

RESEARCH ARTICLE

Safety and tolerability of artesunate-amodiaquine, artemether-lumefantrine and quinine plus clindamycin in the treatment of uncomplicated *Plasmodium falciparum* malaria in Kinshasa, the Democratic Republic of the Congo

Yves Lula Ntamba^{1,2}*, Hypolite Muhindo Mavoko^{2,3}, Marion Kalabuanga⁴, Blaise Fungula⁴, Pierre-Michel Ntamabyaliro Nsengi¹, Gaston Tona Lutete¹, Raquel Inocencio da Luz², Jean-Pierre Van geertruyden², Pascal Lutumba³

1 Clinical Pharmacology and Pharmacovigilance Unit, University of Kinshasa, Kinshasa, Democratic Republic of the Congo, **2** Global Health Institute, Faculty of Medicine, University of Antwerp, Antwerp, Belgium, **3** Department of Tropical Medicine, University of Kinshasa, Kinshasa, Democratic Republic of the Congo, **4** Lisungi Health Centre, Kinshasa, Democratic Republic of the Congo

* These authors contributed equally to this work.

* yveslula@yahoo.fr



OPEN ACCESS

Citation: Lula Ntamba Y, Muhindo Mavoko H, Kalabuanga M, Fungula B, Ntamabyaliro Nsengi P-M, Tona Lutete G, et al. (2019) Safety and tolerability of artesunate-amodiaquine, artemether-lumefantrine and quinine plus clindamycin in the treatment of uncomplicated *Plasmodium falciparum* malaria in Kinshasa, the Democratic Republic of the Congo. PLoS ONE 14(9): e0222379. <https://doi.org/10.1371/journal.pone.0222379>

Editor: Andres Guillermo Lescano, Universidad Peruana Cayetano Heredia, PERU

Received: December 3, 2018

Accepted: August 28, 2019

Published: September 17, 2019

Copyright: © 2019 Lula Ntamba et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All dataset files are available from the figshare database (DOI [10.6084/m9.figshare.7324907](https://doi.org/10.6084/m9.figshare.7324907), <https://figshare.com/s/6553a780d7f78c7ce2b0>).

Funding: The Quinact trial was co-funded by Fonds Wetenschappelijk Onderzoek (FWO, Grant reference G.078.11 to JPVg), Vlaamse

Abstract

Introduction

Artemisinin-based combination therapy is currently the best option for the treatment of uncomplicated malaria. Quinine is recommended as a rescue treatment. Safety information during repeated treatment with the same drug is scarce. We report safety data from the Quinact randomized clinical trial (RCT) that was designed to assess efficacy and safety of artesunate-amodiaquine (ASAQ), artemether-lumefantrine (AL) and quinine+clindamycin (QnC).

Methodology

Males and females aged 12 to 59 months with uncomplicated malaria were treated with ASAQ and followed up during 42 days (preRCT). Clinical failures were randomized to one of the 3 treatments and followed up for 28 days (RCT). Subsequent failures were repeatedly treated with ASAQ several times as needed (postRCT1, postRCT2 and so on) until a 28-days follow up period without parasitaemia.

Results

Eight hundred and sixty-five, 242 and 64 patients were recruited respectively in preRCT, RCT and postRCTs. In preRCT, 433 (50.0%) patients experienced at least one drug-related adverse event (AE). The most reported AEs were anorexia (22.9%), asthenia (19.4%), and abnormal behavior (14.6%). Twenty-nine AEs (3.5%) were reported to be severe. In RCT,

Interuniversitaire Raad-Universitaire Ontwikkelings Samenwerking (VLIR-UOS, Grant reference ZRDC2012MP076 to JPVg, PL), European and Developing Countries Clinical Trials Partnership (EDCTP, Grant reference MS.2010.10800.004 to JPVg) and the Belgian Technical Cooperation-Programme d'Etudes et d'Expertises-in the Democratic Republic of Congo (BTC, Grant reference FEE/06/12 to PL). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: Pharmaceutical companies responsible for the assessed drugs were not involved in data collection nor analysis. However, please note that Sanofi provided Artesunate-amodiaquine and Quinine free of charge. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

at least one drug-related AE was reported in 54.7%, 21.5% and 40.0% of patient randomized respectively to ASAQ, AL and QnC ($p < 0.001$). During postRCT1 ($n = 64$), postRCT 2 ($n = 17$) and postRCT3 ($n = 7$), respectively 32.8%, 35.3% and 71.4% of patients experienced at least one drug-related AE. Three serious adverse events occurred but not judged related to study medication.

Conclusion

The proportion of AEs did not increase over the treatment courses with ASAQ. However, continuous monitoring is important.

Introduction

Artemisinin-based combination therapies (ACTs) are currently regarded as the best available choice for uncomplicated malaria treatment in accordance with the World Health Organization (WHO) guidelines. However, old drugs namely Quinine or Sulfadoxine plus Pyrimethamine (SP) are still used respectively as rescue treatment for uncomplicated malaria or intermittent preventive treatment in pregnancy in many countries [1]. In 2005, the National Malaria Control Programme (NMCP) of the Democratic Republic of Congo (DRC) adopted artesunate-amodiaquine (ASAQ), and a few years later added artemether-lumefantrine (AL) as first line regimens for uncomplicated malaria [2]. Implementation and use of these new combinations on a large scale make surveillance imperative. Besides, comparing to high consumption of antimalarial medicines in endemic countries, there is a dearth of published literature about ACT-induced adverse events (AEs) particularly in Africa. The published data are mainly from clinical trials with a classic design of limited number of participants, strict inclusion criteria or limited follow up [3–4]. However, information about ACT use in real-life settings is scarce [5]. In resource-limited settings especially in Sub-Saharan Africa (SSA), malaria control programmes face particular challenges concerning this surveillance. Pharmacovigilance systems in SSA are either non-existent, just growing or barely functional, sometimes not well or systematically structured, resulting in poor reporting [6]. This fact was emphasized in a recent report which outlined the lack of consistent inclusion of pharmacovigilance activities and requested funding support in proposals and in-country plans [7]. Lack of resources, infrastructure and expertise are the main reasons for the slow development of pharmacovigilance systems in developing countries [8–9]. In addition, weak drug regulatory authorities, counterfeit medicines, widespread use of herbal medicines and over-the-counter medications can really impend strategies addressed to implement pharmacovigilance system [6–7, 10–11]. Therefore, gathering information on the safety and tolerability of ACTs can be challenging [12]. Furthermore, ACTs' choice in SSA was mainly based on the efficacy and safety data of a single malaria episode treatment, the impact of consecutive treatment courses with ACT on safety profile is not adequately known at study time period [10]. This is more relevant considering that in real life, people may use one drug repeatedly for presumed malaria attacks, especially as inappropriate use of antimalarials is a concern in Africa [13].

To bridge these gaps, data collected in the frame of the Quinact trial [14] conducted in the DRC allowed to assess the safety of ASAQ as first line treatment, then ASAQ, AL and oral Quinine plus clindamycin (QnC) when used as rescue treatment. Furthermore, ASAQ safety for repeated recurrent uncomplicated malaria episodes was assessed.

Materials and methods

Study site

The Quinact was a bi-centre clinical trial conducted in Kinshasa, DRC and Kazo, Uganda, from August 2012 (May 2012 for Uganda site) to April 2014. However, for completeness and consistency reasons, only data from the DRC site will be reported in this manuscript. The DRC is a malaria endemic country, where transmission is stable almost all over the country. The trial was conducted in the health zone of Mont-Ngafula 1, where asymptomatic *Plasmodium* infection is reported to be 23.1% in children under 5 years old [15]. Patients were recruited at Lisungi Health Centre.

Study design

This was a phase IIIb, randomized, open label, three-arm trial, performed in three phases involving children aged from 12 to 59 months diagnosed with uncomplicated malaria. The trial was registered in ClinTrials.gov (NCT01374581) and the Pan African Clinical Trials Registry (PACTR 201203000351114). The present manuscript focuses exclusively on safety aspects of all phases to a great extent including descriptive and comparative analyses. Efficacy findings are reported in the separate papers including brief descriptive safety data only during randomized phase [16–17]. Details concerning the study design and procedure are available in the published protocol [14].

First phase (pre-randomized controlled trial phase, pre RCT). Patients having fulfilled recruitment criteria constituted a cohort that was treated with ASAQ and passively followed up for 42 days. In case of a clinical failure patients were eligible for the second phase. Subjects with known hypersensitivity or serious drug-related AE to the study drugs and the presence of significant underlying disease or condition were excluded in the study.

Second phase (randomized controlled trial phase, RCT). Patients who experienced clinical failure during the first phase follow up, were randomly assigned to one of the 3 rescue treatments: either retreatment with ASAQ or AL (as an alternative ACT) or QnC, following a 2:2:1 ratio. Then they were actively followed up for 28 days, with a classic visit schedule for clinical and parasitological assessment [18]. Subjects with known hypersensitivity or serious drug-related AE to the study drugs were excluded in the study.

Third phase (post-randomized controlled trial phase, post RCTs). Patients with clinical or parasitological failure from day 14 onwards were retreated with ASAQ and actively followed up following the same procedure as RCT phase. All subsequent failures were retreated with ASAQ several times as needed (postRCT1, postRCT2 and so on) until each patient was followed during 28 days without parasitaemia. The liver function was clinically monitored from the third ASAQ treatment course, because of the known hepatotoxicity of amodiaquine [19]. Laboratory assessment was performed based on clinical signs.

Safety endpoints. At each visit, AEs (clinical and biological if available) were recorded on the specific case report form (CRF) during the study period. Site investigators were trained for AE collection and assessment. Laboratory tests (haemoglobin, aspartate and alanine aminotransferase) were monitored on basis of worsened clinical signs of either anaemia or hepatotoxicity.

The AEs were assessed for causality using the WHO criteria [20]: certain (plausible time relationship to drug intake, cannot be explained by disease or other drugs, response to withdrawal plausible, rechallenge satisfactory, if necessary), probable (reasonable time relationship to drug intake, unlikely to be attributed to disease or other drugs, response to withdrawal clinically reasonable), possible (reasonable time relationship to drug intake, could also be explained by disease or other drugs) and unlikely (with a time to drug intake that makes a relationship

improbable, disease or other drugs provide plausible explanations). The severity of a clinical AE was scored according to the following scale: mild (awareness of sign or symptom, but easily tolerated), moderate (discomfort enough to cause interference with usual activity), severe (incapacitating with inability to work or perform usual activity), life-threatening (patient at risk of death at the time of the event). International Conference for Harmonisation (ICH) definitions were used to assess AE seriousness [21]. AEs were considered as serious if: resulted in death or persistent disability, life threatened, required hospitalization or prolonged existing hospitalization, related to other medically important condition. At study completion, AEs were grouped according to the WHO adverse reaction terminology (WHO-ART) as System Organ Class (SOC) and Preferred Terms (PT) [22]. Only AEs with at least a “possible” relationship to drug were captured in this manuscript.

Study medication. During the first phase (Pre RCT), all subjects received ASAQ. Then those who experienced a treatment failure were randomly assigned to receive either ASAQ, AL or QnC (RCT phase). Thereafter all subsequent failures were retreated with ASAQ (Post RCT phase).

Treatment intake was directly observed by the study nurses, for all doses and all study phases. The drugs used in this trial were quality assured and storage conditions were regularly monitored. AL (Novartis, Basel, Switzerland) was administered twice daily for 3 days. Tablets contained 20 mg of artemether and 120 mg of lumefantrine. They were administered with a cup of milk (to improve lumefantrine absorption). Dosage was assigned according to manufacturer instructions: 5 to 14.9 kg, 1 tablet; 15 to 24.9 kg, 2 tablets; 25 to 34.9 kg, 3 tablets.

ASAQ (Sanofi, Casablanca, Morocco) was administered once daily for 3 days. Tablets contained 50 mg of artesunate and 135 mg of amodiaquine for patients weighing 9 to 17.9 kg; 100 mg of artesunate and 270 mg of amodiaquine for those weighing 18 to 35.9 kg.

Quinine (Sanofi, Gentilly, France) was administered thrice daily for 7 days. Tablets of 125 mg were available. Half of tablet was administered to patients weighing 9 to 11.9 kg, 1 tablet to those weighing 12 to 19.9 kg and 1.5 tablets to those weighing 20 to 27.9 kg.

Clindamycin (Pfizer SA/ NV Brussels, Belgium), granule for oral suspension 75mg/ 5 ml, was administered twice daily for at least 5 days at 10 mg/kg.

Ethical considerations

The study was conducted in agreement with the principles of the “Declaration of Helsinki” and in accordance with the standards and codes of conduct accepted by the ICH guidelines. The study protocol was approved by the Committee for Medical Ethics of the Antwerp University Hospital, Belgium and the Ethical Committee of the School of Public Health, Kinshasa University, DRC. A first informed consent was signed or thumb-printed by parent/ legal guardian before enrolment in preRCT phase and a second one before enrolment in RCT phase. The last was written so as to also cover postRCT phase.

Sample size and statistical analysis

The sample size was calculated on the basis of the RCT phase. Recruitment in the pre RCT phase was to be continued until the number of failures required for the randomized phase was reached [14]. The number (and percentage) of patients experiencing any AE was compared between treatment groups using Fisher’s exact test. Data analysis was performed using STATA 12 statistical software packages (Stata Corp, Lakeway, College Station, Texas, USA). Categorical variables were compared between the treatment groups using chi-square tests or Fisher’s exact tests, and continuous variables were compared using t test. A p value of <0.05 was considered statistically significant. Univariate analysis using logistic regression was performed to

identify the factors associated with occurrence of AEs and the strength of association. Factors with a $p \leq 0.020$ in univariate analysis were included in a stepwise multivariate modelling exercise using forward selection.

Results

Patient's characteristics at inclusion

In the pre RCT, 865 patients were enrolled and received ASAQ. This gave at least 50% of the chance of observing very common (occurring in 1 out of 10 patients taking the medicine), common (occurring at least in 1 out of 100 patients) and uncommon (occurring at least in 1 out of 1000 patients) adverse events. However, this phase offered little chance (less than 10%) to capture rare and very rare events [23–24]. Among clinical failures, 242 patients were enrolled in RCT phase. They were randomly assigned a rescue treatment as followed: 95 to ASAQ, to 107 to AL and 40 to QnC. Then 64, 17 and 7 were enrolled respectively in post RCT 1, 2 and 3, and they were always treated by ASAQ (Table 1, Fig 1).

Safety and tolerability during pre RCT

Of 865 patients recruited, 433 (50.0%) experienced at least one drug-related AEs. About one fourth ($n = 229$) exhibit two AEs or more. A total of 840 AEs was captured. The following systems were mainly involved in more than 30 AEs: psychiatric (38.6%, anorexia and abnormal behavior), gastro-intestinal (22.4%, especially abdominal pain and diarrhoea), general (20.5%, mainly asthenia), respiratory (12.5%, coughing in majority) and skin (3.8%, pruritus) (Table 2). The most reported AEs (more than 1%) were: anorexia (22.9%), asthenia (19.4%), abnormal behavior (including difficulty of concentration, agitation or confusion, 14.6%), coughing (11.3%), abdominal pain (10.2%), diarrhoea (5.7%), pruritus (3.4%), nausea (3.0%) and vomiting (2.9%) (Table 3). One case of either bullous eruption (verbatim “bullous eruption on lips”) or abnormal urine (verbatim “dark urine”) was reported, when 4 (0.5%) and 2 (0.2%) patients developed jaundice and hepatomegaly respectively. One AE (asthenia) led to drug discontinuation. Twenty-nine (3.5%) AE were graded as severe (Table 4). Three serious adverse events (SAE) were reported during pre RCT phase, 3 hospitalizations of which one resulted in death due to respiratory distress. None of them was judged to be related to the study medication (Table 5).

More than a half of subjects ($n = 453$, median weight 11.0 Kg IQR 10.0–12.0) received higher than ideal dose per body weight ($>4\text{mg/kg}$ for artesunate and $>10\text{mg/kg}$ for amodiaquine) without difference about gender. AEs occurred more frequently in those children and in patients who presented with fever while subjects with mixed infection at the recruitment exhibit less AEs regardless of analysis (uni- or multi-variate) (Table 6).

Safety and tolerability during RCT

At least one event was reported in 91 patients, 52 (54.7%), 23 (21.5%) and 16 (40.0%) respectively in ASAQ, AL and QnC arm. Of which 48 patients complained of AEs in Pre RCT phase

Table 1. Baseline characteristics of patients enrolled in quinact trial (Kinshasa, DRC, 2012–14).

	Pre RCT n = 865	RCT n = 242	PostRCT1 n = 64	PostRCT2 n = 17	PostRCT3 n = 7
Gender, males, n (%)	442 (51.1)	129 (53.3)	31 (48.4)	12 (70.6)	7 (100)
Age (months), mean (SD)	36.2 (13.2)	37.4 (13.1)	37.4 (13.6)	35.7 (14.2)	28.9 (11.4)
Weight (kg), median (IQR)	12.5 (3.7)	13.0 (3.6)	12.9 (3.4)	12.9 (2.5)	13.3 (5.3)
Haemoglobin, mean (SD)	9.3 (1.6)	10.3 (1.6)	10.9 (1.2)	11.6 (1.6)	11.2 (0.7)

<https://doi.org/10.1371/journal.pone.0222379.t001>

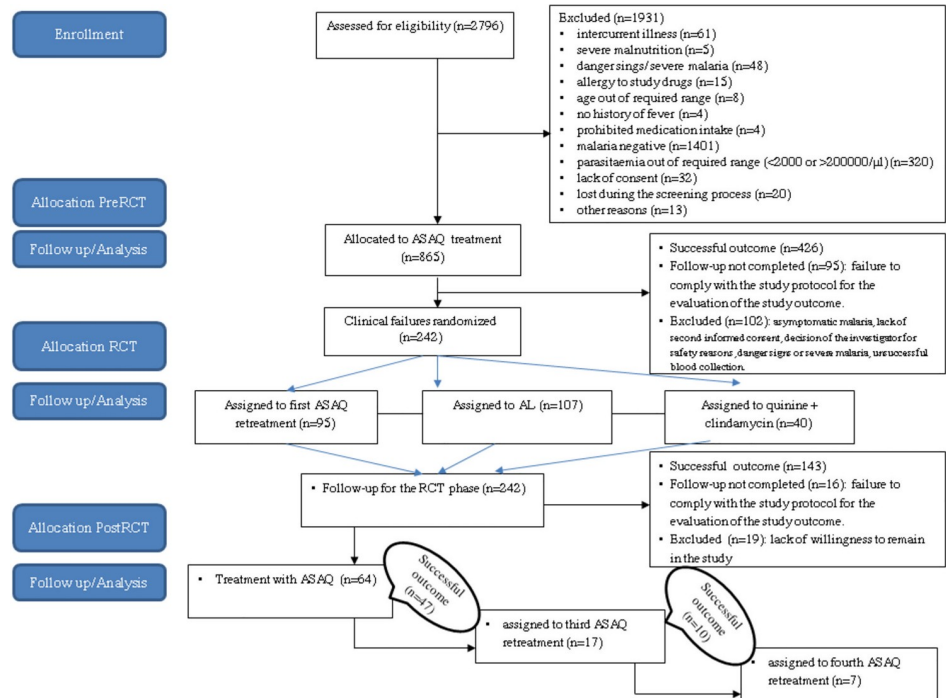


Fig 1. Trial flow chart, patients' randomization and treatment assignment in Lisungi, Kinshasa, DR Congo.

<https://doi.org/10.1371/journal.pone.0222379.g001>

too (30 received ASAQ, 10 AL and 8 QnC). Forty patients experienced two AEs or more. Overall 165 AE were reported, of which 100 in ASAQ group, 35 in AL group and 30 in QnC group. (Table 3). Ten AEs (6.1%) were graded as severe. No SAE was reported during this phase. Psychiatric disorders (46.7% and 34.0% in QnC or ASAQ arm, anorexia and abnormal behavior especially) were the most AE reported, followed by gastro-intestinal disorders (40.0% in AL arm, mainly abdominal pain, diarrhoea, nausea and vomiting), respiratory disorders (coughing particularly), general disorders (especially asthenia), skin disorders (mainly pruritus) (Tables 2 and 3). One case of hypoglycaemia was reported in QnC group. One case of each the following AE *id est* anaemia and convulsions, jaundice were reported respectively for QnC and AL. Significant differences arose from treatment groups, ASAQ tended to be more responsible of AE occurrence than other antimalarials except for general and hearing disorders where QnC was respectively more involved than AL ($p = 0.002$) and both AL ($p = 0.020$) and ASAQ ($p = 0.028$) (Table 7). High proportions were observed in ASAQ vs AL arm regarding general ($p = 0.001$), psychiatric ($p < 0.001$) and skin disorders ($p = 0.010$) whereas compared to QnC, ASAQ induced more gastro-intestinal ($p = 0.049$) and respiratory disorders ($p = 0.003$) (Table 7).

Safety and tolerability during post RCT

Post-RCT1. Twenty-one (32.8%) out of 64 patients complained of at least one AE with a total of 50 AEs recorded. Eleven (17.2%) subjects complained of two or more AEs. Three patients experienced any AE with ASAQ during the 3 phases of study (Pre RCT, RCT and Post RCT1). From those AEs, 3 (6%) were severe. However, no SAE was accounted. Anorexia, asthenia and abnormal behavior were the commonest AE reported (> 5 reports) (Table 2). Psychiatric and general systems were the most affected (> 10 AE) (Table 3).

Post-RCT2. Of 17 patients treated, 6 (35.3%) experienced drug-related AE and 24 AEs were captured. Only 1 AE was assessed as severe. Abdominal pain, coughing and diarrhoea

Table 2. Distribution of most relevant Adverse Event by treatment and phase study according Preferred Term (quinact trial, Kinshasa, DRC, 2012–14).

Phase	PreRCT (N = 865)	RCT (N, ASAQ = 95, AL = 107, QnC = 40)			PostRCT1 (N = 64)	PostRCT2 (N = 17)	PostRCT3 (N = 7)	Overall ASAQ
		ASAQ (n, %)	AL (n, %)	QnC (n, %)				
Total of patients (n)	865	95	107	40	64	17	7	1048*
PT (WHO-ART)								
Abdominal pain	88 (10.2)	7 (7.4)	6 (5.6)	1 (2.5)	4 (6.3)	4 (23.5)	1 (14.3)	104 (9.9)
Abnormal behaviour	126 (14.6)	10 (10.5)	2 (1.9)	6 (15.0)	8 (12.5)	3 (17.6)	5 (71.4)	152 (14.5)
Anaemia	5 (0.6)	0	0	1 (2.5)	0	0	0	5 (0.5)
Anorexia	198 (22.9)	24 (25.3)	6 (5.6)	8 (20.0)	13 (20.3)	3 (17.6)	5 (71.4)	243 (23.2)
Asthenia	168 (19.4)	14 (14.7)	2 (1.9)	6 (15.0)	13 (20.3)	3 (17.6)	5 (71.4)	203 (19.4)
Bradycardia	0	1 (1.0)	0	0	0	0	0	1 (0.1)
Bullous eruption	1 (0.1)	0	0	0	0	0	0	1 (0.1)
Convulsions	0	0	0	1 (2.5)	0	0	0	0
Coughing	98 (11.3)	16 (16.8)	6 (5.6)	0	4 (6.3)	4 (23.5)	3 (42.9)	125 (11.9)
Diarrhoea	49 (5.7)	7 (7.4)	7 (6.5)	1 (2.5)	3 (4.7)	4 (23.5)	1 (14.3)	64 (6.1)
Dizziness	2 (0.2)	0	1 (0.9)	0	0	0	0	2 (0.2)
Hepatomegaly	2 (0.2)	0	0	0	0	0	0	2 (0.2)
Hypoglycaemia	0	0	0	1 (2.5)	0	0	0	0
Jaundice	4 (0.5)	0	1 (0.9)	0	0	0	0	4 (0.4)
Nausea	26 (3.0)	3 (3.2)	1 (0.9)	1 (2.5)	0	1 (5.9)	0	30 (2.9)
Oedema	1 (0.1)	0	0	0	0	0	1 (14.3)	2 (0.2)
Pruritus	29 (3.4)	6 (6.3)	0	0	1 (1.6)	2 (11.8)	0	38 (3.6)
Rash	1 (0.1)	2 (2.1)	1 (0.9)	0	0	0	0	3 (0.3)
Tachycardia	2 (0.2)	0	1 (0.9)	2 (5.0)	0	0	0	2 (0.2)
Tinnitus	0	0	0	2 (5.0)	0	0	0	0
Urine abnormal	1 (0.1)	0	0	0	0	0	0	1 (0.1)
Urticaria	1 (0.1)	0	0	0	1 (1.6)	0	0	2 (0.2)
Vomiting	25 (2.9)	6 (6.3)	0	0	2 (3.1)	0	1 (14.3)	34 (3.2)

*number of treatment courses

<https://doi.org/10.1371/journal.pone.0222379.t002>

represented the half of reported AEs (Table 2). Gastro-intestinal and psychiatric systems were the most concerned (> 50% for both) (Table 3).

Post-RCT3. During the ultimate phase, 22 drug-related AE were accounted from 5 out of 7 patients treated (4.4 AE per patient). Neither severe AE nor SAE were noted. Abnormal behavior, anorexia and asthenia were most common when psychiatric and body as a whole-general system were mainly involved (Tables 2 and 3).

Overall assessment

During the entire period of this study, respectively 1048, 107 and 40 treatment courses of ASAQ, AL and QnC were administered to all patients. Overall 1101 AEs were reported with the 3 antimalarial regimens of which 1036 ASAQ-induced AEs (0.99 AE per treatment), 35 AL-induced (0.33 AE per treatment) and 30 QnC-induced (0.75 AE per treatment). Forty-three AEs (3.9%) were graded as severe (Table 7). The most common system affected (respectively for ASAQ, AL and QnC) were psychiatric (38.1%, 22.9% and 46.7%), gastro-intestinal (22.4%, 40.0% and 10.0%), general (20.2%, 5.7% and 20.0%). The most reported AEs (respectively for ASAQ, AL and QnC) were anorexia (23.2%, 5.6% and 20.0%), asthenia (19.4%, 1.9% and 15.0%) and abnormal behavior (14.5%, 1.9% and 15.0%). Tables 2, 3 and 7 outline AEs

Table 3. Distribution of Adverse Event by treatment and phase study according System Organ Class (SOC) (quinact trial, Kinshasa, DRC, 2012–14).

Phase	PreRCT (N = 865)	RCT (N, ASAQ = 95, AL = 107, QnC = 40)			PostRCT1 (N = 64)	PostRCT2 (N = 17)	PostRCT3 (N = 7)	Overall ASAQ
		ASAQ (n, %)	AL (n, %)	QnC (n, %)				
Total of AEs (n)	840	100	35	30	50	24	22	1036
SOC								
General	172 (20.5)	15 (15.0)	2 (5.7)	6 (20.0)	13 (26.0)	3 (12.5)	6 (27.3)	209 (20.2)
Nervous	3 (0.4)	0	1 (2.9)	1 (3.3)	0	0	0	3 (0.3)
Gastro-intestinal	188 (22.4)	23 (23.0)	14 (40.0)	3 (10.0)	9 (18.0)	9 (37.5)	3 (13.6)	232 (22.4)
Hearing	0	0	0	2 (6.7)	0	0	0	0
Heart rate	2 (0.2)	1 (1.0)	1 (2.9)	2 (6.7)	0	0	0	3 (0.3)
Liver	6 (0.7)	0	1 (2.9)	0	0	0	0	6 (0.6)
Metabolic	0	0	0	1 (3.3)	0	0	0	0
Musculo-skeletal	1 (0.1)	1 (1.0)	0	0	0	0	0	2 (0.2)
Psychiatric	324 (38.6)	34 (34.0)	8 (22.9)	14 (46.7)	21 (42.0)	6 (25.0)	10 (45.5)	395 (38.1)
Red blood cell	5 (0.6)	0	1 (2.9)	1 (3.3)	0	0	0	5 (0.5)
Respiratory	105 (12.5)	18 (18.0)	6 (17.1)	0	5 (10.0)	4 (16.7)	3 (13.6)	135 (13.0)
Skin	32 (3.8)	8 (8.0)	1 (2.9)	0	2 (4.0)	2 (8.3)	0	44 (4.2)
Urinary	1 (0.1)	0	0	0	0	0	0	1 (0.1)
Vision	1 (0.1)	0	0	0	0	0	0	1 (0.1)

<https://doi.org/10.1371/journal.pone.0222379.t003>

classification (PT and SOC) according antimalarial regimen on the one hand and classification by severity on the other one.

Discussion

In malaria endemic countries, ACTs are widely [18] and likely repeatedly used to treat recurrent episodes; though there is a necessity to assess their safety profile [25, 26]. The present findings show numerous related-antimalarial AEs but they were mostly minor. Nonetheless, some particular AEs had been noted. Abnormal behavior was common although the literature

Table 4. Distribution of AE by severity according Preferred Term (PT) (quinact trial, Kinshasa, DRC, 2012–14).

Total of events	PreRCT (n = 840)	RCT (n, ASAQ = 100, AL = 35, QnC = 30)			PostRCT1 (n = 50)	PostRCT2 (n = 24)
		ASAQ	AL	QnC		
	severe (n)	severe (n)	severe (n)	severe (n)	severe (n)	severe (n)
PT (WHO-ART)						
Abnormal behaviour	6	1	0	0	0	0
Allergic reaction	0	0	1	0	0	0
Anaemia	3	0	0	0	0	0
Anorexia	0	1	0	0	0	0
Asthenia	7	2	0	0	0	0
Convulsions	0	0	0	1	0	0
Coughing	9	1	2	0	2	1
Fever	2	0	0	0	0	0
Pruritus	1	0	0	0	0	0
Rash	0	0	1	0	0	0
Urticaria	1	0	0	0	1	0
Total	29	5	4	1	3	1

<https://doi.org/10.1371/journal.pone.0222379.t004>

Table 5. Description of reported SAEs (quinact trial, Kinshasa, DRC, 2012–14).

Reactions	Received drug	Onset date	Relationship to drug	Age (month)	Gender	Co-morbidity	Outcome
Respiratory distress	ASAQ	Next day	Unlikely	31	F	Anemia, enteritis	Death
Convulsion	ASAQ	13 th day	Unlikely	54	F	Bacterial infection	Recovered
Convulsion	ASAQ	12 th day	Unlikely	44	M	None	Recovered

<https://doi.org/10.1371/journal.pone.0222379.t005>

reports behavioral changes as rare AEs of 4-aminoquinoline derivatives (including amodiaquine) and the summary of product characteristics (SmPC) does not mention it among psychiatric disorders [27, 28]. One study about effect of administration of amodiaquine on rats highlighted various behavioral disorders due to drug effects [29]. However, it is not excluded that these (subjective) effects were over-reported considering the fact of participating in a clinical trial was a new experience for both parents and child. Caution may be needed to monitor closely these adverse effects while antimalarial amodiaquine-contained regimen is given. One case of bullous eruption was recorded after ASAQ administration while it is generally not reported in other studies [3, 30]. However, several cases had been captured with AL [31]. Abnormal urine (dark urine) could suggest haemoglobinuria and haemolysis with likely underlying enzymes deficiency (e.g. G6PD). This could be confirmed by laboratory analysis which was not assessed in this study. However, haemoglobinuria has been recorded in clinical trials with artemisinin derivatives (either artemether or artesunate) [32, 33]. For some events such as hepatomegaly, splenomegaly, conjunctivitis, it is unclear if they are related to drugs or occurred as a result of the underlying disease or condition (coincidental event) [27]. Hepatomegaly (graded as mild) reported here occurred simultaneously with asthenia or jaundice in 2 children (0.2%), they may all be prodromal clinical signs of drug induced-hepatotoxicity even if time of onset is relatively short (one day) [34]. In general, most of AEs were mild or moderate even during ultimate phase.

These findings are in line with other studies even when repeated treatment has been given [3, 10, 35]. ASAQ was also found responsible of significantly higher events rate than other anti-malarials in the literature [3, 29]. However, one recent study shows that AEs were no more

Table 6. Predictors of adverse events occurrence (quinact trial, Kinshasa, DRC, 2012–14).

	N = 865 n (%)	cOR (95% CI), p value	aOR (95% CI), p value
Predictors of AE occurrence			
Dosage, higher	453 (52.4)	1.48 (1.14–1.94), 0.004*	1.53 (1.17–2.01), 0.002*
Gender, male	441 (51.0)	0.93 (0.71–1.22), 0.61	NA
Anemia, hemoglobin < 11g/dl	729 (84.3)	1.03 (0.72–1.50), 0.84	NA
Patients with fever, ≥38°C	320 (37.0)	1.45 (1.10–1.92), 0.008*	1.47 (1.11–1.95), 0.007*
Patients sleeping under mosquito bednets the previous night	301 (34.8)	1.13 (0.86–1.50), 0.38	NA
Parasite infection, mixed	252 (29.1)	0.65 (0.48–0.88), 0.004*	0.64 (0.48–0.87), 0.004*

*statistically significant

<https://doi.org/10.1371/journal.pone.0222379.t006>

Table 7. AE occurrence by treatment according SOC (RCT phase) (quinact trial, Kinshasa, DRC, 2012–14).

	RCT, Number of patients with AE (n = 91)			p value		
	ASAQ (n = 52)	AL (n = 23)	QnC (n = 16)	ASAQ vs AL	ASAQ vs QnC	AL vs QnC
Patients allocated to treatment (N)	N = 95	N = 107	N = 40			
% of patients with at least 1 AE	54.7%	21.5%	40.0%			
SOC (WHO-ART)	ASAQ, n = 52 (%)	AL, n = 23 (%)	QnC, n = 16 (%)			
General	13 (25%)	2 (8.7%)	6 (37.5%)	0.001*	0.841	0.002*
Nervous	0	1 (4.3%)	1 (6.3%)	0.345	0.122	0.466
Gastro-intestinal	17 (32.7%)	12 (52.2%)	2 (12.5%)	0.177	0.049*	0.253
Hearing	0	0	2 (12.5%)	NA	0.028*	0.020*
Heart rate	1 (1.9%)	1 (4.3%)	2 (12.5%)	0.933	0.155	0.121
Liver	0	1 (4.3%)	0	0.345	NA	0.54
Metabolic	0	0	1 (6.3%)	NA	0.122	0.101
Musculo-skeletal	1 (1.9%)	0	0	0.287	0.515	NA
Psychiatric	28 (53.8%)	8 (34.8%)	10 (62.5%)	<0.001*	0.598	0.004*
Red blood cells	0	1 (4.3%)	1 (6.3%)	0.345	0.122	0.466
Respiratory	18 (34.6%)	6 (26.1%)	0	0.003	0.003*	0.126
Skin	8 (15.4%)	1 (4.3%)	0	0.010*	0.058	0.54
Total	52	23	16			

*statistically significant

NA: not applicable

<https://doi.org/10.1371/journal.pone.0222379.t007>

numerous in ASAQ group than in AL one, even in cases of readministration [36]. In one cohort, bradycardia has been also identified as a potential risk on the second day of treatment with Amodiaquine [37]. However, electrocardiogram was not performed in this study. Some AEs such as hypoglycaemia, severe asthenia, anaemia may need close monitoring to avoid threatened outcome or discontinuation of the therapy. The analysis indicated relationship between AE occurrence and the ASAQ dose. The dose-dependent effects (gastro-intestinal or neutropenia) of antimalarials (such as ASAQ or AL, artesunate monotherapy) were reported in other studies [38–40].

The findings of this study are mostly similar to other studies that also reported almost same AE pattern and are within the expected type based on the SmPC of the medications expect psychiatric disturbances [3, 27, 30, 41]. Nonetheless, this study was not powered to detect rare events (occurring in < 0.1% of the population treated). Some of antimalarial AEs such as nausea, vomiting, asthenia or anorexia are similar to malaria symptoms; making it often difficult to discriminate possible drug events from disease effects [42]. Moreover, anorexia is only considered as psychiatric disorder in the WHO-ART and includes “loss of appetite” as well as “decreased appetite”, when in other system such as Medical Dictionary for Regulatory Activities “MedDRA” terminology anorexia may fall under metabolism and nutrition disorder or psychiatric disorder categories; this could influence AE reporting following the system used [22, 43]. Nevertheless, this study provides useful information on safety profile of antimalarials especially when administered to young children.

Some limitations must be mentioned. Patients having previous history with serious adverse events were not included in the study; this may affect external validity. The unblinded design of the RCT may bias the result considering the differential reporting or recall between the groups. Electrocardiogram evaluations were not performed while ASAQ is known to be associated with risk of cardiotoxicity [44].

Conclusion

This study indicated a good safety profile in case of repeated treatment, although the number of participants was decreasing over the study phases. However, safety monitoring should continue in routine clinical practice in the context of wide and extend use of ACTs, mainly in Africa. The study did not provide definitely evidence of safe biological profile, laboratory investigations schedule may be necessary but their implementation in the routine activities would be a challenge. Healthcare providers should be recommended to advice and encourage patients to complete their medications as the expected reactions are most often not severe.

Supporting information

S1 File. CONSORT 2010 checklist for quinact study safety paper.
(DOC)

Acknowledgments

We thank all study participants and their parents/ care takers as well as the study staff (Georgette Ndelela, Florence Namazu, Noella Kabamba, Olivier Kaniki, Ezechias Mumbenga, Rodin Mukele, John Milambu, Bibiche Ekoko, Nancy Mwema, Bibi Uмба, Bienvenu Mbuku and Jeanne Badimuena). Thanks to Sanofi for kindly providing Artesunate-amodiaquine and Quinine free of charge. We are also grateful for the fruitful collaboration with Monitors from the Amsterdam Institute for Global Health and Development, based in Kampala, Uganda: Caroline Bako, Sophie Nabasirye and Miriam Nakitto.

Author Contributions

Conceptualization: Jean-Pierre Van geertruyden, Pascal Lutumba.

Data curation: Hypolite Muhindo Mavoko, Marion Kalabuanga, Blaise Fungula, Raquel Inocencio da Luz.

Formal analysis: Yves Lula Ntamba, Hypolite Muhindo Mavoko.

Funding acquisition: Jean-Pierre Van geertruyden, Pascal Lutumba.

Investigation: Hypolite Muhindo Mavoko, Marion Kalabuanga, Blaise Fungula.

Methodology: Hypolite Muhindo Mavoko, Jean-Pierre Van geertruyden, Pascal Lutumba.

Project administration: Pascal Lutumba.

Supervision: Jean-Pierre Van geertruyden, Pascal Lutumba.

Validation: Pierre-Michel Ntamabyaliro Nsengi, Gaston Tona Lutete.

Visualization: Yves Lula Ntamba.

Writing – original draft: Yves Lula Ntamba, Hypolite Muhindo Mavoko.

Writing – review & editing: Yves Lula Ntamba, Hypolite Muhindo Mavoko, Marion Kalabuanga, Blaise Fungula, Pierre-Michel Ntamabyaliro Nsengi, Gaston Tona Lutete, Raquel Inocencio da Luz, Jean-Pierre Van geertruyden, Pascal Lutumba.

References

1. WHO. Guidelines for the treatment of malaria, third edition. Switzerland: World Health Organization, 2015. Available from <http://apps.who.int/medicinedocs/en/m/abstract/Js21839en/>

2. PNL. Guide technique de prévention et de prise en charge du Paludisme, Programme National de Lutte contre le Paludisme, Ministère de la Santé Publique, République Démocratique du Congo, 2012. Available from <https://www.medbox.org/drc-polices-others/drc-guide-technique-de-prevention-et-prise-en-charge-du-paludisme-hopital-general-de-reference/preview?q=>
3. Doodoo AN, Fogg C, Nartey ET, Ferreira GL, Adjei GO, Kudzi W, et al. Profile of Adverse Events in Patients Receiving Treatment for Malaria in Urban Ghana: A Cohort-Event Monitoring Study. *Drug Saf*. 2014, 37:433–448. <https://doi.org/10.1007/s40264-014-0164-9> PMID: 24788801
4. Sinclair D, Zani B, Donegan S, Olliaro P, Garner P. Artemisinin based combination therapy for treating uncomplicated malaria (Review). The Cochrane Collaboration. *Cochrane Database Syst Rev*. 2009 Jul 8;(3):CD007483. <https://doi.org/10.1002/14651858.CD007483.pub2> PMID: 19588433
5. Falade C, Manyando C. Safety profile of Coartem: the evidence base. *Malar J*. 2009 Oct 12; 8 Suppl 1: S6. <https://doi.org/10.1186/1475-2875-8-S1-S6> PMID: 19818173
6. Kuemmerle A, Doodoo A, Olsson A, Erps JV, Burri C, Lalvani PS. Assessment of global reporting of adverse drug reactions for anti-malarials, including artemisinin based combination therapy, to the WHO programme for international drug monitoring. *Malar J*. 2011, 10:57. <https://doi.org/10.1186/1475-2875-10-57> PMID: 21388536
7. Stergachis A, Bartlein RJ, Doodoo A, Nwokike J, Kachur SP. A situational analysis of pharmacovigilance plans in the global fund malaria and U.S. President's Malaria initiative proposals. *Malar J*. 2010, 9:148. <https://doi.org/10.1186/1475-2875-9-148> PMID: 20509971
8. Pirmohamed M, Atuah KN, Doodoo AN, Winstanley P. Pharmacovigilance in developing countries. *BMJ*. 2007, 335:462. <https://doi.org/10.1136/bmj.39323.586123.BE> PMID: 17823149
9. Olsson S, Pal SN, Stergachis A, Couper M. Pharmacovigilance activities in 55 low- and middle-income countries: a questionnaire-based analysis. *Drug Saf*. 2010, 33:689–703. <https://doi.org/10.2165/11536390-000000000-00000> PMID: 20635827
10. Sagara I, Fofana B, Gaudart J, Sidibe B, Togo A, Toure S, et al. Repeated Artemisinin-Based Combination Therapies in a Malaria Hyperendemic Area of Mali: Efficacy, Safety, and Public Health Impact. *Am. J. Trop. Med. Hyg*. 2012, 87(1), pp. 50–56. <https://doi.org/10.4269/ajtmh.2012.11-0649> PMID: 22764291
11. Mehta U, Durrheim D, Mabuza A, Blumberg L, Allen E, Barnes KI. Malaria Pharmacovigilance in Africa. Lessons from a Pilot Project in Mpumalanga Province, South Africa. *Drug Saf*. 2007, 30 (10): 899–910. <https://doi.org/10.2165/00002018-200730100-00008> PMID: 17867727
12. Schramm B, Valeh P, Baudin E, Mazinda CS, Smith R, Pinoges L, et al. Tolerability and safety of artesunate-amodiaquine and artemether-lumefantrine fixed dose combinations for the treatment of uncomplicated *Plasmodium falciparum* malaria: two open-label, randomized trials in Nimba County, Liberia. *Malar J*. 2013, 12:250. <https://doi.org/10.1186/1475-2875-12-250> PMID: 23866736
13. Maiteki-Sebuguzi C, Jagannathan P, Yau VM, Clark TD, Njama-Meya D, Nzarubara B, et al. Safety and tolerability of combination antimalarial therapies, Ugandan children. *Malar J*. 2008, 7:106. <https://doi.org/10.1186/1475-2875-7-106> PMID: 18547415
14. Muhindo MH, Nabasumba C, Tinto H, D'Alessandro U, Grobusch MP, Lutumba P, et al. Impact of retreatment with an artemisinin-based combination on malaria incidence and its potential selection of resistant strains: study protocol for a randomized controlled clinical trial. *Trials*, 2013, 14:307. Available from: <https://doi.org/10.1186/1745-6215-14-307> PMID: 24059911
15. Maketa V, Mavoko HM, da Luz RI, Zanga J, Lubiba J, Kalonji A, et al. The relationship between *Plasmodium* infection, anaemia and nutritional status in asymptomatic children aged under five years living in stable transmission zones in Kinshasa, Democratic Republic of Congo. *Malar J*. 2015; 14:83. <https://doi.org/10.1186/s12936-015-0595-5> PMID: 25880427
16. Mavoko H M, Nabasumba C, Inocencio da Luz R, Tinto H, D'Alessandro U, Kambugu A, et al. Efficacy and safety of re-treatment with the same artemisinin-based combination treatment (ACT) compared with an alternative ACT and quinine plus clindamycin after failure of first-line recommended ACT (QUINACT): a bicentre, open-label, phase 3, randomised controlled trial. *Lancet Glob Health*. November 10, 2016. Available from: [https://doi.org/10.1016/S2214-109X\(16\)30236-4](https://doi.org/10.1016/S2214-109X(16)30236-4)
17. Mavoko H M, Kalabuanga M, Delgado-Ratto C, Maketa V, Mukele R, Fungula B, et al. Uncomplicated Clinical Malaria Features, the Efficacy of Artesunate-Amodiaquine and Their Relation with Multiplicity of Infection in the Democratic Republic of Congo. *PLoS ONE*. 2016, 1(6): e0157074. <https://doi.org/10.1371/journal.pone.0157074> PMID: 27280792
18. WHO. Assessment and monitoring of antimalarial drug efficacy for the treatment of uncomplicated *falciparum* malaria. Switzerland: World Health Organization, 2003.
19. Neffel KA, Woodtly W, Schmid M, Frick PG, and Fehr J. Amodiaquine induced agranulocytosis and liver damage *Br Med J (Clin Res Ed)*. 1986, Mar 15; 292(6522): 721–723.

20. Meyboom RH, Hekster YA, Egberts AC, Gribnau FW, Edwards IR. Causal or Casual? The Role of Causality Assessment in Pharmacovigilance. *Drug Saf.* 1997, 17(6): 374–389. <https://doi.org/10.2165/00002018-199717060-00004> PMID: 9429837
21. ICH Expert Working Group. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. “ICH Harmonised Tripartite Guideline”. Guidelines for Good Clinical Practice (E6), 1996. Available from: <https://ichgcp.net/>.
22. WHO. The WHO Adverse Reaction Terminology “WHO-ART”. Uppsala (Sweden): The Uppsala Monitoring Centre, 2015, Quarter1. (Provided as part of a subscription). Available upon request from: <https://www.who-umc.org/vigibase/services/learn-more-about-who-art>.
23. WHO. A practical handbook on the Pharmacovigilance of antimalarial medicines, the World Health Organization, 2007.
24. Guidelines for preparing core clinical-safety information on drugs, second edition: report of CIOMS working group III and IV, ISBN: 92 9036 070 4, 1999
25. Talisuna AO, Staedke SG, D’Alessandro U. Pharmacovigilance of antimalarial treatment in Africa: is it possible? *Malar J.* 2006, 5:50. <https://doi.org/10.1186/1475-2875-5-50> PMID: 16780575
26. Thiam S, Ndiaye J, Diallo I, Gatonga P, Fall FB, Diallo NE, et al. Safety monitoring of artemisinin combination therapy through a national pharmacovigilance system in an endemic malaria setting. *Malar J.* 2013, 12:54. <https://doi.org/10.1186/1475-2875-12-54> PMID: 23384036
27. Sean C Sweetman. Martindale: The Complete Drug Reference, 35th edition, Pharmaceutical Press, London, UK, 2007.
28. Sanofi-Aventis. Artesunate/Amodiaquine tablets, Summary of Products characteristics, 2014. Available from: <https://extranet.who.int/prequal>.
29. Ekong MB, Igiri AO, and Mesembe OE. The effect of administration of amodiaquine on some parameters of neurobehavior of wistar rats. *Nigerian Journal of Physiological Sciences.* 2008, 23 (1–2): 51–54. PMID: 19434214
30. Bassi PU, Osakwe AI, Isah A, Suku C, Kalat M, Jalo I, et al. Safety of Artemisinin-Based Combination Therapies in Nigeria: A Cohort Event Monitoring Study. *Drug Saf.* 2013 36:747–756. <https://doi.org/10.1007/s40264-013-0044-8> PMID: 23591829
31. Chinawa JM. Adverse Drug Event From Artemether/lumefantrine Ingestion: Case Series. *Niger J Paed.* 2013, 40 (4): 416–418.
32. Tran TH, Day NP, Ly VC, Nguyen TH, Pham PL, Nguyen HP, et al. Black water fever in Southern Vietnam. A prospective descriptive study of 50 cases. *Clin Infect Dis.* 1996, 23:1274–81. PMID: 8953071
33. Tran TH, Day NP, Nguyen HP, Nguyen TH, Pham PL, Dinh XS, et al. Controlled trial of artemether or quinine in Vietnamese adults with severe falciparum malaria. *New Eng J Med.* 1996, 335:76–83. <https://doi.org/10.1056/NEJM199607113350202> PMID: 8649493
34. Andrade RJ, Robles M, Fernández-Castañer A, López-Ortega S, López-Vega MC, Lucena MI. Assessment of drug-induced hepatotoxicity in clinical practice: A challenge for gastroenterologists. *World J Gastroenterol.* 2007, 13(3): 329–340. <https://doi.org/10.3748/wjg.v13.i3.329> PMID: 17230599
35. Ndiaye JA, Faye B, Gueye A, Tine R, Ndiaye D, Tchania C, et al. Repeated treatment of recurrent uncomplicated Plasmodium falciparum malaria in Senegal with fixed dose artesunate plus amodiaquine versus fixed-dose artemether plus lumefantrine: a randomized, open-label trial. *Malar J.* 2011, 10:237. <https://doi.org/10.1186/1475-2875-10-237> PMID: 21838909
36. Yeka A, Lameyre V, Afizi K, Fredrick M, Lukwago R, Kamya MR, et al. Efficacy and Safety of Fixed-Dose Artesunate-Amodiaquine vs. Artemether-Lumefantrine for Repeated Treatment of Uncomplicated Malaria in Ugandan Children. *PLoS ONE.* 2014, 9(12): e113311. <https://doi.org/10.1371/journal.pone.0113311> PMID: 25436614
37. Ngouesse B, Basco L, Ringwald P, Keundjian A, Blackett KN. Cardiac effects of amodiaquine and sulfadoxine-pyrimethamine in malaria-infected African patients. *Am J Trop Med Hyg.* 2001, 65(6):711–6. <https://doi.org/10.4269/ajtmh.2001.65.711> PMID: 11791962
38. The WorldWide Antimalarial Resistance Network (WWARN) AS-AQ Study Group. The effect of dosing strategies on the therapeutic efficacy of artesunate-amodiaquine for uncomplicated malaria: a meta-analysis of individual patient data. *BMC Medicine.* 2015, 13:66. <https://doi.org/10.1186/s12916-015-0301-z> PMID: 25888957
39. The WorldWide Antimalarial Resistance Network (WWARN) AL Study Group TWARNA Dose Impact S Group. The effect of dose on the antimalarial efficacy of artemether-lumefantrine: a pooled analysis of individual patient data. *Lancet Infect Dis.* 2015, 15(6):692–702. [https://doi.org/10.1016/S1473-3099\(15\)70024-1](https://doi.org/10.1016/S1473-3099(15)70024-1) PMID: 25788162
40. Bethell D, Se Y, Lon C, Socheat D, Saunders D, Teja-Isavadharm P, et al. Dose-dependent risk of neutropenia after 7-day courses of artesunate monotherapy in Cambodian patients with acute Plasmodium

falciparum malaria. Clin Infect Dis. 2010, 51:e105–e114. <https://doi.org/10.1086/657402> PMID: 21070142

41. Ngasala BE, Malmberg M, Carlsson AM, Ferreira PE, Petzold MG, Blessborn D, et al. Efficacy and effectiveness of artemether-lumefantrine after initial and repeated treatment in children < 5 years of age with acute uncomplicated *Plasmodium falciparum* malaria in rural Tanzania: a randomized trial. Clin Infect Dis. 2011, 52: 873–882. <https://doi.org/10.1093/cid/cir066> PMID: 21427394
42. Price R, van Vugt M, Phaipun L, Luxemburger C, Simpson J, McGready R, et al. Adverse effects in patients with acute *falciparum* malaria treated with artemisinin derivatives. Am J Trop Med Hyg. 1999, 60:547–55. <https://doi.org/10.4269/ajtmh.1999.60.547> PMID: 10348227
43. IFPMA. Introductory Guide for Standardised MedDRA Queries (SMQs) Version 19.0, March 2016, MSSO-DI-6226-19.0.0. (Provided as part of a subscription). Available from: <https://www.meddra.org/how-to-use/support-documentation?current>.
44. WHO Evidence Review Group Meeting. The cardiotoxicity of antimalarials, October 2016. Available from: <https://www.who.int/malaria/mpac/mpac-mar2017-erg-cardiotoxicity-report-session2.pdf>.