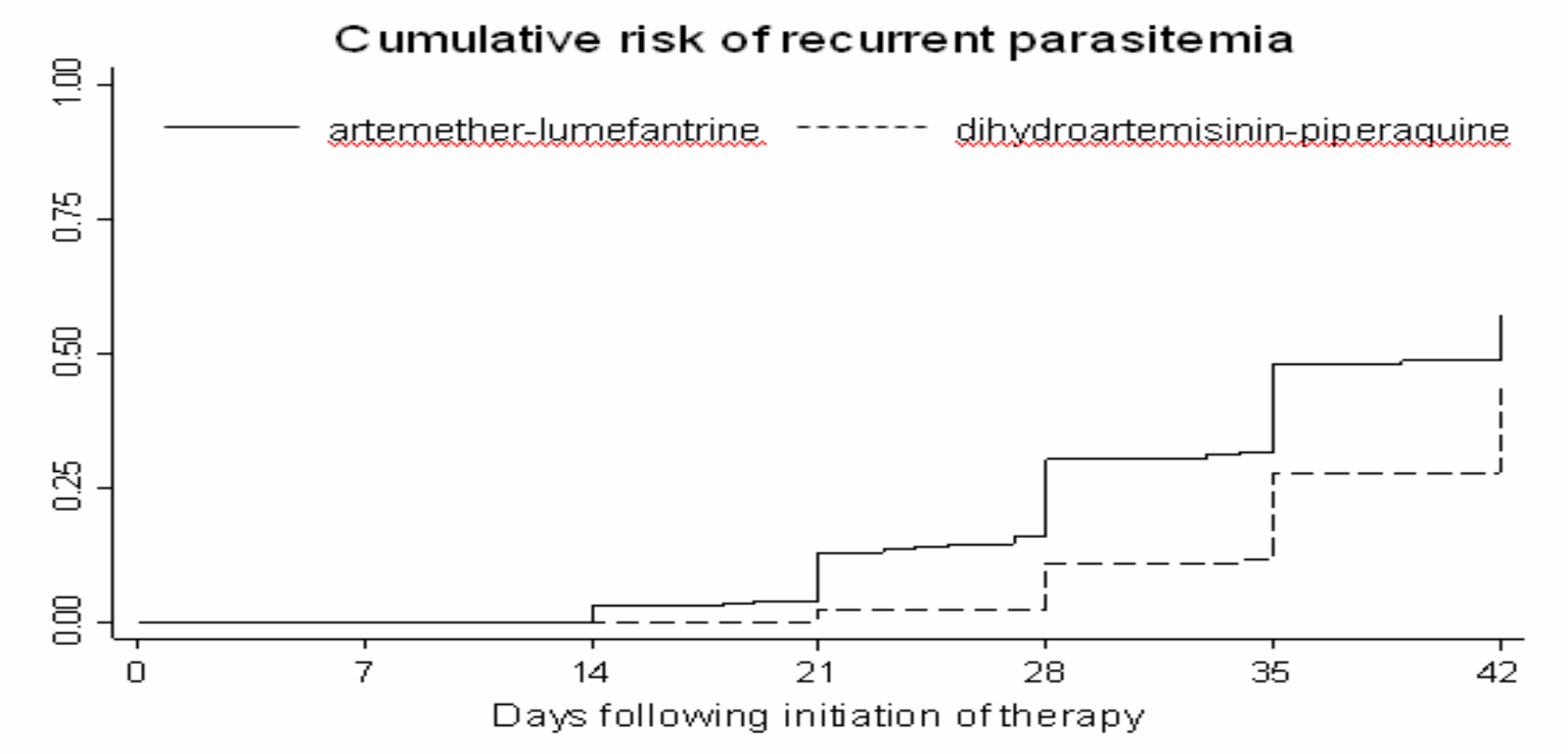
All pair-wise comparisons statistically significant (P<0.05)

42 day Comparative Results



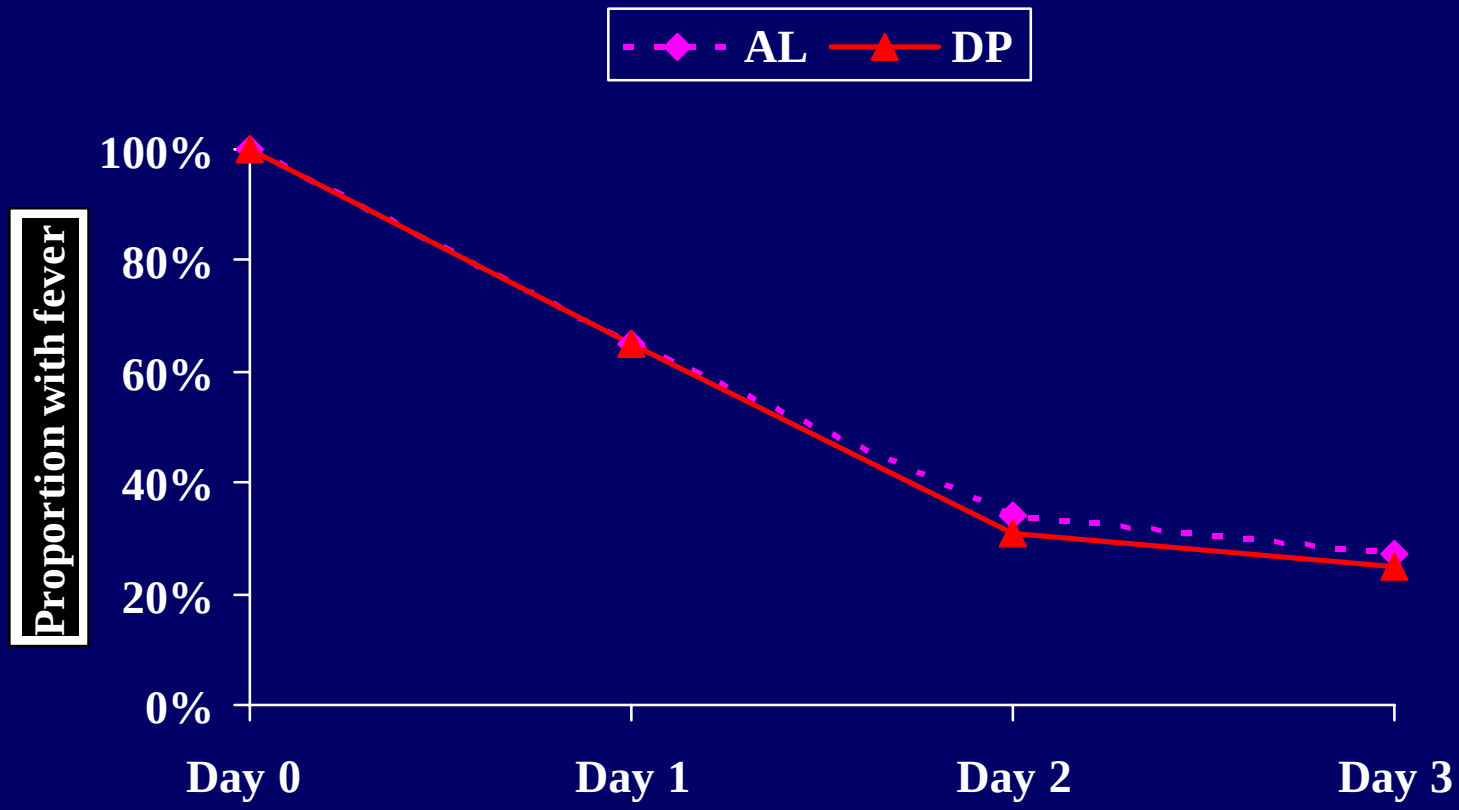
All pair-wise comparisons statistically significant (P<0.05)

Time to recurrent parasitaemia

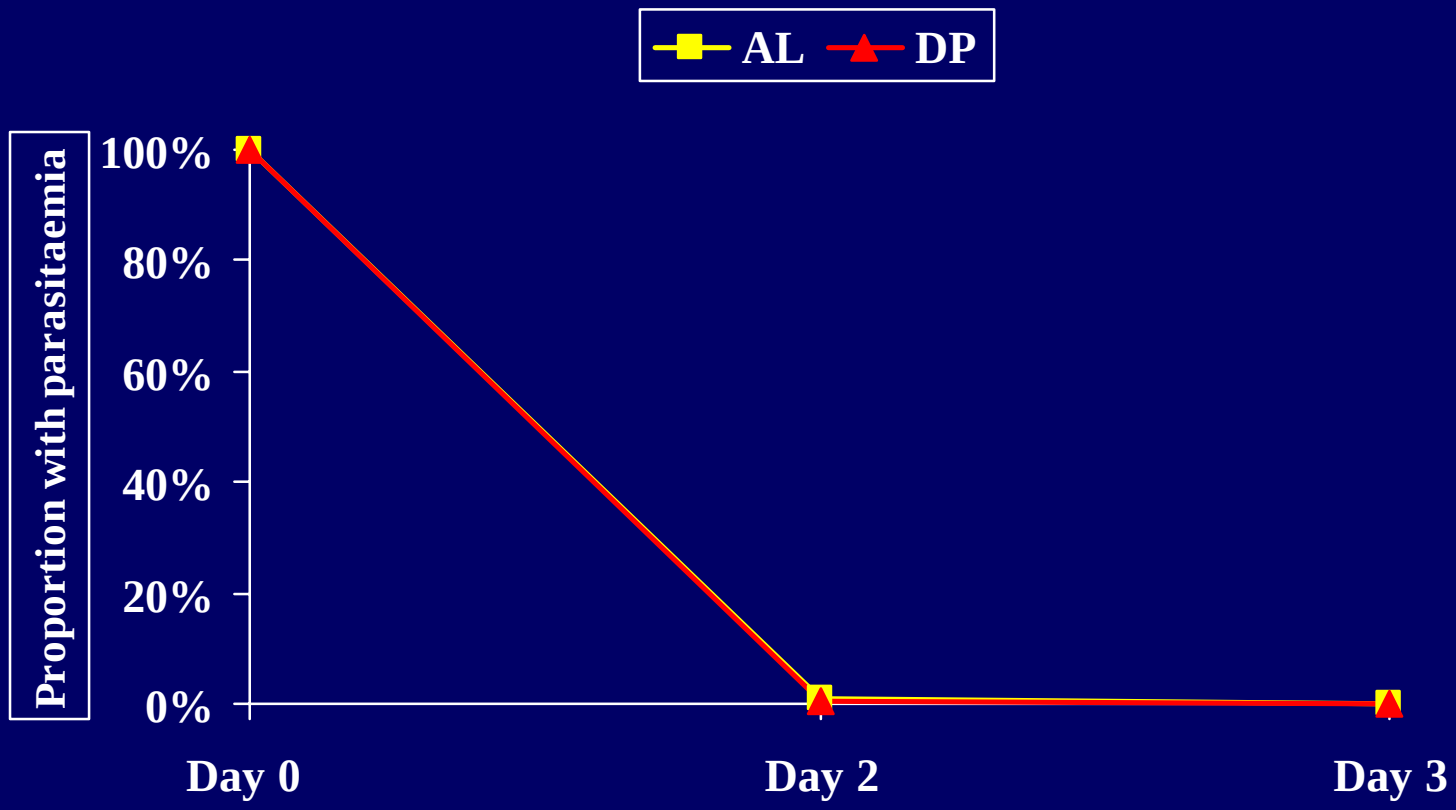


Median time to recurrent parasitaemia was significantly shorter in AL group compared to DP (28 days vs. 35 days, $p<0.0001$).

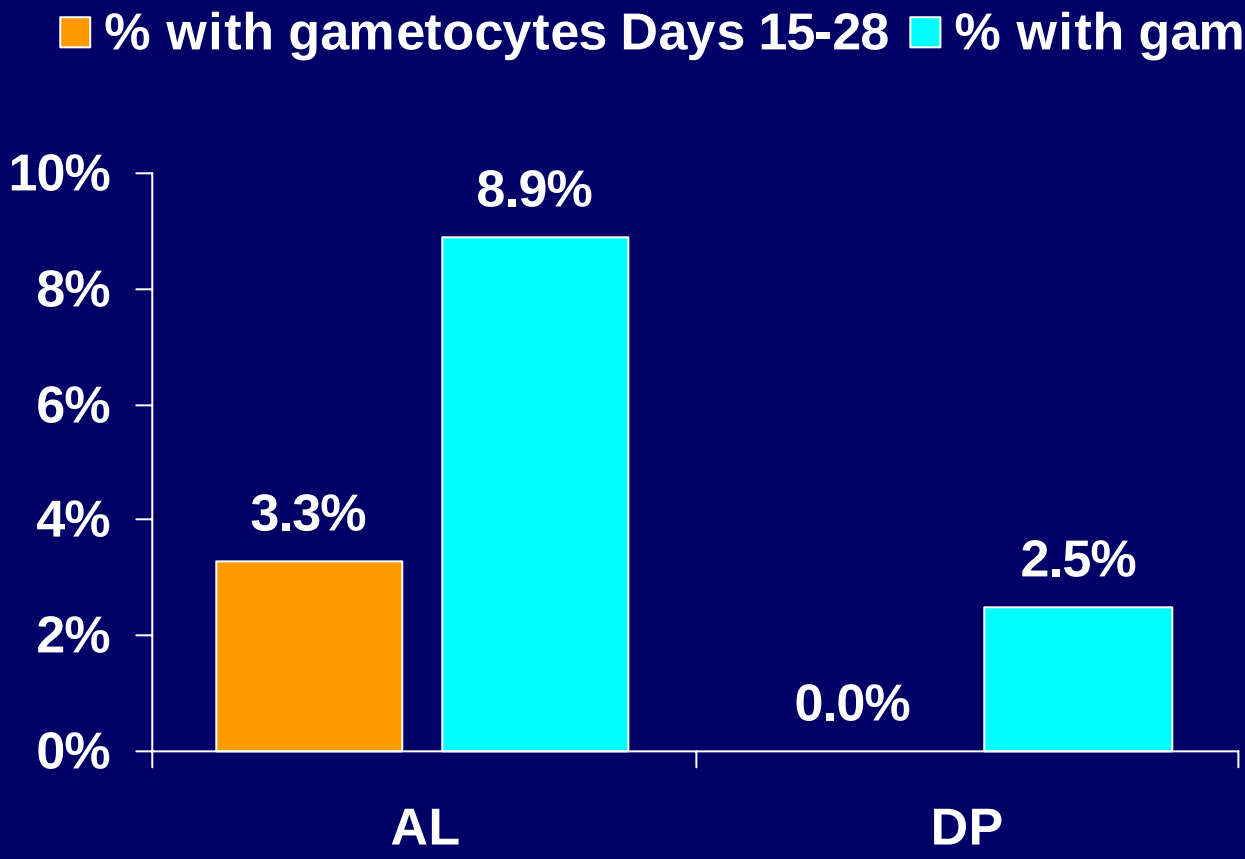
Fever clearance. Proportion of patients with fever during Days 0-3



Parasite clearance. Proportion of patients with parasitaemia during Days 0-3



Gametocyte carriage. Proportion of patients with gametocytes not present on Day 0.



All pair-wise comparisons statistically significant ($P<0.05$)

Hemoglobin recovery

- Mean increase in Hb higher in DP compared to AL group (1.9 vs. 1.5 gm/dL, P=0.05)

- Among patients with recurrent parasitemia there was no difference in the prevalence of anemia (Hb<10 gm/dL) on the day of failure in the AL group (33/117, 28%) compared to the DP group (25/92, 27%)(p=0.87).

Adverse Events: Proportion with adverse events

	AL N=210	DP N= 211	P-value
Cough.	63%	64%	0.84
Coryza.	58%	60%	0.62
Abdominal pain.	44%	53%	0.51
Weakness.	49%	40%	0.08
Anorexia.	43%	43%	0.92
Vomiting.	31%	31%	1.0
Diarrhoea.	9%	12%	0.42
Pruritus.	10%	7%	0.17
Serious adverse events.	2 (1%)	4 (1.9%)	0.67

Summary

- Both regimens were well tolerated and highly efficacious for treatment of uncomplicated malaria in an area with a very high level of malaria transmission.

- The risk of recurrent parasitemia was significantly lower for participants treated with DP than for those treated with AL.

- DP reduced the risk of gametocytemia and improved hemoglobin recovery compared to AL.

Conclusion

- For both ACT regimens, the high rate of re-infection and the implications of frequent retreatment are a major concern.

- The high reinfection rates in areas of very high malaria transmission highlights the need to re-evaluate the approach to treatment of recurrent episodes of malaria following initial ACT therapy

Policy Implications.

- Results have important policy implications.
  - DP is a highly effective alternative to AL as first line therapy for uncomplicated malaria in Africa.
  - DP is relatively inexpensive, and is easy to use (given once a day for 3 days).
  - DP has a potential role for presumptive treatment of fever in Home Based Management of Fever
  - The slowly eliminated “tail” of piperaquine may provide a selective filter for resistant parasites

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