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Original paper

Efficacy and safety of artesuante-amodiaquine and artemether lumefantrine, the first line malaria treatment in six sentinel's sites of Côte d'Ivoire, West Africa

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ABSTRACT. The purpose of this study was to update efficacy data of Artesunate-Amodiaquine (AS+AQ) and Artemether-Lumefantrine (AL) used as first-line malaria treatment in Côte d'Ivoire since 2005. This was an open-label, randomized trial conducted in patients older than 6 months with uncomplicated *P. falciparum* malaria at six sentinel sites. The WHO 2009 protocol on surveillance of anti-malaria drug efficacy was used with primary outcomes as ACPR corrected by PCR at day 42. Secondary endpoints were parasite and fever clearance times and safety. From January to July 2016, 712 patients were included in the trial. 353 and 359 patients were randomly assigned respectively to the AS+AQ and AL arm. Day 42 PCR-adjusted ACPR in the per-protocol analysis was 99.4% and 98.8% in AS+AQ and AL arm respectively. Delayed parasite clearance was observed in six patients at Abidjan and Yamousssoukro sites. Both ACTs were well tolerated. Both ACTs remain efficacious for uncomplicated *P. falciparum* malaria treatment in Côte d'Ivoire. But regarding delayed parasite clearance observed in this study, a close monitoring and supervision for ACT resistance are essential for future malaria treatment and control strategies in Côte d'Ivoire.

Keywords: malaria, ACTs, efficacy, Côte d'Ivoire

Introduction

Over the last decade, significant gains have been made towards the control and elimination of malaria. Despite this progress malaria remains a major public health concern in endemic countries [1]. Artemisinin Combination Therapy (ACTs) are the first-line treatment for malaria in most of malaria countries [2]. Artesunate+amodiaquine (AS+AQ) and Artemether+Lumefantrine (AL) are first line recommended drugs for the treatment of uncomplicated falciparum malaria in Côte d'Ivoire since 2005. More recently, dihydroartemisinin-piperaquine (DHAP) has been added to the list of ACTs used in first line treatment by the National Malaria Control Program (NMCP).

ACTs have remained highly efficacious for almost 2 decades but are now under threat from the emergence of drug-resistant parasites [3–6]. Emergence and spread of artemisinin-resistant malaria parasite populations in Southeast Asian countries and the possibility of extension to other endemic areas [7–11] have led the World Health Organization to recommend that malaria-endemic countries perform routine monitoring of antimalarial drug efficacy at sentinel sites at least once every 24 months in order to detect changes in therapeutic efficacy.

The possibility that artemisinin resistance might spread or emerge independently elsewhere necessitates careful surveillance. Monitoring the efficacy of antimalarial drugs is a key component of malaria control. Moreover, the surveillance of the efficacy of artemisinin-based combination therapies (ACTs) as first- and second-line treatment for *P. falciparum* malaria is today a public health priorities. The standard for monitoring the emergence of artemisinin resistance remains the effectiveness of ACTs. The presence of artemisinin resistance is generally first evaluated during therapeutic efficacy studies (TESs) in which patients received treatment with an ACT [12]. In Côte d'Ivoire, NMCP and its partners have been implementing TESs to monitor the efficacy and safety of ACTs.

According to previous studies at sentinels sites, AS+AQ and AL remain efficacious and safe in Côte d'Ivoire. However, the delayed parasite clearance of ACTs in the country has been reported [13–15]. The current study aims to assess the efficacy and safety of the two ACTs used as first line treatment in Côte d'Ivoire. Findings from this study will provide evidence for guiding national malaria treatment policy in Côte d'Ivoire.

Materials and Methods

Study design and sites

This open-label randomized trial was carried out to assess the efficacy of AS+AQ and AL in uncomplicated *P. falciparum* malaria treatment, in six NMCP sentinel sites for malaria surveillance in Côte d'Ivoire (Abidjan, Abengourou, Man, Yamoussoukro, Korhogo, San-Pedro). These sites have been NMCP sentinel sites for monitoring of anti-malarial efficacy since 1996. Patients older than 6 months were recruited at the health care facilities and assessed for inclusion in the study based on the WHO protocol of 2009 [12].

In Côte d'Ivoire, malaria transmission is heterogeneous with different epidemiological strata in terms of their geographical and ecological characteristics, transmission pattern and endemicity level and main vectors transmitting malaria parasites. There are three main malaria vector species in Côte d'Ivoire: *Anopheles gambiae s.s.*, *An. funestus s.s.* and *Anopheles nili s.s.* [16].

In Abidjan and San Pedro (South), Man (West) and Abengourou (East) malaria transmission is intense with recrudescence during the rainy season.

At Yamoussoukro site located in the centre, malaria transmission is moderate in the dry season and high during the rainy season while Korhogo site experiences low-intensity malaria transmission throughout the year.

P. falciparum is the deadliest species that causes more than 95% of infections [13].

The key malaria control interventions in the sites include use of Long Lasting Insecticidal Nets (LLINs), malaria case management with ACTs, and Intermittent Preventive Treatment during Pregnancy (IPTp).

Inclusion and exclusion criteria

Patients were enrolled in the study according to WHO inclusion and exclusion criteria [12]. Patients of either gender, older than 6 months with minimum body weight of 5 kg who presented with clinical symptoms of malaria were screened for study eligibility after informed consent was obtained from the patient (where possible) or from parents/guardians in addition to children's assent if needed. Patients with microscopically confirmed acute uncomplicated falciparum malaria, with parasite density ranging from 2000 to 200,000 asexual parasites/µl (both inclusive) and an axillary temperature ≥37.5°C or history of fever in the past 24 hours, were included in the study.

Patients with severe malaria symptoms, symptoms of severe malnutrition, or chronic diseases or with mixed infection were excluded.

Sample size

The sample size was calculated using the WHO guidelines on assessment of antimalarial drugs [12]. According to the following criteria: the proportion of probable clinical failures with the antimalarial combinations studied should not be higher than 10%, for a level of confidence (P) of 95% and a precision (p) of 10%, taking into account patients

who were excluded or lost to follow-up. Using these criteria, a minimum of 50 patients was required in each treatment arm in each study site.

Treatment

Patients were randomly assigned to receive either AS+AQ or AL. The drugs were administered according to the body weight of the patient, for 3 consecutive days, as follows:

– AS+AQ: 5 to <9 kg: one tablet/day of artesunate (AS) 25 mg/amodiaquine (AQ) 67.5 mg; 9 to <18 kg: one tablet/day of AS 50 mg/AQ 135 mg; 18 to <36 kg: 1 tablet/day of AS 100 mg/AQ 270 mg; ≥36 kg: 2 tablets/day of AS 100 mg/ AQ 270 mg;

– AL (20 mg artemether/120 mg lumefantrine): 5 to <15 kg: 1 tablet/dose; 15 to <25 kg: 2 tablets/dose; 25 to <35 kg: 3 tablets/dose; ≥35 kg 4 tablets/dose. AL was administrated twice a day. The first dose was taken at enrolment, the second dose eight hours later on day 0, and then two doses at 12-hourly intervals for the subsequent two days.

All the first doses were given at the study site under supervision. To check intake of second doses of AL, patients had to return the next day with empty blisters. For the children, the mothers were trained by the team on how to administer the drug. Patients were observed for 30 min post-treatment; if vomiting occurred within 30 min, a second full dose was repeated. Persistent vomiting of the second dose led to withdrawal from the study and, administration of rescue medicine, with parenteral quinine or injectable artesunate according to the national guidelines for management of complicated and severe malaria.

Patients with repeated vomiting were excluded and were treated according to NMCP treatment guidelines and excluded from the study.

Clinical procedures

Clinical data included a standard physical examination report that included body weight, axillary temperature, vital signs were recorded at baseline (screening), and at all follow-up visits (days 1, 2, 3, 7, 14, 21, 28, 35 and 42) or at any unscheduled visit. Medical history, demographic information and contact details were collected at screening.

Laboratory procedures

Plasmodium falciparum parasite was identified by examining thick and thin blood films. Each slide was air-dried and stained with 5% Giemsa.

Thick and thin blood films for parasite counts were obtained and screened on day 0 to confirm adherence to the inclusion criteria then on days 1, 2, 3, 7, 14, 21, 28, 35 and 42 or at any unscheduled visit.

Parasitaemia was measured by counting the number of asexual parasites and leucocytes in 200 high power fields based on a putative count of 8,000 leucocytes/ml of blood. Two qualified independent microscopists read all slides. Discordant readings were re-examined by a third qualified independent microscopist.

Molecular correction

Dried Blood Spots (DBS) on Whatman® 3MM filter paper (three spots per card) were prepared for polymerase chain reaction (PCR) genotyping for all subjects at screening and at the relevant follow-up visit in the case of treatment failure.

Parasite DNA was extracted from DBS using QIAamp DNA blood mini kits (QiAgen GmbH, Hilden, Germany) according to the manufacturer's instructions. Paired DNA samples (day 0 and day of parasites recurrence) were genotyped by analysing the polymorphic loci of merozoite surface proteins 1 and 2 (*msp1* and *msp2*), and glutamate rich protein (*glurp*) genes to discriminate re-infection from recrudescence as described previously [12,15,17].

Safety assessment

Safety of both ACTs was monitored by passive and active methods through interviews with participants and clinical assessments during the 42 days of follow-up. The reported/captured events were recorded in respective case report forms for each follow-up visit.

Outcomes

Efficacy outcomes were based on WHO definitions [12]. The primary endpoints was the PCR-corrected Adequate Clinical and Parasitological Response (ACPR) at day 42. Parasite and Fever clearance times, crude ACPR at days 28 and 42 were the secondary endpoints. Safety outcomes were incidence of (serious) adverse events.

Statistical analysis

Data generated were recorded in a log book and individual participants case record files. Data were entered and analysed with SPSS Version 17 (SPSS

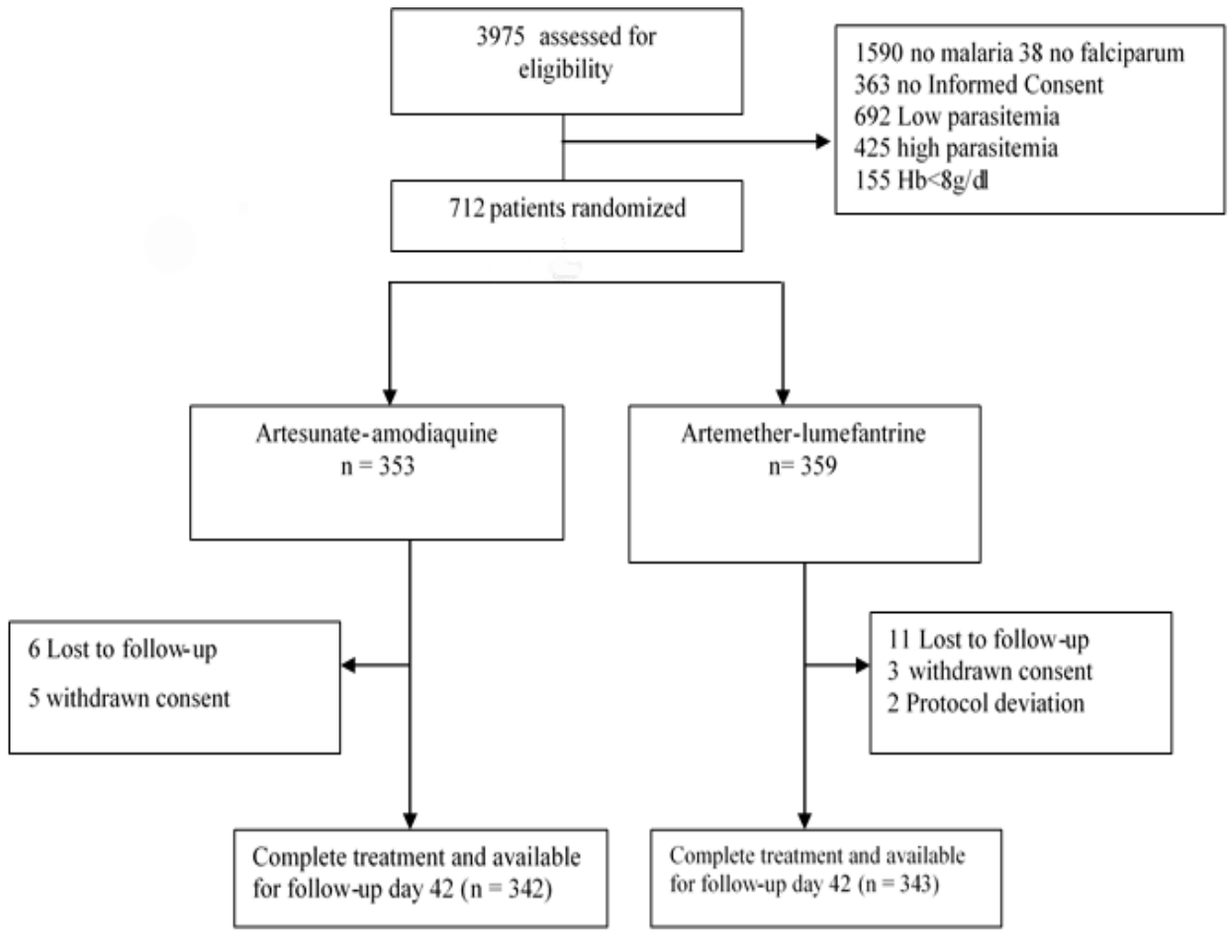

Figure 1. Trial profile

Inc., Chicago, IL, USA). Intention to treat (ITT) and per protocol (PP) analysis were done.

Frequencies were compared by either chi-squared or Fisher's exact tests, as appropriate, and continuous variables by Student's t-tests.

Ethical issues

The protocol was reviewed and approved (Approval Number 049/MSLS/CNER-dkn) by the Comité National d'Ethique des Sciences de la Vie et de la Santé of Côte d'Ivoire (CNESVS). The study was carried out in accordance with International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki and with the laws and regulations, as well as any applicable guidelines, of Côte d'Ivoire.

Table 1. Baseline characteristics in the ITT cohor

	AS + AQ (353)		AL (359)		p-value
Mean age (SD)	7.98	(± 9.04)	9.21	(±10.02)	0.08[b]
Sex ratio (M/F)	0.98	–	0.89	–	0.55[a]
Mean weight kg (SD)	23.13	(± 17.19)	25.59	(±19.19)	0.07[b]
Mean temperature °C (SD)	38.48	(± 0.01)	38.46	(±0.01)	0.80[b]
GM parasite count µl (SD)	42.758	(± 69.429)	39.485	(±44.588)	0.45 [b]

Abbreviations: [a] – Chi-squared test; [b] – Student's t-test; AS + AQ – artesunate + amodiaquine; AL – artemether-lumefantrine; GM – geometric mean, ITT – intention to treat

Table 2. Treatment outcome of AS + AQ versus AL at day 42

Outcomes	AS + AQ	AL	p-value
ITT analysis			
Enrolled patients	353	359	
Patients seen at day 42	342/353 (96.9%)	343/359 (95.5%)	0.45
Missing	11/353 (3.1%)	16/359 (4.5%)	0.45
Crude failure rate at day 42	28/353 (7.9%)	41/359 (11.4%)	0.14
Crude cure rate at day 42	325/353 (92.1%)	318/359 (88.6%)	0.14
PCR adjusted failure rate at day 42	13/353 (3.7%)	20/359 (5.6%)	0.30
PCR adjusted cure rate at day 42	340/353 (96.3%)	339/359 (94.4%)	0.30
PP analysis			
Patients seen at day 42	342	343	
Crude failure rate at day 42	17/342 (5.0%)	25/343 (7.2%)	0.26
Crude cure rate at day 42	325/342 (95.0%)	318/343 (92.7%)	0.26
PCR adjusted failure rate at day 42	02/342 (0.6%)	04/343 (1.2%)	0.68
PCR adjusted cure rate at day 42	340/342 (99.4%)	339/343 (98.8%)	0.68

Abbreviations: AS + AQ – artesunate + amodiaquine; AL – artemether-lumefantrine; GM – geometric mean; ITT – intention to treat; PP – per protocol

Results

Baseline characteristics

Of 3,975 patients screened at six sites, 712 met the inclusion criteria and were enrolled. Of these, 353 and 359 were randomized to receive AS+AQ and AL, respectively. A total of 342 patients ended up in AS-AQ group and 343 patients in AL group (Fig. 1).

The baseline characteristics in the ITT cohort of both groups were similar (Table 1) regarding age, gender, weight, axillary or rectal temperature and

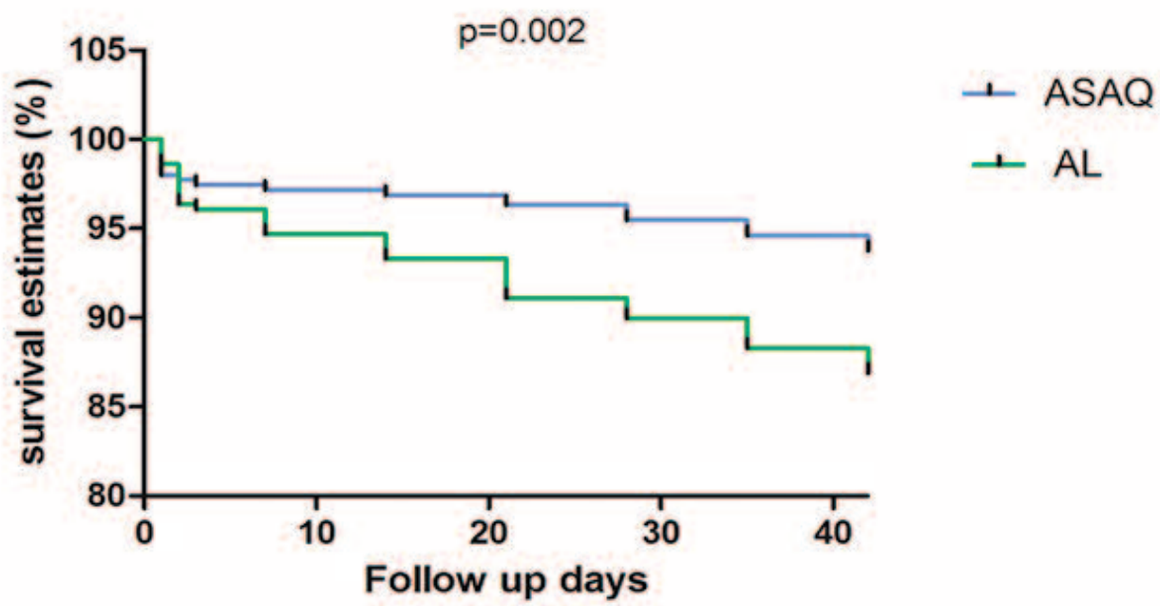

Figure 2. Kaplan-Meier of survival curves to show the probability of survival in both treatment arms during follow-up

Table 3. Treatment outcomes stratified by study sites

Treatment outcome stratified by locality	Artesunate/Amodiaquine	Artemether/Lumefantrine	p-value
ABIDJAN (121 patients)	60	61	
PP analysis			
Crude failure rate at day 42	1/59 (1.7%)	10/58 (17.2%)	0.009
Crude cure rate at day 42	58/59 (98.3%)	48/58 (82.8%)	0,61
PCR adjusted failure rate at day 42	00/59 (00%)	3/58 (5.2%)	1
PCR adjusted ACPR at day 42	59/59 (100%)	55/58 (94.8%)	0.23
KORHOGO (120 patients)	60	60	
PP analysis			
Crude failure rate at day 42	00/59 (00%)	00/59 (00%)	1
Crude cure rate at day 42	59/59 (100%)	59/59 (100%)	1
PCR adjusted failure rate at day 42	00/59 (00%)	00/59 (00%)	1
PCR adjusted ACPR at day 42	59/59 (100%)	59/59 (100%)	1
MAN (120 patients)	60	60	
PP analysis			
Crude failure rate at day 42	04/59 (6.8%)	04/58 (6.8%)	1
Crude cure rate at day 42	55/59 (93.2%)	54/58 (93.2%)	0,9
PCR adjusted failure rate at day 42	1/59 (1.7%)	00/58 (00%)	1
PCR adjusted ACPR at day 42	58/59 (98.3%)	58/58 (100%)	0,93
ABENGOUROU (120 patients)	60	60	
PP analysis			
Crude failure rate at day 42	0/55 (00%)	5/55 (9.1%)	0.06
Crude cure rate at day 42	55/55 (100%)	50/55 (90.9%)	0.06
PCR adjusted failure rate at day 42	0/55 (00%)	1/55 (1.8%)	1
PCR adjusted ACPR at day 42	55/55 (100%)	54/55 (98.2%)	1
YAMOUSSOUKRO (111 patients)	53	58	
PP analysis			
Crude failure rate at day 42	2/51 (3.9%)	2/56 (3.4%)	0.67
Crude cure rate at day 42	49/51 (96.1%)	54/56 (96.4%)	0.67
PCR adjusted failure rate at day 42	1/51 (2.0%)	00/56 (00%)	1
PCR adjusted ACPR at day 42	50/51 (98.0%)	56/56 (100%)	1
SAN-PEDRO (120 patients)	60	60	
PP analysis			
Crude failure rate at day 42	10/59 (16.9%)	04/57 (7.0%)	0.17
Crude cure rate at day 42	49/59 (83.1%)	53/57 (96.9%)	0.17
PCR adjusted failure rate at day 42	00/59 (00%)	00/57 (00%)	1
PCR adjusted ACPR at day 42	59/59 (100%)	57/57 (100%)	1

parasite density. The average age was 7.98 ± 9.04) and 9.21 ± 10.02 years in AS+AQ and AL group respectively (p=0.08).

The mean weight in AS+AQ was 23.13 ± 17.19 kg against 25.59 ± 19.19 kg in AL group (p=0.07). The sex ratio was not significantly different: 0.98 in AS-AQ group and 0.89 in AL group (p=0.55).

Efficacy outcomes

The overall PCR-corrected ACPR on day 42 in the per-protocol population, the primary efficacy outcome, was 99.4% in the AS+AQ group and 98.8% in the AL group (Table 2). The lowest PCR-corrected ACPR was observed at Abidjan site in AL group (94.8%) (Table 3).

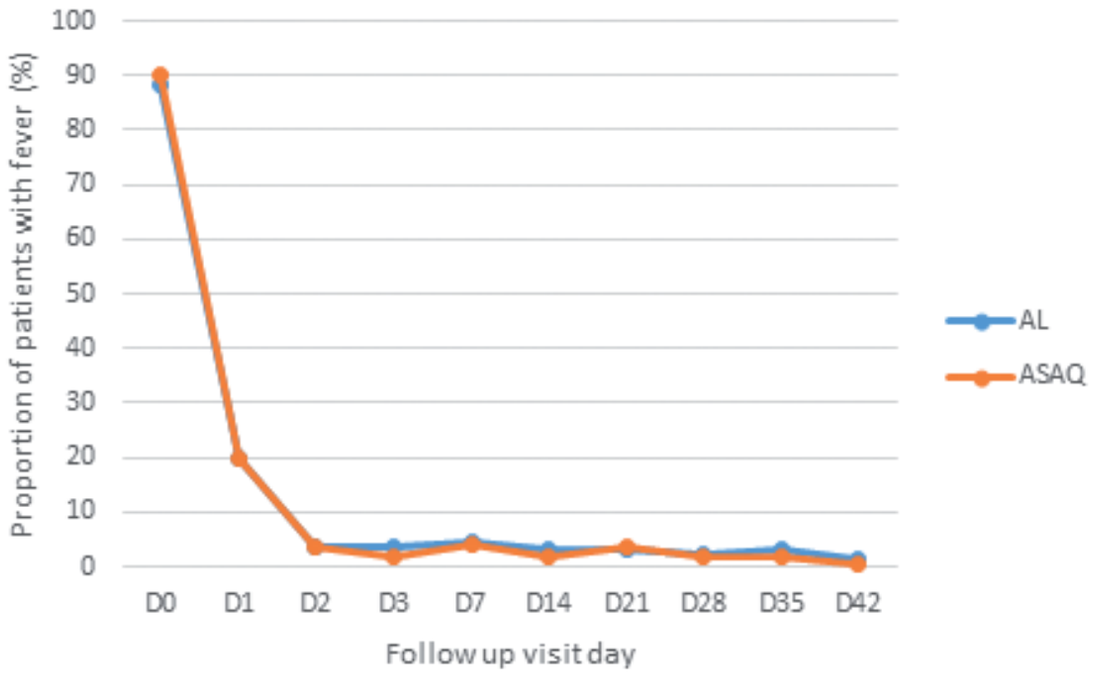

Figure 3. Proportion of patients with fever during follow-up
Note: No significant differences were found for the proportions of subjects with fever between both treatment regimens from baseline to day 42 (p>0.05; Fisher's exact test or chi-squared test as appropriate)
Abbreviations: AL – artemether-lumefantrine; AS+AQ – artesunate + amodiaquine

Per protocol analysis of treatment outcomes for 342 and 343 evaluable patients who received AS+AQ and AL, respectively, showed day 42 PCR-uncorrected cure rates ranging between 83.1% and 100% for AS+AQ and between 82.8 % and 100% for AL. PCR-corrected cure rates ranged between 98% and 100% for AS+AQ and between 94.8% and 100% for AL (Table 3).

In ITT analysis PCR-corrected ACPR was 96.3% and 94.4% in AS+AQ and AL group respectively. The per protocol analysis 42-day ACPR without PCR correction was 95.0% in AS+AQ and 92.7% in AL (Table 2).

The Kaplan-Meier curves from survival showed a significant difference (p=0.0021) in cure rates between two-study treatment arms (Fig. 2).

Fever clearance

As showed in Fig. 3, the proportion of participants who cleared the fever was similar on days 2 and 3 between the two groups.

The proportion of participants with fever at the screening was 90% and 88.5% in AS+AQ and AL group respectively. At day 3 this proportion was 2% (AS+AQ) and 3.4% (AL).

No significant differences were found for the proportions of participants with a fever between both treatment regimens from baseline to day 42 (p >0.05) (Fig. 4).

Parasite clearance

No significant differences were found for the proportions of participants with parasites between the two treatment regimens from baseline to day 42 (p>0.05) (Fig. 4).

However, four patients had parasitaemia on day 3 post-treatment in AL group at Abidjan site while one patient in each group had parasitaemia on day 3 at Yamoussoukro site and no patients from the others sites (Abengourou, Korhogo, Man and San-Pedro) had parasites on day 3. Only one participant from Abidjan site cleared parasite before day 7.

Safety

Most of the recorded adverse events were signs and symptoms of malaria, thereby making their assessment difficult. None of the patients presented with serious adverse events that necessitated withdrawal from the study or hospitalization was observed in both groups.

Table 4 shows details of the distribution of clinical AEs recorded during the study.

The following adverse events were more frequent in AS+AQ group: headache (24.3 vs 16.4)

Table 4. Clinical adverse events in the ITT population

Adverse events	ASAQ (N=353)			AL (N=359)			Fisher's Exact Test
	n	%	95%IC	n	%	95%IC	p-value
Asthenia	49	13.8	10.5–18.0	36	10.0	7.2–13.7	0.11
Headache	86	24.3	20.0–29.2	59	16.4	12.8–20.7	0.008
Anorexia	58	16.4	12.8–20.8	34	9.4	6.7–13.1	0.005
Abdominal pain	12	3.4	1.8–6.0	8	2.2	1.0–4.5	0.34
Nausea	14	3.9	2.2–6.7	8	2.2	1.0–4.5	0.18
Vomiting	26	7.3	4.9–10.7	17	4.7	2.8–7.6	0.14
Drowsiness	43	12.1	9.0–16.1	0	–	–	<0.00001
Dizziness	36	10.2	7.3–13.9	3	0.8	0.2–2.6	<0.00001
Rash	2	0.5	0.1–2.2	0	–	–	0.47

Notes: Headache, anorexia, drowsiness and dizziness were more frequent in AS + AQ; p-values were obtained by Fisher's exact test
Abbreviations: AL – artemether-lumefantrine; ASAQ – artesunate + amodiaquine

(p=0.08), anorexia (16.4 vs 9.4) (p=0.005), drowsiness (12.1 vs 0) (p<0.00001) and dizziness (10.2 vs 0.8) (p<0.00001).

Discussion

WHO recommends that Therapeutic Efficacy Tests (TETs) for antimalarials be conducted at least once every 24 months in qualified sentinel sites. The National Malaria Control Program in Côte d'Ivoire has been implementing this recommendation since

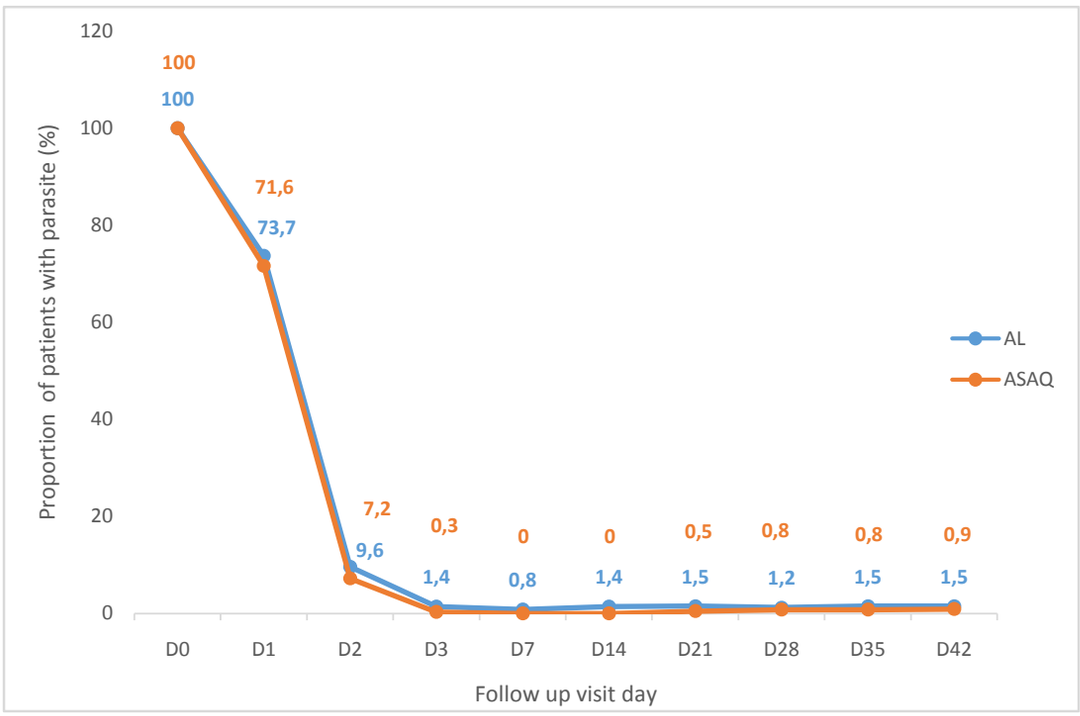

Figure 4. Proportion of patients with parasites during follow-up
Note: The proportion of participants with parasitemia was similar in both treatment arms
Abbreviations: AL – artemether-lumefantrine; ASAQ – artesunate + amodiaquine

2009 with the support of the ACT consortium. These studies track the expansion or emergence of antimalarial drug resistance. The use of standardized procedures makes it easier to compare results within and across regions and to track trends over time.

The present study based on the *in vivo* efficacy using 42-follow up days protocol was conducted among children and adults with uncomplicated falciparum malaria in six NMCP sentinel sites to provide supporting evidence for the clinical efficacy of AS+AQ and AL in Côte d'Ivoire.

The results showed that both AS+AQ and AL are still efficacious for uncomplicated *P. falciparum* malaria treatment with PCR corrected ACPR ranging between 98–100% and 94.8–100 % on day 42 for AS+AQ and AL, respectively.

Indeed, the ACPR after PCR correction is above 98% at day 42 in all the sites with both ACTs except Abidjan where this response was 94.8% with AL.

Previous studies conducted in the country have demonstrated also similar PCR-corrected cure rate of AS+AQ and AL in the treatment of uncomplicated falciparum malaria [13–15].

These results are also consistent with the high cure rates that have been reported for ACTs elsewhere in Africa [18–24].

In addition, molecular studies in Côte d'Ivoire and others countries in Africa have showed absence of the known mutations in the *kelch* 13 (*Pfk-13*) gene associated with artemisinin resistance [3,9,25], further suggesting that artemisinins are still effective.

Both AS-AQ and AL achieved effective fever and parasite clearance in the six sites. However, the study showed the presence of parasitaemia on day 3 following treatment with AS-AQ in one participant from Yamoussoukro whilst four patients had parasitaemia on day 3 following treatment with AL in Abidjan and one participant in Yamoussoukro. This finding is far below the WHO threshold of 10%, and therefore suggests that artemisinin (partial) resistance following ACT treatment of *P. falciparum* malaria is not a concern in Côte d'Ivoire.

Patients enrolled in both studies took the evening doses of AL at home unsupervised, and this might explain the relatively high treatment failure rate. Due to the delayed of parasites observed in this study and the previous in the country and the spread of artemisinin resistance in SEA [8], NMCP has to be vigilant about its potential emergence through continuous monitoring of the efficacy and parasite clearance of ACT, and surveillance of polymorphism in the *Pfk-13* gene.

There were high parasite recurrences in Abidjan site with AL and San-Pedro site with AS+AQ, which were due for the most to re-infection as confirmed by PCR analysis.

This study also reported that both drugs were well tolerated with minor AEs and no any SAEs have been found. This study also showed that AL had a safety profile, compare to previous studies and was well tolerated with minimal AEs compared to AS+AQ. Most of the AEs were minor and mainly reported in all study sites.

This good tolerance of both ACTs has also been observed in other studies in Côte d'Ivoire and elsewhere in Africa [13–15,26–28].

The current study has some limitations related to the fact that drug levels were not tested and only the first doses of AL were observed.

This study showed that the two artemisinin-based combinations had high efficacy for the treatment of uncomplicated falciparum malaria supporting recommendation of the two ACTs in first line malaria treatment in the country. Nevertheless, delayed parasite clearance time and high rates of treatment failures before PCR correction observed support evidence for a close monitoring of ACTs efficacy.

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