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Original papers

Efficacy and tolerability of artesunate-amodiaquine versus artemether-lumefantrine in the treatment of uncomplicated *Plasmodium falciparum* malaria at two sentinel sites across Côte d'Ivore

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ABSTRACT. Malaria remains a major public health problem in Côte d'Ivoire. The aim of this study is to compare the efficacy and tolerability of artesunate-amodiaquine (ASAQ) versus artemether-lumefantrine (AL) for the treatment of uncomplicated malaria, at two malaria surveillance sites in Côte d'Ivoire. The World Health Organization 2003 protocol was used for this multicenter open randomized clinical trial with a 42-day follow-up. We recruited 240 patients (120 per arm), of whom 114 (ASAQ group) and 112 (AL group) were fully followed-up. According to intention-to-treat statistical analysis, PCR-corrected cure rates for ASAQ and AL treatments were 95.8% and 92.5% on day 28, and 95% and 92.5% on day 42, respectively. Based on per-protocol statistical analysis, ASAQ and AL treatment rates reached 100% and 99.1%, respectively, on day 28 and remained the same on day 42. Overall, both drugs were well-tolerated at the clinical and biological level. This study shows that ASAQ and AL are still effective and well-tolerated. Accordingly, they can continue being used to treat uncomplicated malaria in Côte d'Ivoire. However, monitoring of their efficacy should remain a priority for health authorities.

Key words: malaria, efficacy, *Plasmodium falciparum*, artesunate-amodiaquine, artemether-lumefantrine

Introduction

Despite an overall decline in the burden posed by malaria, this disease remains a major public health problem [1], particularly in Côte d'Ivoire (a sub-Saharan African country). In this area, reports from the National Malaria Control Program (NMCP) indicate that malaria is responsible for 43% of all causes of outpatient visits and one third of reported deaths in health facilities [2]. Worldwide, malaria elimination efforts is threatened by resistance of *Plasmodium falciparum* to most of antimalarial drugs including artemisinin derivatives. Artemisinin resistance has already been confirmed in five countries of the Greater Mekong subregion: Cambodia, the Lao People's Democratic Republic, Myanmar, Thailand, and Vietnam [3,4]. This phenomenon risks following the same historical trajectory from Asia to Africa seen previously with chloroquine resistance [5]. Indeed, a case of

indigenous artemisinin-resistant *P. falciparum* has recently emerged in a patient from Equatorial Guinea, Africa [6]. Therefore, World Health Organization (WHO) recommends routine monitoring of the therapeutic efficacy of artemisinin-based combination therapies (ACTs) that is essential to ensure timely changes in treatment policy and to help detect early changes in *P. falciparum* susceptibility to antimalarial drugs [7]. In 2007, artesunate-amodiaquine (ASAQ), and artemether-lumefantrine (AL) were recommended by the NMCP of Côte d'Ivoire for uncomplicated cases as first-line and second-line treatments, respectively. The first studies were conducted on both drug combinations in 2012 [8] and 2013 [9] at six sentinel sites. Survey reports estimated combined ASAQ and AL treatment failure rates of 0.7% in 2012 [8] and 0% in 2013 [9], indicating a same and high efficacy. These results were followed by the adoption of both regimens as first-line treatments since 2013. However, owing to patients' complaints following the use of ASAQ frequently reported by physicians, a greater use of AL compared to ASAQ is common [10], posing a high risk of selection of resistant strains by AL. Failure rate is one of the main indicators of drug resistance [7]. In this context, a non-inferiority assessment of efficacies of both combinations after this therapeutic change and its impact on failures rates was finally due. The aim of this study was to evaluate the efficacy of ASAQ *versus* AL for the treatment of uncomplicated *falciparum* malaria at two sentinel sites in Côte d'Ivoire.

Materials and Methods

Study design. This study was a controlled randomized multicenter and open therapeutic trial with a 42-day follow-up period. It was carried out at two sentinel sites of the NMCP according to the standard WHO 2003 protocol [11]: Abengourou (forest zone) and San Pedro (coastal and forest zone). At both sites, the survey took place in health centers from popular neighborhoods: the Dioulakro Health Clinic at Abengourou and the Bardot Urban Health Center at San Pedro. Both sites are characterized by four seasons: two rainy seasons (from April to July and from October to November) and two dry seasons (from December to March and from August to September). The transmission of malaria occurs throughout the year, but peaks during the rainy seasons. The survey compared the efficacy, safety, and tolerability of ASAQ and AL. It was conducted between January and May 2016 and it focused on outpatients suffering from uncomplicated malaria. Inclusion criteria were: minimum age of six months, monospecific *P. falciparum* infection detected by microscopy, parasitemia between 2,000 and 200,000 asexual forms/μL, axillary temperature ≥37.5°C or a history of fever within the last 24 h. Exclusion criteria included: patients with signs or evidence of severe malaria [12], low body weight (<5 kg), signs of malnutrition, repeated vomiting, intercurrent infectious disease, history of previous serious side effects to the drugs used during the trial, past cardiac, hepatic, or renal history, patients with recent antimalarial treatment, and patients who were pregnant (positive test) or breast-feeding. Criteria for stopping the treatment and/or withdrawal from the study were: occurrence of serious adverse effects, unsatisfactory therapeutic response, violation of the protocol, withdrawal of consent, and loss during follow-up. Before inclusion, the study protocol was explained and written informed consent was obtained from the patient or the patient's legal guardian. An official approval was obtained from the National Ethic and Research Committee (CNER-CI) before the start of the study.

A total of 60 patients per arm were included per site. Sample size was calculated based on an assumed efficacy of 90% for both artemisinin-based combination therapies (ACTs), a non-inferiority margin of 6%, a power of 80%, and a one-sided 5% significance level. Treatments used in this study included a coblister ASAQ (Winthrop®, Sanofi-Aventis, France) and fixed-dose combination AL tablets (Ipca, Laboratories, India). These anti-malarial drugs were free and available from participating health facilities; they were provided through the NMCP by the Global Fund to Fight AIDS, Tuberculosis and Malaria. Each ASAQ tablet contained either 25 mg AS and 67.5 mg AQ, 50 mg AS and 135 mg AQ, 100 mg AS and 270 mg AQ, or 200 mg AS and 540 mg AQ. ASAQ treatments varied according to body weight: 4.5–8 kg, one tablet (25 mg/67.5 mg); 9–17 kg, one tablet (50 mg/135 mg) per dose; 18–36 kg, one tablet (100 mg/270 mg) per dose; and >36 kg, one tablet (200 mg/540 mg) per dose. AL tablets were administered at 0 and 8 h on day 0, and then twice daily for two subsequent days according to body weight: 5–14 kg, one tablet per dose; 15–24 kg, two tablets per dose; 25–34 kg, three tablets per dose; ≥35 kg, four tablets

per dose. Any treatment against other concomitant diseases was noted in the Case Report Form (CRF).

Study procedures. Patients with malaria-like symptoms were received at selected health centers. Meticulous clinical examinations of the patients and laboratory investigations were conducted immediately after inclusion. Patients who met baseline inclusion criteria were randomly assigned to one of the two treatment groups. Drug administration was supervised by a member of the research team and patients were kept under observation. After the initial dose, patients had a follow-up within 42 days. All data collected from this study were recorded in a personal and confidential CRF. Each patient was scheduled for follow-up examinations on day 0, 1, 2, 3, 7, 14, 21, 28, 35, and 42 and any other time the participant felt unwell during the study period. On each visit day, the following information was collected: 1) clinical data, 2) biological data (diagnosis of malaria and determination of parasitemia), 3) any details about drug adverse events. In case of treatment failure, a replacement therapy was offered according to the national treatment guidelines. Laboratory analysis included thick and thin blood films used for malaria diagnosis and performed during each visit. Parasitemia was determined by counting the number of asexual parasites in 200 white blood cells. A double reading was performed for all slides. A negative result was declared after checking at least 100 microscope fields. The presence of gametocytes was also noted. Discrepancy results included difference in species diagnosis, difference in parasite density of 25%, or any difference that able to affect inclusion or study outcome. In case of discrepancy, a third reading was made by a third microscopist. The parasitemia was calculated by averaging the two closest densities while the final parasite species was determined by the two concordant reads. An external quality control was carried out on 10% of the slides. On day 0, before any treatment, and on day 3, hematological (hemoglobin rate) and biochemical (aspartate transaminase, alanine transaminase, and total bilirubin) parameters were determined from venous blood collected in EDTA-containing tubes using a photometric method (DiaSpect Tm Hemoglobin Analyzer, Germany) and a Cobas® c311 analyzer 135907 (Hitachi-Roche, Switzerland), respectively. Filter paper blood spots (Whatman International Ltd., UK) were collected from finger pricks on day 0 and in the case of recurrent fever or parasitemia (after day 7). Samples were used for molecular genotyping to distinguish recrudescence from new infection. The parasite DNA was extracted using a Chelex-based method [13] and subjected to nested PCR as previously described [14]. The latter was used to determine length polymorphisms in the genes encoding merozoite surface protein-1 (*msp1*) and merozoite surface protein-2 (*msp2*). The response to treatment was measured and defined according to WHO guidelines [11]. The primary and secondary endpoints were described elsewhere [8]. Any clinical or biological sign not present at the

Table 1. Baseline characteristics of patients at inclusion

	ASAQ N=120	AL N=120	*p-value	Global
Sex				
Male, n (%)	63 (52.5)	63 (52.5)	1.00	126 (52.5)
Female, n (%)	57 (47.5)	57 (47.5)		114 (47.5)
Mean Age (SD) year	5.76 (6.4)	5.89 (6.4)	0.54	5.8 (6.3)
Mean Temperature (SD) °C	38.7 (1.0)	38.4 (0.9)		38.5 (0.97)
37.5–38.5, n (%)	59 (49.2)	65 (54.2)	0.52	124 (51.7)
38.5–41.2, n (%)	61 (50.8)	55 (45.8)		116 (48.3)
Mean Parasitemia (SD) trophozoite/µL	50668 (49360)	45565 (49653)	0.42	48117 (49469)
Mean AST (SD) UI/L	40.9 (22.1)	35.2 (14.3)	0.04	37.9 (18.7)
Mean ALT (SD) UI/L	10.2 (6.4)	9.1 (4.2)	0.13	9.6 (5.4)
Creatinine mean rate (SD) mg/L	5.3 (2.1)	5.2 (2.1)	1.00	5.3 (2.01)
Bilirubin mean rate (SD) mg/L	10.1 (7.5)	8.9 (6.3)	0.02	9.5 (6.9)
Hemoglobin mean rate (SD) g/dL	9.7 (1.6)	9.7 (1.7)	1.00	9.7 (1.7)

*Independent samples t-test; AST: aspartate transaminase; ALT: alanine transaminase

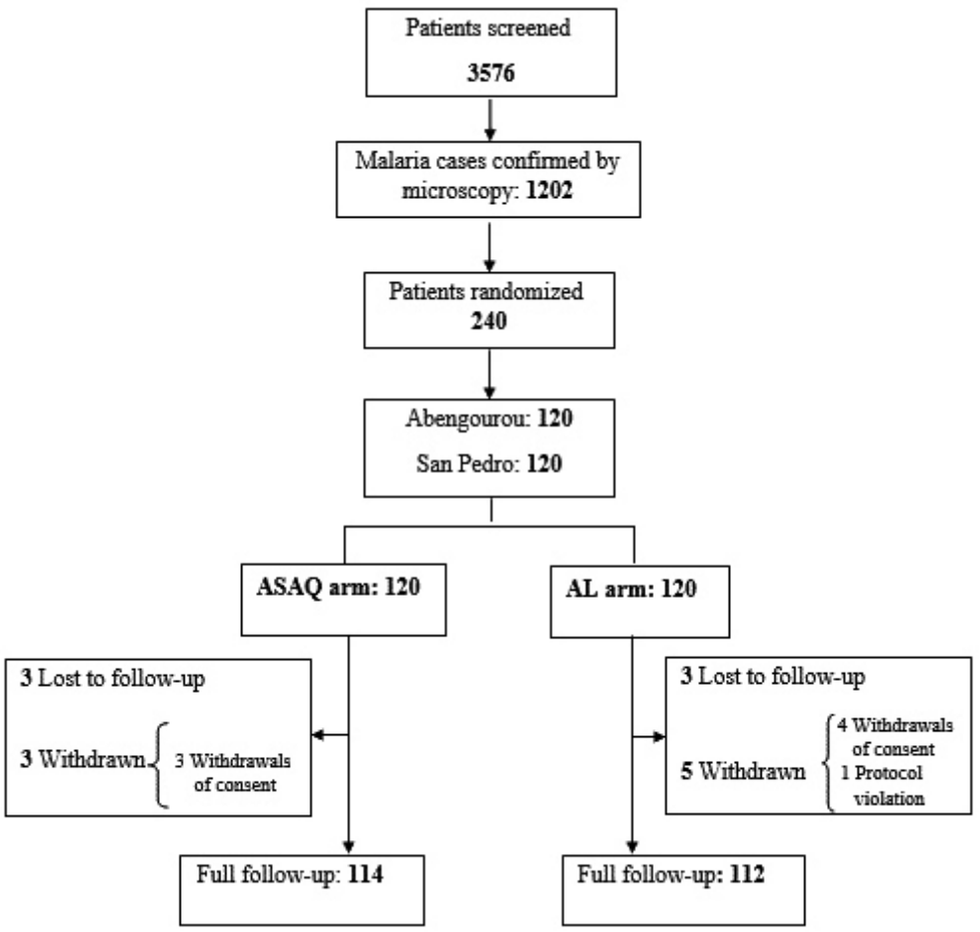

Fig. 1. Trial profile

moment of inclusion and that appeared during follow-up, or any sign present on day 1 that worsened thereafter was considered as an adverse event.

Statistical analysis. All data were recorded using IBM SPSS Statistics, version 21. Comparisons of different parameters in both arms were done using Mann-Whitney's test, Fisher's exact test, and the independent samples t -test. Intention-to-treat (ITT) data included all randomized subjects who took at last one full dose and had one post-baseline efficacy without major protocol deviation. The per-protocol (PP) analysis included all subjects who received the three ASAQ or six AL doses and presented no major protocol deviation. The level of significance for statistical tests was set at 0.05.

Results

Among the 1202 malaria cases confirmed by microscopy, 240 met inclusion criteria and were randomized, amounting to an inclusion rate of 20%. One hundred and twenty patients were randomized per treatment arm. A 42-day follow-up was achieved for 114 patients in ASAQ group and 112 in AL group (Fig. 1). Table 1 shows the baseline characteristics of patients at inclusion for each arm. No statistical differences were observed between the two populations. ITT and PP analysis were performed on days 28 and 42. On day 28, PCR-adjusted cure rates were better with ASAQ than AL following ITT analysis (95.8% *versus* 92.5%) or PP analysis (100% *versus* 99.1%). The same trend was observed on day 42, with ASAQ and AL PCR-adjusted cure rates of 95% *versus* 92.5% by ITT analysis and 100% *versus* 99.1% by PP analysis. Among the 226 patients still followed-up at day 42, adequate clinical and parasitological response (ACPR) was 91.2% (104/114) in ASAQ group and 92% (103/112) before PCR correction showing a same efficacy. A total of 19 failures were found in this study. Eleven of these cases were classified as late clinical failure (LCF), whereas the others were

Table 2. Treatment outcomes on days 28 and 42

	ITT Analysis					PP Analysis				
	ASAQ		AL			ASAQ		AL		
	n/N	%	n/N	%	*p-value	n/N	%	n/N	%	*p-value
DAY 28										
Crude failure rate	4/120	3.3	3/120	2.5	1,00	4/115	3.5	3/112	2.7	1.00
Crude cure rate	111/120	92.5	109/120	90.8	0.82	111/115	96.5	109/112	97.3	1.00
PCR adjusted failure rate	0/120	0	1/120	0.8	1.00	0/115	0	1/112	0.9	0.49
PCR adjusted cure rate	115/120	95.8	111/120	92.5	0.41	115/115	100	111/112	99.1	0.49
DAY 42										
Crude failure rate	10/120	8.3	9/120	7.5	1.00	10/114	8.8	9/112	8	1.00
Crude cure rate	104/120	86.7	103/120	85.8	1.00	104/114	91.2	103/112	92	1.00
PCR adjusted failure rate	0/120	0	1/120	0.8	1.00	0/114	0	1/112	0.9	0.49
PCR adjusted cure rate	114/120	95	111/120	92.5	0.59	114/114	100	111/112	99.1	0.49

*Fisher's exact test

described as late parasitological failure (LPF). Overall, no patients experienced early treatment failure (ETF). Most of failure cases were observed with ASAQ on day 28 (4 *versus* 3 for AL) and day 42 (10 *versus* 9 for AL). After DNA genotyping, nearly all cases (18/19) were characterized as being due to reinfection, with a single case of recrudescence in AL group in Abengourou. The findings are summarized in table 2. Overall, a similar evolution of the proportion of patients with parasites was observed during follow-up for both combinations. On day 2, parasite clearance was 90.7% (107/118) and 93.2% (109/117) in ASAQ and AL groups, respectively. On day 3, only one patient presented parasites in ASAQ arm. Thus, both treatments allowed for rapid parasite clearance but AL was more effective (Fig. 2). A decrease of fever during follow-up was noticed with both associations (Fig. 3), but was faster in ASAQ group than in AL one. Indeed, on day 1, fever clearance

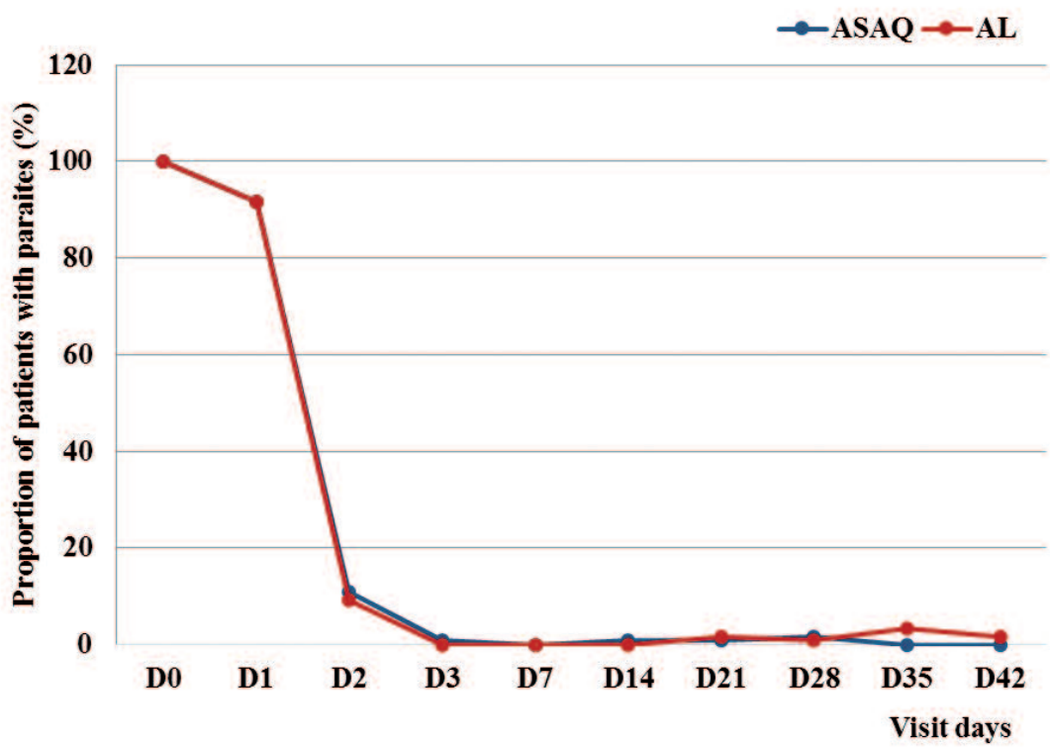

Fig. 2. Parasite clearance rate during the follow-up. Mann-Whitney's test; p=0.54, α=0.05

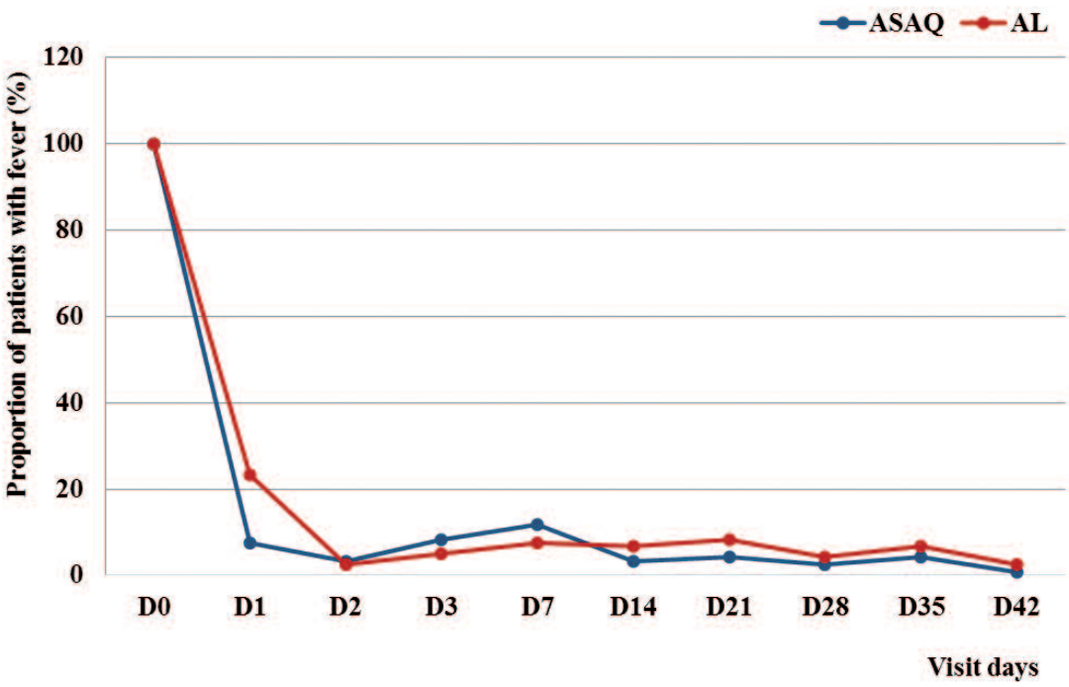

Fig. 3. Proportion of patients with fever according to visit days. Mann-Whitney's test; p=0.10, α=0.05

was 92.4% (110 of 119) and 76.7% (92 of 120) in the ASAQ and AL groups, respectively. At clinical level, 19 cases of adverse events were detected in ASAQ group among which 8 cases of drowsiness; 7 cases of asthenia; 3 cases of pruritus and 1 case of anorexia. However, with AL, only one such case of abdominal pain was reported. A decrease of the mean of all biological parameters was observed between inclusion and day 3 excepted alanine transaminase in ASAQ group. The reduction was most significant for aspartate transaminase in ASAQ group and for creatinine in AL arm. Changes in bilirubin were statistically significant in both treatment arms (Table 3).

Discussion

In line with several studies carried out in Côte d'Ivoire and other African countries, our results confirmed a high efficacy of ASAQ and AL for the treatment of uncomplicated *falciparum* malaria, as indicated by PCR correction on day 42. Indeed, in Côte d'Ivoire, efficacy outcomes of these associations based on PP analysis after PCR correction showed high levels of ACPR: 99.3% and 100% in 2012 [8] and 2013 [9]. In Most studies [15,16], cure rates above 90% were reported when drug administration was supervised by the research team. In spite of such high cure rates, some concerns

Table 3. Changing patterns for biological parameters in the both treatments

	ASAQ				AL			
	D0	D3	D0-D3	*p-value	D0	D3	D0-D3	*p-value
Hemoglobin (g/dL) (SD)	9.69 (1.62)	9.08 (1.59)	0.61 (0.03)	1.00	9.72 (1.73)	9.14 (1.62)	0.58 (0.11)	1.00
AST (IU/L) (SD)	40.85 (22.14)	30.89 (15.50)	9.96 (6.64)	<0.0001	35.17 (14.26)	32.36 (19.68)	2.81 (-5.42)	0.16
ALT (IU/L) (SD)	10.24 (6.4)	10.32 (8.23)	-0.08 (1.83)	1.00	9.09 (4.20)	8.79 (4.61)	0.3 (-0.41)	0.054
Creatinine (mg/L) (SD)	5.33 (2.08)	5.1 (1.93)	0.23 (0.15)	1.00	5.23 (2.1)	4.66 (1.77)	0.57 (0.33)	<0.0001
Bilirubin (mg/L) (SD)	10.08 (7.5)	2.8 (2.01)	7.28 (5.49)	<0.0001	8.8 (6.28)	2.66 (1.86)	6.14 (4.42)	<0.0001

*Paired t-test; AST: aspartate transaminase; ALT: alanine transaminase

remain. Anti-malarial treatment failures are a useful indicator for assessing ACT resistance [7] and may be caused by many factors other than the intrinsic susceptibility of *P. falciparum* to the drug being tested [17]. Therefore, an understanding of the different factors that influence the clinical and parasitological response is important for the correct interpretation of drug efficacy estimations [16]. In line with previous reports [8,9,15], the low failure rate observed in our study indicates the important role of supervised ACT administration on this parameter. Furthermore, this result may due to the fact that the study was conducted mainly during the dry season (January, February and, March) when the transmission is low in the country [2]. Nevertheless, a comparison between our results and those obtained in 2012 [8] at the same sites with the same transmission conditions (both studies involved two months of rainy season and three months of dry season) reveals higher crude failure rates in 2016. Additionally, as observed in 2012 [8], several studies that compared AL with ACT regimens consisting of longer-acting partner drugs demonstrated a shorter time to reinfection for AL [18]. In contrast, in 2016, most reinfection cases were due to ASAQ. After PCR correction, only one case of recrudescence was found in 2012 with ASAQ and in 2016 with AL. These results suggest the importance of confirming the same trend at other sentinel sites and also to monitor any cases of treatment failure that may arise in community settings or during home management of malaria. In agreement with findings from other authors [8,15], prompt parasite and fever clearance times by both AL and ASAQ were observed during the early days of treatment. Determination of parasite clearance according to the World Wide Antimalarial Resistance Network (WWARN) Parasite Clearance Estimator (PCE) could not be calculated in the present study. Only one patient from ASAQ arm presented parasites on day 3, indicating that susceptibility to the artemisinin derivative component persisted during follow-up. The faster fever clearance observed in ASAQ group was also in line with previous studies [8,9]. This phenomenon could be related to the antipyretic properties of amodiaquine and not just to an overestimation caused by the administration of antipyretics during the 3-day treatment. Overall, our results confirm previous efficacy studies on artemisinin-containing combination treatments, which led to improved cure rates, decreased transmission of *falciparum* malaria, and reduced spreading of resistance to non-artemisinin drugs [19]. As reported in most studies [8,9,15], both regimen treatments were well tolerated with absence of any serious events. The latter were more frequent in ASAQ arm than previously described [8,9]. In most health facilities in Côte d'Ivoire, AL is prescribed at higher rates than ASAQ because of patients' complaints following the use of the latter [10]. However, a study on the safety of ASAQ in real-life conditions in Côte d'Ivoire [20] found the rate of adverse events to be 13%, similar to that reported in our study. Regarding biological aspects, an increase in the number of patients suffering from anemia was observed in both groups, confirming previous studies [8,9]. Most studies reported an increase in hemoglobin between day 7 and day 28 after treatment with ACTs [21]. The impossibility to evaluate changes in hemoglobin rates represents a limitation of this study. Indeed, the variation was determined only between day 0 and day 3, which is relatively short for assessing recovery from anemia. Additional hemoglobin dosages on day 14, 21, 28, and 42 would provide more information on changes in hemoglobin after treatment with ACTs [15]. The bilirubin decrease was significant in both groups indicating improvement of liver function following treatment.

Both ASAQ and AL remain effective and well-tolerated for the treatment of uncomplicated malaria in Abengourou and San Pedro, Côte d'Ivoire. However, evolution of therapeutic failure rates with both combinations should be more investigated. Furthermore, an increase in reinfections compared to previous studies performed at the same sites with the same malaria exposure conditions suggests that monitoring of these ACTs should remain a high priority at national level.

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