



HAL
open science

Systematic review of artesunate pharmacokinetics: Implication for treatment of resistant malaria

Yobouet Ines Kouakou, Michel Tod, Gilles Leboucher, Adeline Lavoignat,
Guillaume Bonnot, Anne-Lise Bienvenu, Stephane Picot

► To cite this version:

Yobouet Ines Kouakou, Michel Tod, Gilles Leboucher, Adeline Lavoignat, Guillaume Bonnot, et al..
Systematic review of artesunate pharmacokinetics: Implication for treatment of resistant malaria.
International Journal of Infectious Diseases, 2019, 89, pp.30 - 44. 10.1016/j.ijid.2019.08.030 . hal-03488979

HAL Id: hal-03488979

<https://hal.science/hal-03488979v1>

Submitted on 20 Jul 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Systematic review of artesunate pharmacokinetics: implication for treatment of resistant malaria

Yobouet Ines Kouakou, Michel Tod, Gilles Leboucher, Adeline Lavoignat, Guillaume Bonnot, Anne-Lise Bienvenu*, Stephane Picot*

*Joint last authors

ICBMS CNRS 5246, SMITH, Malaria Research Unit, Campus Lyon-Tech La Doua, Lyon University, Lyon, France (YI Kouakou PharmD, A Lavoignat MSc, G Bonnot MSc, A-L Bienvenu PharmD, Prof S Picot MD); **Groupement Hospitalier Nord, Service Pharmacie, Hospices Civils de Lyon, Lyon, France** (Prof M Tod PharmD, G Leboucher PharmD); **and Groupement Hospitalier Nord, Institut de Parasitologie et Mycologie Médicale, Hospices Civils de Lyon, Lyon, France** (Prof S Picot MD)

Correspondence to:

Dr Anne-Lise Bienvenu, Groupement Hospitalier Nord, Service Pharmacie, Hospices Civils de Lyon, 103 Grande Rue de la Croix-Rousse, F-69004 Lyon, France

anne-lise.bienvenu@chu-lyon.fr

Phone +33 6 64 27 27 03

Summary

Background

Artesunate (ART) is an artemisinin derivative used as monotherapy for the treatment of severe malaria and in combination with a partner drug for non-severe malaria. Resistance of malaria parasites to artemisinins have emerged in Southeast Asia. Adjustment of drug regimen may be an option to prevent therapeutic failures considering the relative favourable safety profile of ART high doses.

Methods

For that purpose, a systematic review was done using PubMed, Scopus and Web of Science databases. All studies on ART and DHA pharmacokinetic post-administration of artesunate in human patients or volunteers were included. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist 2009 was used.

Findings

Fifty studies exploring oral, intravenous, rectal, and intramuscular route (1470 persons, volunteers and patients) were included. Correlations between artesunate doses and C_{max} or $AUC_{0-\infty}$ of dihydroartemisinin (DHA) and DHA+ART were evaluated. This correlation was good ($R^2 > 0.9$) using intravenous (IV) route. DHA and ART+DHA average concentrations (C_{av}) were well above estimated *in vivo* half-maximal effective concentration (EC_{50}) for intravenous route, but this was not the case for oral route.

Interpretation

The favorable C_{av}/EC_{50} ratio for IV route provides an evidence that IV ART will remain efficient even in the case of increased resistance level, whereas for oral route, a two-fold increase in EC_{50} may lead to therapeutic failures, thus providing a rationale for oral dose escalation. Considering the inter-individual variability of ART pharmacokinetic, Therapeutic Drug Monitoring through antimalarial stewardship activities is needed to optimize drug exposure and avoid resistance development.

Keywords

Artesunate; Dihydroartemisinin; Pharmacokinetic; Systematic review; Correlation analysis; Inter-individual variability; Dose escalation; Average concentration over time

Introduction

Significant progresses have been made in the fight against malaria during the last decade whereas this trend stalled in the last three years (World Health Organization 2018). Intravenous (IV) artesunate (ART) is the first line drug to treat severe malaria. Where complete treatment of severe malaria is not possible but injections available, a single intramuscular (IM) dose of ART must be given as a pre-referral treatment. When IM injections of ART are not available, only children < 6 years must be treated with a single rectal dose of ART before immediate reference to a higher level facility. Artesunate is a hemisuccinate ester of dihydroartemisinin (DHA), known as the most potent compound of the class of artemisinin derivatives. Artesunate is also included in drug combination (Artemisinin-based combined therapies: ACTs) to be used orally for non-severe malaria treatment.

Resistance poses one of the greatest threats to malaria control and is responsible for increased malaria-related morbidity and mortality (Lubell et al. 2014; Oujii et al. 2018). This threat is particularly alarming as the use of ACTs, considered as the gold standard antimalarials, was demonstrated to be associated with slow parasitic clearance in South-East Asia (Imwong et al. 2017). Under-dosing of antimalarial drugs contributes in part to an increase in resistance (Barnes et al. 2008) particularly in children (Hawkes et al. 2015a, 2015b). The drug regimens remained as low as possible to obtain antimalarial effects leading to oral dose as low as 2 mg/kg to obtain high efficacy in non-severe malaria (Angus et al. 2002; Barnes et al. 2008).

It was very recently stressed that adjustments of artemisinins regimen has to be seriously considered (Wang et al. 2019). Extended treatment duration was proposed to increase parasites exposure to artemisinins in case of delayed parasite clearance phenotype. A second option could be to increase the dose of artemisinins. Most of the dose escalation studies were designed to treat orally non-severe malaria patients (Bethell et al. 2011; Metzger et al. 2012; Das et al. 2013). These studies failed to demonstrate a positive effect of dose increase on parasite clearance time, clinical and parasitological failures in the context of non-severe malaria with ART total doses no higher than 42 mg/kg (Bethell et al. 2011).

ART demonstrated anticancer activity in pre-clinical models leading to prospective studies of intravenous (IV) ART in patients with advanced malignancies (Hou et al. 2008; Krishna et al. 2015; Picot 2015; von Hagens et al. 2017, 2019;). One of these studies determined the maximum tolerated dose to be as high as 18 mg/kg using a D1/D8, 3 weeks cycle of administration (108 mg/kg total dose) (Deeken et al. 2018) higher than maximum

recommended doses to treat severe malaria (IV: 4 mg/kg bw/dose, IR:10 mg/kg bw) and higher than dose-escalation studies performed during non-severe malaria (Bethell et al. 2011). It should be kept in mind that 19% of patients receiving 42 mg/kg became neutropenic within 14 days during that study. Injectable artesunate during severe malaria were proved to be associated with a low incidence of adverse events including post-artemisinin delayed haemolysis (PADH) (Fanello et al. 2017; Roussel et al. 2017). A wide therapeutic window, as well as the relative favorable safety profile of ART, may give an opportunity to re-assess the ART regimen in malaria, based on pharmacokinetics (PK) and pharmacodynamics (PD) information.

The need for more PK and PD controlled studies of accurate antimalarial drugs has been stressed a decade ago (Barnes et al. 2008). The PK and PD properties of ART were extensively described but some degrees of uncertainties remained, supporting an extensive review of literature. Data from an increasing number of studies have been accumulated since the last comprehensive review in 2011 and more recent reviews were focusing on the impact of resistance on pharmacodynamics properties in non-severe malaria (Morris et al. 2011a; Das et al. 2017, 2018). It is expected that this data analysis would provide significant contribution on pharmacokinetics.

Methods

Bibliographic research

An extensive research for studies published before January 2019 was made using three databases: MEDLINE, Web of science (WoS) and Scopus. Keys words of interest were “artesunate” and “pharmacokinetic”. Search details are as follow: ("artesunate"[MeSH Terms] OR "artesunate"[All Fields]) AND (pharmacokinetic[All Fields] OR pharmacokinetic'[All Fields] OR pharmacokinetic,[All Fields] OR pharmacokinetica[All Fields] OR pharmacokinetical[All Fields] OR pharmacokinetically[All Fields] OR pharmacokinetician[All Fields] OR pharmacokineticians[All Fields] OR pharmacokineticist[All Fields] OR pharmacokineticists[All Fields] OR pharmacokineticly[All Fields] OR pharmacokineticparameters[All Fields] OR pharmacokineticpharmacodynamic[All Fields] OR pharmacokineticpharmacodynamics[All Fields] OR pharmacokineticproperties[All Fields] OR pharmacokineticrich[All Fields] OR pharmacokinetics[All Fields] OR pharmacokinetics'[All Fields] OR pharmacokinetics,[All Fields] OR pharmacokineticsand[All Fields] OR

pharmacokineticsclinical[All Fields] OR pharmacokineticscsir[All Fields] OR pharmacokineticsgermany[All Fields] OR pharmacokineticsishenyang[All Fields] OR pharmacokineticism[All Fields] OR pharmacokineticspharmacodynamics[All Fields] OR pharmacokineticstudiesconductedinalbinospraguedawleyratsshowed[All Fields] OR pharmacokineticstype[All Fields]) for PUBMED MEDLINE; TOPIC: (artesunate) AND TOPIC: (pharmacokinetic*) for Web of Science; (TITLE-ABS-KEY (artesunate) AND TITLE-ABS-KEY (pharmacokinetic*)) for Scopus. No filter or date limitation were used. To increase the completeness of the search, a snowballing approach was used. The duplicates were removed. The remaining papers were then assessed for eligibility by one author (YIK), based on their abstract, title and key words. The full texts of the eligible records were assessed to determine those to be included. Inclusion and exclusion criterion were established *a priori*. All studies on ART and DHA pharmacokinetic post-administration of ART in human patients or volunteers were included. Reviews, studies in which PK parameters were expressed in DHA equivalents and/or antimalarial activities (results of bioassays), and studies on population PK, were not included.

Data management

The PRISMA checklist 2009 was used as a methodological support of the systematic review. PK data was extracted from the included studies by one author (YIK) and an independent sampling of those data was done by another author (AL) to insure their correctness. Information collected included first author, year of publication, type and geographical origins of subjects included, ART and DHA PK parameters, ART regimens and the sampling and analytical protocols. When different physiological status (adults, pregnant women, children) were mixed in a same cohort, the PK data of such cohort were not collected . PK parameters expressed as medians were not used in statistical analysis. When the dose expressed in mg/kg was not available whereas the mean weight of a population group was, it was calculated. PK parameters units were harmonized to allow comparison between data.

Statistical analysis

Correlation analyses were done to evaluate the impact of ART regimen on PK. The dose-dependent PK parameters (maximal plasmatic concentration (C_{max}) and area under the concentration-time curve ($AUC_{0-\infty}$))

were expressed as functions of the dose (mg/kg of body weight). R^2 was obtained for ART and DHA taken and for their sum (ART+DHA). When the dose of ART administered could not be retrieved or calculated in a study, the dose-dependent PK parameters were excluded from the correlation analysis. The impact of ART and DHA exposure in terms of anti-parasitic efficacy was evaluated by calculating the average concentration over time (C_{av} , $\mu\text{g/L}$) of DHA and ART+DHA in patients after *per os* (PO) and IV ART and comparing them with the half-maximal effective concentration (EC_{50} , $9.92 \mu\text{g/L}$) of DHA (Das et al. 2017). It was assumed that the ART EC_{50} was equivalent to DHA EC_{50} . C_{av} were calculated using the formula: $C_{av} = \frac{AUC_{0-\infty} \text{ (for a single dose of ART)}}{24 \text{ (PO) or } 8 \text{ (IV)}}$ (note that $AUC_{0-\infty}$ after a single dose is equal to AUC over a dosing interval at steady-state). C_{av} and C_{av}/EC_{50} were calculated separately for ART and DHA and sums of the C_{av} and C_{av}/EC_{50} (ART+DHA) were then calculated). A correlation analysis between DHA C_{av} and ART+DHA C_{av} and ART dose was performed. Variability of dose-independent PK parameters ($t_{1/2}$, T_{max} , V_d , and CL) was evaluated using their coefficient of variation (CV). Analysis of variance (ANOVA) was used to compare dose-independent PK parameters of *per os* (PO) ART administered alone and in combination. Mann-Whitney rank sum tests were performed to compare dose-independent PK parameters of volunteers and patients for IV and PO routes. All statistical tests were done using BiostatTGV (Inserm, France, <https://biostatgv.sentiweb.fr/?module=tests>) with a significant level of $p \leq 0.050$.

Results

Included studies

The literature search identified 1207 records through three different sources: 297 for MEDLINE, 386 for SCOPUS and 524 for WoS (figure 1). After removal of the duplicates, the remaining studies ($n=720$) were screened. In total, 652 records were excluded as they did not meet the previous selection criteria. The 68 eligible remaining ones were assessed in detail. Fifty studies were included (table 1). The reasons for exclusion of the 18 studies were the expression of the PK parameters in DHA equivalents and/or antimalarial activity ($n=8$) and the description of populations PK models only ($n=10$).

Global population description

The included studies were published between 1997 and 2018 (figure 2). Most of the studies (54%, 27/50) were conducted in South-East Asian countries, mainly in Thailand (10/27) and Vietnam (9/27). The other studies were conducted in Africa (34%, 17/50) and in other continents such as North America, Oceania and Europa (12%, 6/50). The global population (n=1470) corresponds to volunteers (all non-pregnant adults, n=479, 32.6%) and patients (n=991, 67.4%). Among patients, 856 (58.2%) had non-severe *falciparum* malaria (NS), 112 (7.6%), severe *falciparum* malaria, and 23 (1.6%), a malaria-infection caused by *P. vivax*. The patients were also segregated as follow: non-pregnant adults (n=688, 46.8%), pregnant women (n=90, 6.1%), and children (n=213, 14.5%). Adults were defined as people of 15 years and above.

Sampling regimen and Analytical methods

There was a significant variability in sampling regimen (figure 3). In most cases, heparin (lithium or potassium) was used (38%, 19/50) as anticoagulant, followed by fluoride-oxalate derivatives (32%, 16/50) and EDTA (2%, 1/50). For 14 studies (28%, 14/50), there were no indications on the anticoagulant used. The plasma was stored at least below -20°C (range: -20 to -80°C) until analytical procedures; for the samples stored at -20°C and -25°C, fluoride-oxalate was used in most cases (6/7). There were three different techniques to quantify ART and DHA including high-pressure LC-MS/MS (56%, 28/50), HPLC with electrochemical detection (HPLC-ECD, 22%, 11/50), and HPLC with subsequent UV detection (20%, 10/50). One article did not specify the HPLC method used to quantify ART and DHA (Sinou et al. 2009).

Population and studies description sort by administration route

Doses of ART administrated and distribution of studies sorted per route of administration are described in table 2. IV route was unfrequently used to explore the PK of ART and DHA (figure 4). The drug was administered as a 2 min infusion (8/13), a bolus of less than five seconds (1/13), a slow-bolus of 3–4 min (1/13), a 4 h infusion (1/13), or by other unspecified protocols (3/13). Oral route was the most used (38/50 studies) (figure 4). Artesunate was administered as tablets, powder or granules, alone (17/38) or coadministered with another drug (21/38). For coadministrations, seven studies used ART + mefloquine (MQ, n=212), seven studies ART + amodiaquine (AMQ, n=140), one study ART + pyronaridine (n=57), and six

other studies ART + either azithromycin (1/38, n=18), sulfadoxine/pyrimethamine (1/38, n=16), pyronaridine-ritonavir (1/38, n=33), chlproguanil-dapsone (1/38, n=86), nevirapine-amodiaquine (1/38, n=21), or pyronaridine-primaquine (1/38, n=15) for a total population of 598 (n=260 volunteers and n=338 patients). Oral ART was taken with water after a period of fasting (11/38), with milk (1/38) (Kyaw et al. 2013), independently of meals (1/38) (Krudsood et al. 2010), after a meal (1/38) (Valea et al. 2014), or using other protocols (24/38). Five studies out of 50 explored IR route and three, IM route (figure 4). Out of the 68 patients of the intrarectal (IR) group, the 24 volunteers received their dose after an overnight fast. For IM route, ART was administered in the anterior thigh (2/3, n=30) or in the gluteal muscle (1/3, n=11).

PK-PD data obtained after IV administration of ART

Mean and median values of C_{\max} and $AUC_{0-\infty}$ are presented in table 3. The correlation analysis of dose-dependent parameters (DHA C_{\max} (figure 5) and DHA $AUC_{0-\infty}$ (figure 6)) obtained for the whole population and the volunteers, demonstrated R^2 above 0.920 except for DHA C_{\max} ($R^2=0.656$) in the whole population. The correlation analysis of the sum (ART+DHA) of C_{\max} (figure 5) and $AUC_{0-\infty}$ (figure 6) showed R^2 above 0.970 for the whole population and for volunteers. No correlation analysis was performed in patient groups because of limited data. Mean and median values of T_{\max} (time to maximal plasmatic concentration), $t_{1/2}$ (half-life), Vd (volume of distribution), and CL (clearance), for ART and DHA are presented in table 3. ART and DHA $t_{1/2}$ were significantly longer ($p=0.018$ and $p=0.012$ respectively) in volunteers (9.17 ± 3.96 min for ART and 79.06 ± 25.01 min for DHA) than in patients (4.07 ± 2.61 min for ART and 51.78 ± 14.27 min for DHA). DHA Vd was significantly increased ($p=0.00016$) in volunteers (1.97 ± 0.31 L/kg) than in patients (0.83 ± 0.16 L/kg) and ART CL was significantly reduced ($p=0.022$) in volunteers (1.67 ± 0.56 L/h/kg) than in patients (2.40 ± 0.59 L/h/kg).

PK-PD data obtained after PO administration of ART

Mean and median values of C_{\max} and $AUC_{0-\infty}$ are presented in table 3. The correlation analysis of dose-dependent parameters (DHA C_{\max} (figure 7) and DHA $AUC_{0-\infty}$ (figure 8)) were obtained for the whole population, volunteers, and patients. The correlation of C_{\max} (figure 7) and $AUC_{0-\infty}$ (figure 8) was improved using the sum of ART+DHA. The very low correlation between C_{\max} and doses in volunteers could be

explained by the tight dose-range tested. DHA and ART+DHA C_{av} and C_{av}/EC_{50} were calculated for patients after oral administration of ART (table 3). The correlation analysis demonstrated that C_{av} increased with ART dose after oral administration (figure 9). Mean and median values of T_{max} , $t_{1/2}$, Vd/F (apparent volume of distribution), and CL/F (apparent clearance) for ART and DHA are presented in table 3. ART and DHA $t_{1/2}$ were significantly shorter ($p=0.011$ and $p=0.0034$ respectively) in people who received ART alone (0.50 ± 0.05 h for ART and 0.94 ± 0.39 h for DHA) than in people who received ART in combination with AMQ (0.82 ± 0.46 h for ART and 1.64 ± 0.70 h for DHA). DHA $t_{1/2}$ was also significantly shorter ($p=0.043$) after administration of ART alone (0.94 ± 0.39 h) than after administration of ART with pyronaridine (1.30 ± 0.51 h). ART Vd/F and CL/F were significantly reduced when ART was administered alone (11.92 ± 3.06 L/kg and 16.88 ± 4.04 L/h/kg respectively; $p=0.029$) than when administered in combination with pyronaridine (32.50 ± 7.00 L/kg and 28.00 ± 2.16 L/h/kg respectively; $p=0.029$). DHA $t_{1/2}$ was significantly longer ($p=0.043$) in volunteers (1.38 ± 0.66 h) than in patients (0.95 ± 0.19 h).

Discussion

The artemisinin derivatives are the most potent antimalarial drugs currently used, with artesunate being the first line treatment for severe malaria. A number of cases of delayed haemolytic anaemia after injectable artesunate for severe malaria have been described, but successfully managed with transfusions. However, according to the Experts Group Meeting on delayed haemolytic anaemia following treatment with injectable artesunate, the high clinical benefits of artesunate compared to quinine must be emphasized to ensure the continued use of injectable artesunate considered as a life-saving treatment in severe malaria. Healthcare professionals should be made aware of the potential of ART for haemolytic anaemia and the need for continued monitoring of patients for up to one month post treatment, particularly those with high pre-treatment parasitaemia. Increased failure rates were firstly reported in south-east Asia and more recently in Africa (Huong et al. 2001; Sahr et al. 2001; Dondorp et al. 2009). The present study was an extensive review of ART and DHA PK parameters after PO, IV, IM, and IR routes. Fifty studies were compiled giving us an overview for the last 22 years (1997-2018). A limitation of this review could be related to grey literature that may have been missed. The discrepancies between the methods used including drug dosages, fasting or not, sampling time, ART and DHA dosage methods, and data reports (mean, median), were taken into account. The impact

of these discrepancies demonstrated by the great CV of some dose-independent PK parameters, remained probably low compared to the overall results.

Inter-individual variability may be linked to physiological and pathological differences between subjects (Morris et al. 2011a). In children under 2, the immaturity of enzyme systems may impact the metabolism of drugs (Hines 2007). Studies on population PK in children (2/3) or in children and adults (1/3) found weight and/or age to be a significant covariable on DHA Vd after rectal or PO administration (Karunajeewa et al. 2004; Simpson et al. 2006; Stepniewska et al. 2009). Pregnancy may also modify drug processing (Pariante et al. 2016)., It was reported that pregnancy was associated with a decrease in DHA total exposure ($AUC_{0-\infty}$) coupled with higher plasma drug concentrations after PO administration of ART (Morris et al. 2011b; Onyamboko et al. 2011) as a consequence of an increase in DHA clearance (Onyamboko et al. 2011). Another study exploring the oral route (Valea et al. 2014) reported an increase in ART total exposure due to deteriorated clearance . A study of the IV route concluded to an overall similarity of the PK parameters between pregnant women and the same three month postpartum women (McGready et al. 2012). Effect of food intake was also identified as a significant factor affecting ART absorption rate constant with a reduction in absorption of 84% if ART was administered with a high calorie meal (Tan et al. 2009). The malaria-infection was also reported to have an impact on ART PK (Binh et al. 2001; Teja-Isavadharm et al. 2001; McGready et al. 2012). Acute malaria was reported to reduce the pre-systemic biotransformation of ART thus increasing the oral bioavailability and plasma concentration (McGready et al. 2012). Disease-related reduction of first-pass glucuronidation led to an increase in plasma concentration of DHA (McGready et al. 2012). In two other studies (Binh et al. 2001; Teja-Isavadharm et al. 2001), C_{max} and $AUC_{0-\infty}$ of DHA were significantly higher in patients than in volunteers. DHA $t_{1/2}$ was shorter for patients compared to volunteers for IV and oral routes, as well as ART $t_{1/2}$ for IV route. Moreover, there was a significant decrease in DHA Vd and increase in ART CL for patients treated with intravenous ART. These observations may be a consequence of an increased binding of drugs to alpha-1-acid glycoprotein during acute malaria leading to a reduction in the apparent volume of distribution (Meshnick et al. 1996). Combination of ART with amodiaquine led to a longer DHA $t_{1/2}$ whereas no significant influence of pyronaridine on ART and DHA PK was reported (Orrell et al. 2008; Tan et al. 2009).

The differences in studies' methodology, including the sampling time are another source of variability which limits the reproducibility of PK data. After IV administration of ART, blood sampling should start in the minutes after dosing because of the short ART $t_{1/2}$. The anticoagulant used may also impact the PK parameters (Lindegardh et al. 2008): fluoride-oxalate, by disabling the plasma esterases, reduces the *ex-vivo* degradation of ART into DHA and is also responsible for blood cells shrinkage which increases plasma volume. Fluoride-oxalate was used as the anticoagulant in 16/50 studies. The differences in sensitivity of the analytical method is another potential source of variability (Morris et al. 2011a). Inter-individual variability due to fast or slow metabolizers has not been described for ART.

It is of interest to anticipate the issue of potential decreased artesunate efficacy during severe malaria in a context of rise of artemisinin resistance in non-severe malaria. The first step was to provide a comprehensive review of the pharmacokinetic properties of ART and DHA through correlation analyses and C_{av} calculations. For IV administration, a positive correlation between dose and C_{max} ($R^2=0.99$) or $AUC_{0-\infty}$ ($R^2=0.97$) was found in volunteers. The previous correlation analysis was essentially based on two studies (Li et al. 2009; Miller et al. 2012) made by the same research team. For oral route, a positive correlation was found for C_{max} in patients ($R^2 = 0.9$) but not in volunteers ($R^2=0.5$). As expected, correlation analyses were improved if ART and DHA PK parameters were summed. These analyses demonstrated a linear relationship between ART dose and some PK parameters for IV and oral routes. DHA and ART+DHA C_{av} increased with dose escalation of ART after oral administration, as demonstrated by correlation analyses. Intravenous route led to C_{av} values of 340 to 566 $\mu\text{g/L}$, well above *in vivo* EC_{50} value (9.92 $\mu\text{g/L}$) (Das et al. 2017). Oral route led to C_{av} values of 22 to 123 $\mu\text{g/L}$. Thus, the ratio C_{av}/EC_{50} is much higher for intravenous route (34 to 57) than for oral route (2.5 to 13.4). This difference means that in the case of increase in the *in vivo* half-maximal effective concentration due to resistance, the therapeutic window will remain highly favorable for intravenous route but will be limited for oral route. Assuming a concentration dependent parasite killing (Das et al. 2017), an increase in C_{av} may have an impact on parasite clearance time. Besides C_{av} , another key determinant of outcome during severe malaria is the interval from starting treatment to the time to maximal plasmatic concentration (T_{max}) (Barnes et al. 2008). This T_{max} is approximately 2 minutes for intravenous ART and 7 to 24 minutes for DHA, leading to excellent efficacy provided the C_{max} is higher than the minimum parasitocidal concentrations (MPC). The MPC in blood to clear the parasites during severe malaria is not experimentally documented. One could suspect that

the MPC during severe malaria is different from the MPC during non-severe malaria due to the role of parasites sequestration in the brain vasculature and the effect of high parasitemias. The challenge of obtaining prospectively *in vivo* MPC of antimalarial drugs was recalled while this threshold was successfully estimated for the new antimalarial cipargamin (Halpaap et al. 1998; Na-Bangchang et al. 1998).

Considering the great inter-individual variability of ART and DHA PK parameters, Therapeutic Drug Monitoring (TDM) is a cornerstone in the fight against ART resistance development (Bienvenu et al. 2019) and the management of ART side effects such as delayed haemolysis or neutropenia linked to high doses (Bethell et al. 2011). TDM may be promote through antimalarial stewardship programs which goal are to optimize clinical outcomes while minimizing unintended consequences of drug use, including emergence of resistance, selection of pathogenic organisms, and toxicity.

Author contribution

YIK performed the bibliographic search, the data collection, and prepared the first draft. MT and GL reviewed the paper. AL and GB checked the accuracy of data collection. ALB and SP launched the study, prepared the study design, analyzed data and references, wrote, and edited the manuscript.

Funding

None

Ethics approval and consent to participate

Not applicable

Conflict of interest

None

Acknowledgments

None

References

- Angus BJ, Thaiaporn I, Chanthapadith K, Suputtamongkol Y, White NJ. Oral artesunate dose-response relationship in acute falciparum malaria. *Antimicrob Agents Chemother*. 2002 Mar;46(3):778–82.
- Awad MI, Eltayeb IB, Baraka OZ, Behrens RH, Alkadru AMY. Pharmacokinetics of artesunate following oral and rectal administration in healthy Sudanese volunteers. *Trop Doct*. 2004 Jul;34(3):132–5.
- Barnes KI, Watkins WM, White NJ. Antimalarial dosing regimens and drug resistance. *Trends Parasitol*. 2008 Mar;24(3):127–34.
- Batty KT, Ilett KE, Powell SM, Martin J, Davis TME. Relative bioavailability of artesunate and dihydroartemisinin: investigations in the isolated perfused rat liver and in healthy Caucasian volunteers. *Am J Trop Med Hyg*. 2002 Feb 1;66(2):130–6.
- Batty KT, Le AT, Ilett KF, Nguyen PT, Powell SM, Nguyen CH, et al. A pharmacokinetic and pharmacodynamic study of artesunate for vivax malaria. *Am J Trop Med Hyg*. 1998a Nov;59(5):823–7.
- Batty KT, Thu LT, Davis TM, Ilett KF, Mai TX, Hung NC, et al. A pharmacokinetic and pharmacodynamic study of intravenous vs oral artesunate in uncomplicated falciparum malaria. *Br J Clin Pharmacol*. 1998b Feb;45(2):123–9.
- Benakis A, Paris M, Loutan L, Plessas CT, Plessas ST. Pharmacokinetics of artemisinin and artesunate after oral administration in healthy volunteers. *Am J Trop Med Hyg*. 1997 Jan;56(1):17–23.
- Bethell D, Se Y, Lon C, Tyner S, Saunders D, Sriwichai S, et al. Artesunate dose escalation for the treatment of uncomplicated malaria in a region of reported artemisinin resistance: a randomized clinical trial. *PLoS One*. 2011;6(5):e19283.
- Bienvenu A-L, Djimdé A, Picot S. Antimalarial stewardship programs are urgently needed for malaria elimination: a perspective. *Parasite Paris Fr*. 2019;26:16.
- Binh TQ, Ilett KF, Batty KT, Davis TME, Hung NC, Powell SM, et al. Oral bioavailability of dihydroartemisinin in Vietnamese volunteers and in patients with falciparum malaria. *Br J Clin Pharmacol*. 2001 Jun;51(6):541–6.
- Byakika-Kibwika P, Lamorde M, Mayito J, Nabukeera L, Mayanja-Kizza H, Katabira E, et al. Pharmacokinetics and pharmacodynamics of intravenous artesunate during severe malaria treatment in Ugandan adults. *Malar J*. 2012;11(1):132.
- Chanthap L, Tsuyuoka R, Na-Bangchang K, Nivanna N, Suksom D, Sovannarith T, et al. Investigation of bioavailability, pharmacokinetics and safety of new pediatric formulations of artesunate and mefloquine. *Southeast Asian J Trop Med Public Health*. 2005 Jan;36(1):34–43.
- Chinh NT, Quang NN, Anh CX, Thanh NX, Dai B, Birrell GW, et al. Pharmacokinetics and Ex Vivo Antimalarial Activity of Artesunate-Azithromycin in Healthy Volunteers. *Antimicrob AGENTS Chemother*. 2011 Sep;55(9):4412–4415.
- Das D, Tripura R, Phyo AP, Lwin KM, Tarning J, Lee SJ, et al. Effect of high-dose or split-dose artesunate on parasite clearance in artemisinin-resistant falciparum malaria. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2013 Mar;56(5):e48-58.

- Das JL, Dondorp AM, Nosten F, Phyo AP, Hanpithakpong W, Ringwald P, et al. Population Pharmacokinetic and Pharmacodynamic Modeling of Artemisinin Resistance in Southeast Asia. *AAPS J*. 2017 Nov;19(6):1842–1854.
- Das JPL, Kyaw MP, Nyunt MH, Chit K, Aye KH, Aye MM, et al. Population pharmacokinetic and pharmacodynamic properties of artesunate in patients with artemisinin sensitive and resistant infections in Southern Myanmar. *Malar J*. 2018 Mar;17.
- Davis TME, England M, Dunlop A-M, Page-Sharp M, Cambon N, Keller TG, et al. Assessment of the Effect of Mefloquine on Artesunate Pharmacokinetics in Healthy Male Volunteers. *Antimicrob Agents Chemother*. 2007 Mar;51(3):1099–101.
- Davis TME, Phuong HL, Ilett KF, Hung NC, Batty KT, Phuong VDB, et al. Pharmacokinetics and Pharmacodynamics of Intravenous Artesunate in Severe Falciparum Malaria. *Antimicrob Agents Chemother*. 2001 Jan 1;45(1):181–6.
- Deeken JF, Wang H, Hartley M, Cheema AK, Smaglo B, Hwang JJ, et al. A phase I study of intravenous artesunate in patients with advanced solid tumor malignancies. *CANCER Chemother Pharmacol*. 2018 Mar;81(3):587–596.
- Diem Thuy LT, Ngoc Hung L, Danh PT, Na-Bangchang K. Absence of time-dependent artesunate pharmacokinetics in healthy subjects during 5-day oral administration. *Eur J Clin Pharmacol*. 2008 Oct;64(10):993–8.
- Dondorp AM, Nosten F, Yi P, Das D, Phyo AP, Tarning J, et al. Artemisinin Resistance in Plasmodium falciparum Malaria. *N Engl J Med*. 2009 Jul 30;361(5):455–67.
- Fanello C, Onyamboko M, Lee SJ, Woodrow C, Setaphan S, Chotivanich K, Buffet P, Jauréguiberry S, Rockett K, Stepniewska K, Day NPJ, White NJ, Dondorp AM. Post-treatment haemolysis in African children with hyperparasitaemic falciparum malaria; a randomized comparison of artesunate and quinine. *BMC Infect Dis*. 2017 Aug 17;17(1):575.
- Fehintola FA, Scarsi KK, Ma Q, Parikh S, Morse GD, Taiwo B, et al. Nevirapine-Based Antiretroviral Therapy Impacts Artesunate and Dihydroartemisinin Disposition in HIV-Infected Nigerian Adults. *AIDS Res Treat* [Internet]. 2012 [cited 2018 Nov 19];2012. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3303559/>
- Fortin A, Verbeeck RK, Jansen FH. Comparative oral bioavailability of non-fixed and fixed combinations of artesunate and amodiaquine in healthy Indian male volunteers. *Eur J Clin Pharmacol*. 2011 Mar;67(3):267–75.
- von Hagens C, Walter-Sack I, Goeckenjan M, Osburg J, Storch-Hagenlocher B, Sertel S, et al. Prospective open uncontrolled phase I study to define a well-tolerated dose of oral artesunate as add-on therapy in patients with metastatic breast cancer (ARTIC M33/2). *Breast Cancer Res Treat*. 2017 Jul;164(2):359–69.
- von Hagens C, Walter-Sack I, Goeckenjan M, Storch-Hagenlocher B, Sertel S, Elsässer M, et al. Long-term add-on therapy (compassionate use) with oral artesunate in patients with metastatic breast cancer after participating in a phase I study (ARTIC M33/2). *Phytomedicine Int J Phytother Phytopharm*. 2019 Feb 15;54:140–8.
- Halpaap B, Ndjave M, Paris M, Benakis A, Kremsner PG. Plasma levels of artesunate and dihydroartemisinin in children with Plasmodium falciparum malaria in Gabon after administration of 50-milligram artesunate suppositories. *Am J Trop Med Hyg*. 1998 Mar;58(3):365–8.

- Hawkes M, Conroy AL, Opoka RO, Namasopo S, Zhong K, Liles WC, et al. Slow Clearance of Plasmodium falciparum in Severe Pediatric Malaria, Uganda, 2011-2013. *Emerg Infect Dis*. 2015a Jul;21(7):1237–9.
- Hawkes MT, Forgie S, Brophy J, Crockett M. Artesunate treatment of severe pediatric malaria: A review of parasite clearance kinetics and clinical implications. *Can J Infect Dis Med Microbiol J Can Mal Infect Microbiol Medecale*. 2015b Oct;26(5):237–40.
- Hien TT, Davis TME, Chuong LV, Ilett KF, Sinh DXT, Phu NH, et al. Comparative Pharmacokinetics of Intramuscular Artesunate and Artemether in Patients with Severe Falciparum Malaria. *Antimicrob Agents Chemother*. 2004 Nov 1;48(11):4234–9.
- Hines RN. Ontogeny of human hepatic cytochromes P450. *J Biochem Mol Toxicol*. 2007;21(4):169–75.
- Hou J, Wang D, Zhang R, Wang H. Experimental therapy of hepatoma with artemisinin and its derivatives: in vitro and in vivo activity, chemosensitization, and mechanisms of action. *Clin Cancer Res Off J Am Assoc Cancer Res*. 2008 Sep 1;14(17):5519–30.
- Huong NM, Hewitt S, Davis TM, Dao LD, Toan TQ, Kim TB, et al. Resistance of Plasmodium falciparum to antimalarial drugs in a highly endemic area of southern Viet Nam: a study in vivo and in vitro. *Trans R Soc Trop Med Hyg*. 2001 Jun;95(3):325–9.
- Ilett KF, Batty KT, Powell SM, Binh TQ, Thu LTA, Phuong HL, et al. The pharmacokinetic properties of intramuscular artesunate and rectal dihydroartemisinin in uncomplicated falciparum malaria: Pharmacokinetics of artesunate and dihydroartemisinin. *Br J Clin Pharmacol*. 2002 Jan 11;53(1):23–30.
- Imwong M, Suwannasin K, Kunasol C, Sutawong K, Mayxay M, Rekol H, et al. The spread of artemisinin-resistant Plasmodium falciparum in the Greater Mekong subregion: a molecular epidemiology observational study. *Lancet Infect Dis*. 2017;17(5):491–7.
- Jittamala P, Pukrittayakamee S, Ashley EA, Nosten F, Hanboonkunupakarn B, Lee SJ, et al. Pharmacokinetic Interactions between Primaquine and Pyronaridine-Artesunate in Healthy Adult Thai Subjects. *Antimicrob Agents Chemother*. 2015 Jan;59(1):505–13.
- Karbwang J, Na-Bangchang K, Congpoung K, Thanavibul A, Harinasuta T. Pharmacokinetics of Oral Artesunate in Thai Patients with Uncomplicated Falciparum Malaria: *Clin Drug Investig*. 1998;15(1):37–43.
- Karunajeewa HA, Ilett KF, Dufall K, Kemiki A, Bockarie M, Alpers MP, et al. Disposition of Artesunate and Dihydroartemisinin after Administration of Artesunate Suppositories in Children from Papua New Guinea with Uncomplicated Malaria. *Antimicrob Agents Chemother*. 2004 Aug 1;48(8):2966–72.
- Krishna S, Ganapathi S, Ster IC, Saeed MEM, Cowan M, Finlayson C, et al. A Randomised, Double Blind, Placebo-Controlled Pilot Study of Oral Artesunate Therapy for Colorectal Cancer. *EBioMedicine*. 2015 Jan;2(1):82–90.
- Krishna S, Planche T, Agbenyega T, Woodrow C, Agranoff D, Bedu-Addo G, et al. Bioavailability and Preliminary Clinical Efficacy of Intrarectal Artesunate in Ghanaian Children with Moderate Malaria. *Antimicrob Agents Chemother*. 2001 Feb 1;45(2):509–16.
- Krudsood S, Looareesuwan S, Tangpukdee N, Wilairatana P, Phumratanaprapin W, Leowattana W, et al. New Fixed-Dose Artesunate-Mefloquine Formulation against Multidrug-Resistant Plasmodium falciparum in Adults: a Comparative Phase IIb Safety and Pharmacokinetic Study with Standard-Dose Nonfixed Artesunate plus Mefloquine. *Antimicrob Agents Chemother*. 2010 Sep;54(9):3730–7.

- Kyaw MP, Nyunt MH, Chit K, Aye MM, Aye KH, Aye MM, et al. Reduced susceptibility of *Plasmodium falciparum* to artesunate in southern Myanmar. *PLoS One*. 2013;8(3):e57689.
- Li Q, Cantilena LR, Leary KJ, Saviolakis GA, Miller RS, Melendez V, et al. Pharmacokinetic profiles of artesunate after single intravenous doses at 0.5, 1, 2, 4, and 8 mg/kg in healthy volunteers: a phase I study. *Am J Trop Med Hyg*. 2009 Oct;81(4):615–21.
- Li Q, Remich S, Miller SR, Ogutu B, Otieno W, Melendez V, et al. Pharmacokinetic evaluation of intravenous artesunate in adults with uncomplicated *falciparum* malaria in Kenya: a phase II study. *Malar J*. 2014 Jul 22;13:281.
- Lindegardh N, Hanpithakpong W, Kamanikom B, Singhasivanon P, Socheat D, Yi P, et al. Major pitfalls in the measurement of artemisinin derivatives in plasma in clinical studies. *J Chromatogr B*. 2008 Dec;876(1):54–60.
- Liu Y, Hu C, Liu G, Jia J, Yu C, Zhu J, et al. A Replicate Designed Bioequivalence Study To Compare Two Fixed-Dose Combination Products of Artesunate and Amodiaquine in Healthy Chinese Volunteers. *Antimicrob Agents Chemother*. 2014 Oct;58(10):6009–15.
- Lubell Y, Dondorp A, Guérin PJ, Drake T, Meek S, Ashley E, et al. Artemisinin resistance--modelling the potential human and economic costs. *Malar J*. 2014 Nov 23;13:452.
- Matar KM, Awad AI, Elamin SB. Pharmacokinetics of Artesunate Alone and in Combination with Sulfadoxine/Pyrimethamine in Healthy Sudanese Volunteers. *Am J Trop Med Hyg*. 2014 Jun 4;90(6):1087–93.
- McGready R, Phyo AP, Rijken MJ, Tarning J, Lindegardh N, Hanpithakpon W, et al. Artesunate/dihydroartemisinin pharmacokinetics in acute *falciparum* malaria in pregnancy: absorption, bioavailability, disposition and disease effects: ARS and DHA pharmacokinetics in pregnancy. *Br J Clin Pharmacol*. 2012 Mar;73(3):467–77.
- Meshnick SR, Taylor TE, Kamchonwongpaisan S. Artemisinin and the antimalarial endoperoxides: From herbal remedy to targeted chemotherapy. *Microbiol Rev*. 1996;60(2):301–15.
- Metzger WG, Magris M, Vivas-Martínez S, Giron A, Brooms JD, Villalobos N, et al. High dose artesunate in combination with mefloquine: pharmacovigilance in the Venezuelan Amazon. *Trans R Soc Trop Med Hyg*. 2012 Mar;106(3):196–8.
- Miller AK, Bandyopadhyay N, Wootton DG, Duparc S, Kirby PL, Winstanley PA, et al. Pharmacokinetics of chlorproguanil, dapsone, artesunate and their major metabolites in patients during treatment of acute uncomplicated *Plasmodium falciparum* malaria. *Eur J Clin Pharmacol*. 2009 Oct;65(10):977–87.
- Miller R, Li Q, Cantilena LR, Leary KJ, Saviolakis GA, Melendez V, et al. Pharmacokinetic profiles of artesunate following multiple intravenous doses of 2, 4, and 8 mg/kg in healthy volunteers: Phase 1b study. *Malar J*. 2012;11(1):255.
- Morris CA, Duparc S, Borghini-Fuhrer I, Jung D, Shin C-S, Fleckenstein L. Review of the clinical pharmacokinetics of artesunate and its active metabolite dihydroartemisinin following intravenous, intramuscular, oral or rectal administration. *Malar J*. 2011a Sep 13;10:263.
- Morris CA, Lopez-Lazaro L, Jung D, Methaneethorn J, Duparc S, Borghini-Fuhrer I, et al. Drug-Drug Interaction Analysis of Pyronaridine/Artesunate and Ritonavir in Healthy Volunteers. *Am J Trop Med Hyg*. 2012 Mar 1;86(3):489–95.

- Morris CA, Onyamboko MA, Capparelli E, Koch MA, Atibu J, Lokomba V, et al. Population pharmacokinetics of artesunate and dihydroartemisinin in pregnant and non-pregnant women with malaria. *Malar J*. 2011b;10(1):114.
- Mwesigwa J, Parikh S, McGee B, German P, Drysdale T, Kalyango JN, et al. Pharmacokinetics of Artemether-Lumefantrine and Artesunate-Amodiaquine in Children in Kampala, Uganda. *Antimicrob Agents Chemother*. 2010 Jan 1;54(1):52–9.
- Na-Bangchang K, Karbwang J, Congpoung K, Thanavibul A, Ubalee R. Pharmacokinetic and bioequivalence evaluation of two generic formulations of oral artesunate. *Eur J Clin Pharmacol*. 1998 Jan;53(5):375–6.
- Na-Bangchang K, Krudsood S, Silachamroon U, Molunto P, Tasanor O, Chalermrut K, et al. The pharmacokinetics of oral dihydroartemisinin and artesunate in healthy Thai volunteers. *Southeast Asian J Trop Med Public Health*. 2004 Sep;35(3):575–82.
- Navaratnam V, Mansor SM, Mordi MN, Akbar A, Abdullah MN. Comparative pharmacokinetic study of oral and rectal formulations of artesunic acid in healthy volunteers. *Eur J Clin Pharmacol*. 1998 Jul;54(5):411–4.
- Navaratnam V, Ramanathan S, Wahab MSAb, Siew Hua G, Mansor SM, Kiechel J-R, et al. Tolerability and pharmacokinetics of non-fixed and fixed combinations of artesunate and amodiaquine in Malaysian healthy normal volunteers. *Eur J Clin Pharmacol*. 2009 Aug;65(8):809–21.
- Nealon C, Dzeing A, Muller-Romer U, Planche T, Sinou V, Kombila M, et al. Intramuscular Bioavailability and Clinical Efficacy of Artesunate in Gabonese Children with Severe Malaria. *Antimicrob Agents Chemother*. 2002 Dec 1;46(12):3933–9.
- Newton PN, Barnes KI, Smith PJ, Evans AC, Chierakul W, Ruangveerayuth R, et al. The pharmacokinetics of intravenous artesunate in adults with severe falciparum malaria. *Eur J Clin Pharmacol*. 2006 Nov 17;62(12):1003–9.
- Onyamboko MA, Meshnick SR, Fleckenstein L, Koch MA, Atibu J, Lokomba V, et al. Pharmacokinetics and pharmacodynamics of artesunate and dihydroartemisinin following oral treatment in pregnant women with asymptomatic Plasmodium falciparum infections in Kinshasa DRC. *Malar J*. 2011;10(1):49.
- Orrell C, Little F, Smith P, Folb P, Taylor W, Olliaro P, et al. Pharmacokinetics and tolerability of artesunate and amodiaquine alone and in combination in healthy volunteers. *Eur J Clin Pharmacol*. 2008 Jul;64(7):683–90.
- Ouji M, Augereau J-M, Paloque L, Benoit-Vical F. Plasmodium falciparum resistance to artemisinin-based combination therapies: A sword of Damocles in the path toward malaria elimination. *Parasite Paris Fr*. 2018;25:24.
- Pariante G, Leibson T, Carls A, Adams-Webber T, Ito S, Koren G. Pregnancy-Associated Changes in Pharmacokinetics: A Systematic Review. *PLoS Med*. 2016 Nov;13(11):e1002160.
- Picot S. The Other Face of Artesunate: Southern Drug to Treat Northern Diseases. *EBioMedicine*. 2015 Jan;2(1):17–8.
- Ramharther M, Kurth F, Schreier AC, Nemeth J, Glasenapp I von, B elard S, et al. Fixed-Dose Pyronaridine-Artesunate Combination for Treatment of Uncomplicated Falciparum Malaria in Pediatric Patients in Gabon. *J Infect Dis*. 2008 Sep 15;198(6):911–9.

- Ramharter M, Kurth FM, B elard S, Bouyou-Akotet MK, Mamfoumbi MM, Agnandji ST, et al. Pharmacokinetics of two paediatric artesunate mefloquine drug formulations in the treatment of uncomplicated falciparum malaria in Gabon. *J Antimicrob Chemother.* 2007 Nov;60(5):1091–6.
- Rattanapunya S, Cressey TR, Rueangweerayut R, Tawon Y, Kongjam P, Na-Bangchang K. Pharmacokinetic interactions between artesunate-mefloquine and ritonavir-boosted lopinavir in healthy Thai adults. *Malar J.* 2015 Oct 9;14:400.
- Roussel C, Caumes E, Thellier M, Ndour PA, Buffet PA, Jaur guiberry S. Artesunate to treat severe malaria in travellers: review of efficacy and safety and practical implications. *J Travel Med.* 2017 Mar 1;24(2).
- Sahr F, Willoughby VR, Gbakima AA, Bockarie MJ. Apparent drug failure following artesunate treatment of *Plasmodium falciparum* malaria in Freetown, Sierra Leone: four case reports. *Ann Trop Med Parasitol.* 2001 Jul;95(5):445–9.
- Saunders D, Khemawoot P, Vanachayangkul P, Siripokasupkul R, Bethell D, Tyner S, et al. Pharmacokinetics and Pharmacodynamics of Oral Artesunate Monotherapy in Patients with Uncomplicated *Plasmodium falciparum* Malaria in Western Cambodia. *Antimicrob Agents Chemother.* 2012 Nov;56(11):5484–93.
- Simpson JA, Agbenyega T, Barnes KI, Di Perri G, Folb P, Gomes M, et al. Population pharmacokinetics of artesunate and dihydroartemisinin following intra-rectal dosing of artesunate in malaria patients. *PLoS Med.* 2006 Nov;3(11):e444.
- Sinou V, Malaika LTM, Taudon N, Lwango R, Alegre SS, Bertaux L, et al. Pharmacokinetics and pharmacodynamics of a new ACT formulation: Artesunate/Amodiaquine (TRIMALACT) following oral administration in African malaria patients. *Eur J Drug Metab Pharmacokinet.* 2009 Sep;34(3–4):133–42.
- Sirivichayakul C, Sabchareon A, Pengsaa K, Thairporn I, Chaivisuth A, Na-Bangchang K, et al. Comparative study of the effectiveness and pharmacokinetics of two rectal artesunate/oral mefloquine combination regimens for the treatment of uncomplicated childhood falciparum malaria. *Ann Trop Paediatr.* 2007 Mar;27(1):17–24.
- Stepniewska K, Taylor W, Sirima SB, Ouedraogo EB, Ouedraogo A, Gansan  A, et al. Population pharmacokinetics of artesunate and amodiaquine in African children. *Malar J.* 2009;8(1):200.
- Tan B, Naik H, Jang I-J, Yu K-S, Kirsch LE, Shin C-S, et al. Population pharmacokinetics of artesunate and dihydroartemisinin following single- and multiple-dosing of oral artesunate in healthy subjects. *Malar J.* 2009;8(1):304.
- Teja-Isavadharm P, Watt G, Eamsila C, Jongsakul K, Li Q, Keeratithakul G, et al. Comparative pharmacokinetics and effect kinetics of orally administered artesunate in healthy volunteers and patients with uncomplicated falciparum malaria. *Am J Trop Med Hyg.* 2001 Dec;65(6):717–21.
- Valea I, Tinto H, Traore/Coulibaly M, Toe LC, Lindegardh N, Tarning J, et al. Pharmacokinetics of co-formulated mefloquine and artesunate in pregnant and non-pregnant women with uncomplicated *Plasmodium falciparum* infection in Burkina Faso. *J Antimicrob Chemother.* 2014 Sep 1;69(9):2499–507.
- Walimbwa SI, Lamorde M, Waitt C, Kaboggoza J, Else L, Byakika-Kibwika P, et al. Drug Interactions between Dolutegravir and Artemether-Lumefantrine or Artesunate-Amodiaquine. *Antimicrob Agents Chemother.* 2018 Nov 12;63(2):1310-18.

Wang J, Xu C, Liao FL, Jiang T, Krishna S, Tu Y. A Temporizing Solution to “Artemisinin Resistance.” *N Engl J Med*. 2019 May 30;380(22):2087–9.

World Health Organization. World malaria report 2018. Geneva; 2018.

Zhang S, Hai T, Ilett K, Huong D, Davis T, Ashton M. Multiple dose study of interactions between artesunate and artemisinin in healthy volunteers. *Br J Clin Pharmacol*. 2001 Oct;52(4):377–385.

Table 1: Description of the studies included in the review

| Articles (ref) | Route of administration | Population treated (n) | Treatment regimen |
|-----------------------------|-------------------------|------------------------|--|
| Benakis et al. 1997 | Oral | n=6 | 6 healthy adults (Geneva) 200 mg of ART once |
| Karbwang et al. 1998 | Oral | n=11 | 11 adults with uncomplicated malaria (Thailand) 200 mg ART at T ₀ , followed by 100 mg at T _{12h} and then 100 mg once daily for another 4 days |
| Na-Bangchang et al. 1998 | Oral | n=8 | 8 healthy adults (men, Thailand) 300 mg of ART either from Guilin or Arenco formulations (crossover study) |
| Halpaap et al. 1998 | IR | n=12 | 12 children with uncomplicated <i>falciparum</i> malaria (Gabon) Rectal administration of a single 50 mg ART suppository twice a day (4h interval) |
| Navaratnam et al. 1998 | IR, Oral | n=12 | 12 healthy adults (Malaysia) Either rectal or oral administration of a single 200 mg dose or artesunate (crossover study) |
| Batty et al. 1998a | IV, Oral | n=12 | 12 adults with <i>Plasmodium vivax</i> malaria (Vietnam) 120 mg ART administered during a 2 min bolus injection at T ₀ followed by 100 mg ART administered PO at T _{8h} or vice-versa (crossover study) |
| Batty et al. 1998b | IV, Oral | n=26 | 26 adults with uncomplicated <i>falciparum</i> malaria (Vietnam) 120 mg ART administered during a 2 min bolus injection at T ₀ followed by 100 mg ART administered PO at T _{8h} or vice-versa (crossover study) |
| Davis et al. 2001 | IV | n=30 | 30 adults with severe <i>Plasmodium falciparum</i> malaria (Vietnam) 120 mg of ART (G1: with complications, n=12; G2: without complications, n=8) followed by adequate treatment to ensure healing 240 mg of ART (G3: with moderately severe complications, n=10) /by IV bolus followed by adequate treatment to ensure healing |
| Krishna et al. 2001 | IV, IR | n=34 | 34 children with moderate <i>falciparum</i> malaria (Ghana) G1: 10 mg/kg ART at T ₀ (IR) followed by 2.4 mg/kg (IV) Art at T _{12h} G2: 20 mg/kg ART at T ₀ (IR) followed by 2.4 mg/kg (IV) Art at T _{12h} G3: 2.4 mg/kg ART et T ₀ (IV) followed by 20 mg/kg ART(IR) et T _{12h} |
| Binh et al. 2001 | IV, Oral | n=25 | G1: 10 healthy Vietnamese adults, 120 mg ART at T ₀ (IV) followed by 150 mg ART and T _{8h} (Oral) G2: 7 healthy Vietnamese adults, 120 mg ART(IV) G3: 8 Vietnamese adults with uncomplicated <i>falciparum</i> malaria, 150 mg ART (Oral) |
| Teja-Isavadharm et al. 2001 | Oral | n=12 | G1: 6 adult men with uncomplicated <i>falciparum</i> malaria, 100 mg ART once (Thailand) G2: 6 healthy adult men, 100 mg ART once (Thailand) |
| Zhang et al. 2001 | Oral | n=10 | 10 healthy adults (Vietnam) 100 mg ART once |
| Ilett et al. 2002 | IV, IM | n=24 | G1: 12 adults (Vietnam) with uncomplicated <i>falciparum</i> malaria, 120 mg ART at T ₀ (IV bolus) followed by 120 mg ART at T _{8h} (IM) or vice versa (crossover arm) G2: 12 adults (Vietnam) with uncomplicated <i>falciparum</i> malaria, 120 mg ART (IV bolus) |
| Batty et al. 2002 | Oral | n=8 | 8 healthy adults (Australia) 150 mg ART once |
| Nealon et al. 2002 | IV, IM | n=28 | 28 children with severe <i>falciparum</i> malaria (Gabon) |

| Author(s) Year | Route | n | Study Description |
|----------------------------|----------|------|---|
| | | | G1: 2.4 mg/kg ART(IV) at T ₀ followed by 1.2 mg/kg ART (IM) at T _{12h} (n=11) G2: 2.4 mg/kg ART at T ₀ (IM) followed by 1.2 mg/kg ART (IV) at T _{12h} (n=10) |
| Awad et al. 2004 | Oral, IR | n=12 | 12 healthy adults (Sudan) 200 mg ART once (crossover study) |
| Na-Bangchang et al. 2004 | Oral | n=20 | 20 healthy adults (Thailand) 4 mg/kg ART once |
| Hien et al. 2004 | IM | n=9 | 9 adults with severe <i>falciparum</i> malaria (Vietnam) 2.4mg/kg ART (stat) followed by 1.2mg/kg daily |
| Chanthap et al. 2005 | Oral | n=15 | 15 healthy adults (Cambodia) 4 mg/kg ART once coadministered with mefloquine |
| Newton et al. 2006 | IV | n=17 | 17 adults with severe <i>falciparum</i> malaria (Thailand) 2.4 mg/kg at T ₀ (stat) followed by 1.2mg/kg et T _{12h} and 1.2 mg/kg once every 24h |
| Davis et al. 2007 | Oral | n=20 | 20 healthy adult men (Australia), treatment regimen in two period Period 1 (P1): 200 mg ART once a day for 3 days followed by a washout period Period 2 (P2): 200 mg ART once a day for 3 days coadministered with mefloquine |
| Sirivichayakul et al. 2007 | IR | n=17 | 17 Children with uncomplicated <i>falciparum</i> malaria (Thailand) receiving either 10 (G1) or 20 (G2) mg/kg/d ART once a day for 3 days |
| Ramharter et al. 2007 | Oral | n=24 | 24 children (Gabon) with uncomplicated <i>falciparum</i> malaria receiving either granules of a fixed ART-mefloquine formulation (GA: n=12, 4 mg/kg/d once a day for 3 days) or co-tablets blisters of another artesunate-mefloquine combination (GB: n=12, 4 mg/kg/day once a day for 3 days) |
| Orrell et al. 2008 | Oral | n=15 | 15 healthy adults (Africa) receiving either 4 mg/kg of ART alone (ART) or coadministered with amodiaquine (ACT) once (crossover study) |
| Ramharter et al. 2008 | Oral | n=60 | 60 children (Gabon) with uncomplicated <i>falciparum</i> malaria receiving coformulations tablets of ART-pyronaridine (GA, GB, GC) or coformulation granules of the same molecules (GD) Median doses of ART per group: 2.1 (n=15), 3.3 (n=15), 4.8 (n=15) and 3.8 (n=15) mg/kg/d for GA, GB, GC and GD respectively, once daily for 3 days |
| Diem Thuy et al. 2008 | Oral | n=10 | 10 healthy adult men (Vietnam) 200 mg ART once a day for 5 days |
| Dondorp et al. 2009 | Oral | n=80 | 80 patients with uncomplicated <i>falciparum</i> malaria on two sites: 40 adults and children in Cambodia and 40 adults in Thailand On each site, patients received either ART as a monotherapy (G1: 2 mg/kg/d for 7 days, n=20) or coadministered with mefloquine (G2: 4 mg/kg/d for 3 days and 10 mg/kg on day 4, n=20) |
| Navaratnam et al. 2009 | Oral | n=24 | 24 healthy adults (Malaysia) Oral administration of a fixed or a non-fixed combination of 200 mg ART coadministered with amodiaquine, once (crossover study) |
| Sinou et al. 2009 | Oral | n=13 | 13 adults with acute uncomplicated <i>falciparum</i> malaria (Democratic Republic of Congo) 200 mg ART once a day for 3 days coadministered with amodiaquine |
| Li et al. 2009 | IV | n=30 | 30 healthy adults 0.5 (G1, n=6), 1 (G2, n=6), 2 (G3, n=6), 4 (G4, n=6) or 8 (G5, n=6) mg/kg ART once (IV bolus) |
| Miller et al. 2009 | Oral | n=86 | 86 adults with acute uncomplicated <i>falciparum</i> malaria (Malawi and Gambia) 1 (n=30), 2 (n=29) or 4 mg/kg (n=27) ART once a day for 3 days |

| | | | |
|-----------------------------|----------|-------|--|
| Mwesigwa et al. 2010 | Oral | n=21 | coadministered with dapsone and chlorproguanil 21 children with uncomplicated <i>falciparum</i> malaria (Uganda) |
| Krudsood et al. 2010 | Oral | n=50 | 4 mg/kg ART twice a day for 3 days coadministered with amodiaquine 50 adults with uncomplicated <i>falciparum</i> malaria (Thailand) G1: fixed tablet of 200 mg ART with mefloquine once a day for 3 days (n=25) G2: non-fixed combination of 4 mg/kg ART with mefloquine once a day for 3 days (n=25) |
| Onyamboko et al. 2011 | Oral | n=51 | 26 pregnant women, the same 26 women at 3 months postpartum and 25 non-pregnant women with asymptomatic uncomplicated <i>falciparum</i> malaria (Democratic Republic of Congo) 200 mg ART once |
| Fortin et al. 2011 | Oral | n=60 | 60 healthy adult men (India) 100 mg ART once as a fixed (G1) or non-fixed (G2) combination with amodiaquine (crossover study) |
| Chinh et al. 2011 | Oral | n=18 | 18 healthy adults (Vietnam) 200 mg ART once a day for 3 days coadministered with azithromycin |
| Byakika-Kibwika et al. 2012 | IV | n=14 | 14 adults with severe <i>falciparum</i> malaria (Uganda) 2.4 mg/kg ART at T ₀ , T _{12h} , T _{24h} and then and once daily until oral treatment was possible |
| Fehintola et al. 2012 | Oral | n=21 | 10 HIV positive adults (Nigeria) under ARV treatment (G1) and 11 HIV positive patients without ARV treatment (G2) 200 mg ART once a day for 3 days coadministered with amodiaquine |
| Miller et al. 2012 | IV | n=24 | 24 healthy adults 2 (G1, n=8), 4 (G2, n=8) or 8 (G3, n=8) mg/kg ART once a day for 3 days |
| McGready et al. 2012 | IV, Oral | n=20 | 20 pregnant women with acute uncomplicated <i>falciparum</i> malaria and 14 of those women postpartum (Thailand) 4 mg/kg ART (IV) on day 0 followed by 4 mg/kg ART (oral) for 6 days OR 4 mg/kg ART (oral) on day 0 followed by 4 mg/kg ART (IV) on day 1 and then oral ART at the same dose daily for 5 days |
| Morris et al. 2012 | Oral | n=34 | 34 Healthy volunteers (Switzerland) Arm A: Ritonavir (day 0–day 17, n=17) with a fixed formulation of Pyronaridine-ART (day 8–day 10, n=17) Arm B: fixed formulation of pyronaridine-ART only for 3 days (n=17) ART dosing was 180 mg when < 65kg and 240 mg when ≥ 65kg |
| Saunders et al. 2012 | Oral | n=143 | 143 adults with uncomplicated <i>falciparum</i> malaria (Cambodia) 2 (G1, n=75), 4 (G2, n=40) or 6 (G3, n=28) mg/kg ART once a day for 7 days |
| Kyaw et al. 2013 | Oral | n=52 | 52 Adults with uncomplicated <i>falciparum</i> malaria (Myanmar) 4 mg/kg/ ART once a day for 7 days with 8 oz. of milk on days 0–6 |
| Matar et al. 2014 | Oral | n=16 | 16 healthy adults (Sudan) 200 mg ART once as a monotherapy or coadministered with sulfadoxine/pyrimethamine |
| Li et al. 2014 | IV | n=28 | 28 adults with uncomplicated <i>falciparum</i> malaria (Kenya) 2.4 mg/kg ART once a day for 2 days (2 min infusion) |
| Valea et al. 2014 | Oral | n=48 | 24 pregnant women and 24 non-pregnant women with uncomplicated <i>falciparum</i> malaria (Burkina Faso) 3.6 mg/kg ART once a day for 3 days coadministered with mefloquine (coformulation) |
| Liu et al. 2014 | Oral | n=31 | 31 healthy men (China), comparison of two coformulation of ART- Amodiaquine 100/270mg per tablet (Artesun®; ASAQ Wintrop®) Study in 4 periods (separated by washout periods): On each period, 200 mg |

| | | | |
|--------------------------|------|------|---|
| Jittamala et al. 2015 | Oral | n=17 | ART administered as 2 cp of Artesun® or ASAQ Wintrop® (crossover study) 17 healthy adults (Thailand, crossover study) G1: 180 mg ART in a fixed formulation of ART-Pyronaridine G2: 180 mg ART in the same fixed formulation of ART-Pyronaridine coadministered with primaquine |
| Rattanapunya et al. 2015 | Oral | n=16 | 16 healthy adults (Thailand); Regimen in 3 periods (P1-P3) P1: 200 mg ART coadministered with mefloquine once a day for 3 days (washout period of 2 month) P2: Boosted lopinavir (LPV/r) for 14 days (no washout period between P2 and P3) P3: ART with mefloquine (same doses as in P1) coadministered with LPV/r for 3 days |
| Walimbwa et al. 2018 | Oral | n=13 | 13 healthy adults (Uganda) 4 mg/kg ART once a day for 3 days coadministered with amodiaquine |

ART=artesunate; GX=group X; T_x=dosing time; ACT=artemisinin-based combination therapy; HIV=human immunodeficiency virus; ARV=antiretroviral; IV=intravenous; PO=*per os*; IR=intrarectal; IM=intramuscular

Table 2: Description of the dose of ART administered and the number of studies per PK parameters

| Administration route | Dose of ART administered (mg/kg or mg) | | | Number of studies per PK parameters | | | | | |
|----------------------|--|--------------------------|----------------------------|-------------------------------------|--------------------|--------------------|--------------------|-------------------|-------------------|
| | Volunteers | Adults patients | Paediatric patients | C_{max} | T_{max} | $t_{1/2}$ | AUC _{0-∞} | Vd or Vd/F | CL or CL/F |
| IV | 120 mg ^μ | 120–240 mg ^μ | NA | ART: | ART: | ART: | ART: | ART: | ART: |
| | 0.5–8 mg/kg [¥] | 2.4–4 mg/kg [¥] | 1.2–2.4 mg/kg [¥] | 5/13 [†] | 3/13 [†] | 8/13 [†] | 7/13 [†] | 7/13 [†] | 7/13 [†] |
| | | | | 3/13 ^α | 1/13 ^α | 4/13 ^α | 3/13 ^α | 4/13 ^α | 4/13 ^α |
| | | | | DHA: | DHA: | DHA: | DHA: | DHA: | DHA: |
| | | | | 5/13 [†] | 4/13 [†] | 8/13 [†] | 8/13 [†] | 7/13 [†] | 6/13 [†] |
| 8/13 ^α | 7/13 ^α | 5/13 ^α | 4/13 ^α | 4/13 ^α | 5/13 ^α | | | | |
| PO | 100–300 mg ^{*μ} | 100–200 mg ^{*μ} | NA | ART: | ART: | ART: | ART: | ART: | ART: |
| | 100–200 mg ^{§μ} | 200 mg ^{§μ} | NA | 17/38 [†] | 14/38 [†] | 13/38 [†] | 8/38 [†] | 3/38 [†] | 4/38 [†] |
| | | | | 8/38 ^α | 14/38 ^α | 9/38 ^α | 3/38 ^α | 4/38 ^α | 5/38 ^α |
| | 4 mg/kg ^{¥¥} | 2–6 mg/kg ^{¥¥} | NA | DHA: | DHA: | DHA: | DHA: | DHA: | DHA: |
| | 4 mg/kg ^{§¥} | 1–4 mg/kg ^{§¥} | 2–4.8 mg/kg ^{§¥} | 19/38 [†] | 15/38 [†] | 23/38 [†] | 12/38 [†] | 2/38 [†] | 2/38 [†] |
| 11/38 ^α | | | | 19/38 ^α | 14/38 ^α | 6/38 ^α | 4/38 ^α | 5/38 ^α | |
| IR | 200 mg ^μ | NA | 50 mg ^μ | ART: | ART: | ART: | ART: | ART: | ART: |
| | NA | NA | 9.3–20 mg/kg [¥] | 2/5 [†] | 2/5 [†] | NA | NA | NA | NA |
| | | | | 1/5 ^α | 1/5 ^α | 1/5 ^α | 1/5 ^α | NA | NA |
| | | | | DHA: | DHA: | DHA: | DHA: | DHA: | DHA: |
| | | | | 2/5 [†] | 3/5 [†] | NA | NA | NA | NA |
| 2/5 ^α | 2/5 ^α | 2/5 ^α | 2/5 ^α | 1/5 ^α | 1/5 ^α | | | | |
| IM | NA | 120 mg ^μ | NA | ART: | ART: | ART: | ART: | ART: | ART: |
| | NA | 2.4 mg/kg [¥] | 1.2–2.4 mg/kg [¥] | NA | NA | 1/3 [†] | 1/3 [†] | 1/3 [†] | 1/3 [†] |
| | | | | 3/3 ^α | 2/3 ^α | 2/3 ^α | 2/3 ^α | 2/3 ^α | 2/3 ^α |
| | | | | DHA: | DHA: | DHA: | DHA: | DHA: | DHA: |
| | | | | NA | NA | 1/3 [†] | 1/3 [†] | 1/3 [†] | 1/3 [†] |
| 3/3 ^α | 3/3 ^α | 2/3 ^α | 2/3 ^α | 2/3 ^α | 2/3 ^α | | | | |

ART=artesunate; DHA=dihydroartemisinin; PK=pharmacokinetic; IV=intravenous; PO=*per os*; IR=intra-rectal; IM=intramuscular; C_{max} =maximal plasmatic concentration; T_{max} =time to maximal plasmatic concentration; $t_{1/2}$ =half-life; AUC=area under the concentration-time curve; Vd=volume of distribution; Vd/F=apparent volume of distribution; CL=clearance; CL/F=apparent clearance; NA=Non-Applicable; * ART administered alone (PO route); § ART administered in a combination (PO route); ^μ ART dose given in mg in the studies; [¥] ART dose given in mg/kg in the studies; [†] mean data type; ^α median data type

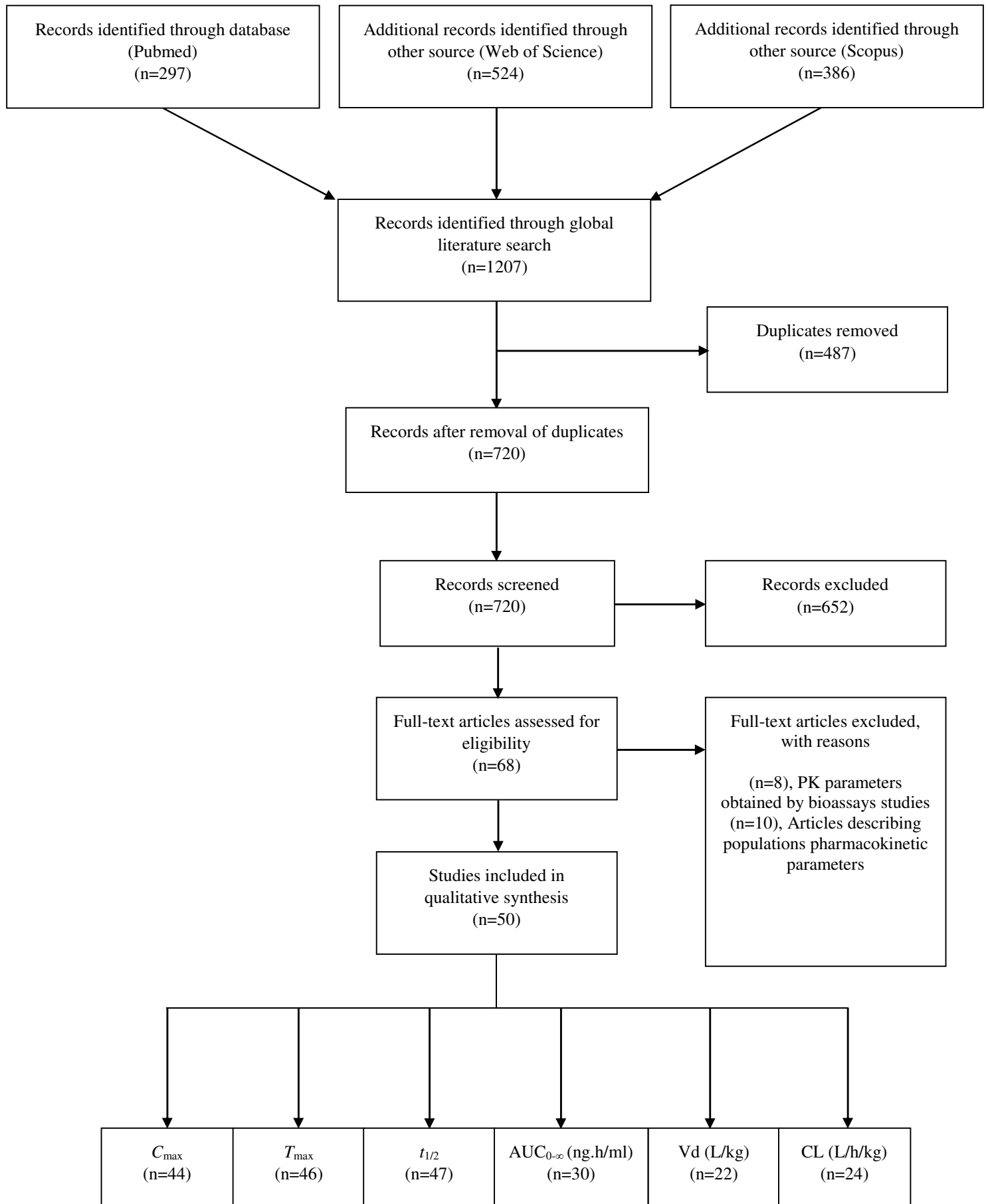
Table 3: Pharmacokinetic parameters per administration route

| PK parameters | Administration route | | | | |
|----------------------------|-------------------------------|----------------------------|----------------------|----------------------|------------------------|
| | ART/DHA | IV | PO | IR | IM |
| Range (CV) | | | | | |
| C_{max} (ng/ml) | ART (mean data) | 4,797–83,340 | 48.9–451 | 90–448.5 | NA |
| | <i>ART dose range (mg/kg)</i> | 0.5–8 | 1–6 | 1.79–3.2 | NA |
| | DHA (mean data) | 428–6,056 | 180.4–2,129 | 180–385.6 | NA |
| | <i>ART dose range (mg/kg)</i> | 0.5–8 | 1–6 | 1.79–3.2 | NA |
| | ART (median data) | 3,260–29,677 | 62.9–1,040 | 507–561 | 615–2,195 |
| | <i>ART dose range (mg/kg)</i> | 1.2–4 | 2–4 | 10–20 | 1.2–2.4 |
| | DHA (median data) | 605–3,210 | 519–1,850 | 682–1,535 | 341–1,166 |
| | <i>ART dose range (mg/kg)</i> | 1.2–4 | 2–4 | 9.3–20 | 1.2–2.4 |
| T_{max} (min OR h) | ART (mean data) | 1.7–2 min (5.40%) | 0.25–1.4 h (40.37%) | 0.58–1.43 h (59.81%) | NA |
| | DHA (mean data) | 7.2–24 min (36.68%) | 0.5–2.08 h (30.03%) | 1.13–1.95 h (26.84%) | NA |
| | ART (median data) | NA | 0.33–1.5 h (40.68%) | 0.8–1 h (15.71%) | 7.2–12 min (28.36%) |
| | DHA (median data) | 0.5–12 min (54.63%) | 0.5–2.04 h (33.94%) | 1.5–2 h (CV:11.90%) | 25.9–45 min (22.47%) |
| $t_{1/2}$ (min OR h) | ART (mean data) | 2.19–14.4 min (61.35%) | 0.3–1.85 h (51.69%) | NA | NA |
| | DHA (mean data) | 36.7–128.4 min (36.89%) | 0.49–3.2 h (46.21%) | NA | NA |
| | ART (median data) | 1.5–15 min (52.31%) | 0.24–0.7 h (28.55%) | NA | 25.2–48.2 min (35.20%) |
| | DHA (median data) | 18–78.6 min (58.68%) | 0.64–4.02 h (57.50%) | 0.79–1.8 h (39.57%) | 31.9–52.7 min (19.03%) |
| $AUC_{0-\infty}$ (ng.h/ml) | ART (mean data) | 386–6,994 | 64.6–400 | NA | NA |
| | <i>ART dose range (mg/kg)</i> | 0.5–8 | 1–4.8 | NA | NA |
| | DHA (mean data) | 385–10,410 | 433.2–3,837 | NA | NA |
| | <i>ART dose range (mg/kg)</i> | 0.5–8 | 1–4.8 | NA | NA |
| | ART (median data) | 49–1,042 | 62.9–217 | 692–1,076 | 535–856 |
| | <i>ART dose range (mg/kg)</i> | 1.2–4 | 3–4 | 10–20 | 1.2–2.4 |
| | DHA (median data) | 418–2,450 | 1,160–2,689 | 2,403–5,633 | 396–1,496 |
| | <i>ART dose range (mg/kg)</i> | 1.2–4 | 2–4 | 9.3–20 | 1.2–2.4 |
| Vd or Vd/F (L/kg) | ART (mean data) | 0.08–0.24 (33.19%) | 8.56–41 (54.43%) | NA | NA |
| | DHA (mean data) | 0.55–2.403 (45.41%) | 1.33–4.2 (39.53%) | NA | NA |

| | | | | | |
|----------------------|-------------------------------|---------------------|---------------------|------------------|--------------------|
| | ART (median data) | 0.14–15.2 (201.18%) | 6.8–26 (49.63%) | NA | 1.9–3.98 (61.75%) |
| | DHA (median data) | 0.6–2.37 (54.23%) | 1.91–4.9 (31.07%) | 4.4–5.9 (20.60%) | 1.28–1.79 (19.38%) |
| CL or CL/F (L/h/kg) | ART (mean data) | 1.16–3.07 (33.97%) | 12.9–31.16 (29.41%) | NA | NA |
| | DHA (mean data) | 0.48–1.3 (23.70%) | 1.22–2.7 (23.07%) | NA | NA |
| | ART (median data) | 2.33–64 (177.93%) | 9.6–60 (50.49%) | NA | 2.4–3.48 (18.68%) |
| | DHA (median data) | 0.75–5.6 (86.34%) | 1.07–2.2 (24.30%) | 2.6–3.9 (28.28%) | 1.18–2.16 (30.98%) |
| Cav (µg/L) | DHA (mean data) | 230.63–412.25 | 22.42–123.38 | NA | NA |
| | <i>ART dose range (µg/kg)</i> | 2,200–2,500 | 1,000–4,800 | NA | NA |
| | ART+DHA (mean data) | 340.13–566.00 | 25.11–133.04 | NA | NA |
| | <i>ART dose range (µg/kg)</i> | 2,200–2,500 | 1,000–4,800 | NA | NA |
| Cav/EC ₅₀ | DHA (mean data) | 23.25–41.56 | 2.26–12.44 | NA | NA |
| | <i>ART dose range (µg/kg)</i> | 2,200–2,500 | 1,000–4,800 | NA | NA |
| | ART+DHA (mean data) | 34.29–57.06 | 2.53–13.41 | NA | NA |
| | <i>ART dose range (µg/kg)</i> | 2,200–2,500 | 1,000–4,800 | NA | NA |

ART=artesunate; DHA=dihydroartemisinin; PK=pharmacokinetic; CV=coefficient of variation; IV=intravenous; PO=*per os*; IR=intrarectal; C_{max}=maximal plasmatic concentration; T_{max}=time to maximal plasmatic concentration; t_{1/2}=half-life; AUC=area under the concentration-time curve; Vd=volume of distribution; Vd/F=apparent volume of distribution; CL=clearance; CL/F=apparent clearance; NA=Non-Applicable; Dose-independent PK parameters are provided as range (CV) and dose-dependent parameters as range with the corresponding ART dose range (in mg/kg); Cav=average DHA or ART+DHA concentration over time; Cav (µg/L) are presented as a range with the corresponding ART dose range (in µg/kg); EC₅₀=half-maximal effective concentration equal to 9.92 µg/L for DHA as described in a previous study,(Das et al. 2017) and is here considered equivalent for both ART and DHA; Cav/EC₅₀: provided as a range with the corresponding ART dose range (in µg/kg)

Figure 1. Bibliographic research flow chart.



C_{\max} =maximal plasmatic concentration; T_{\max} =time to maximal plasmatic concentration; $t_{1/2}$ =half-life; $AUC_{0-\infty}$ =area under the concentration-time curve; V_d =volume of distribution; CL =clearance

Figure 2. Publication time-slate of the studies included in the present review

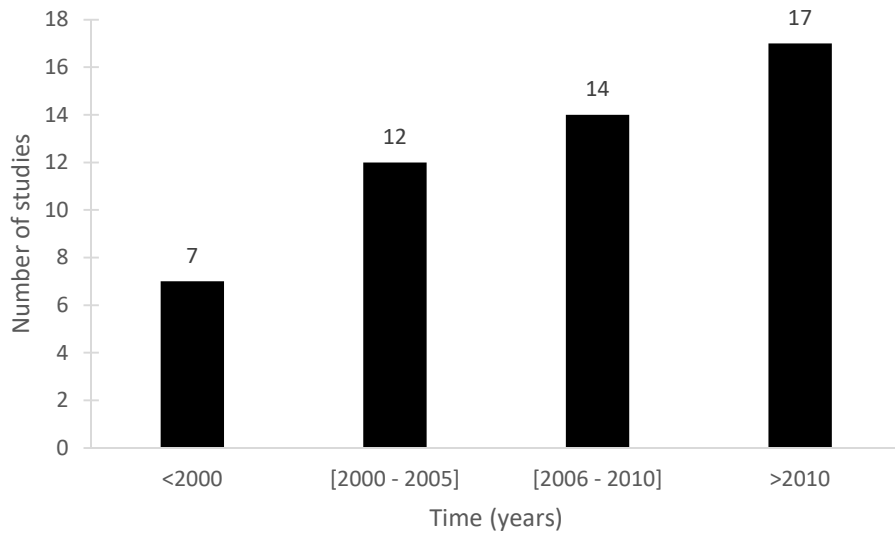
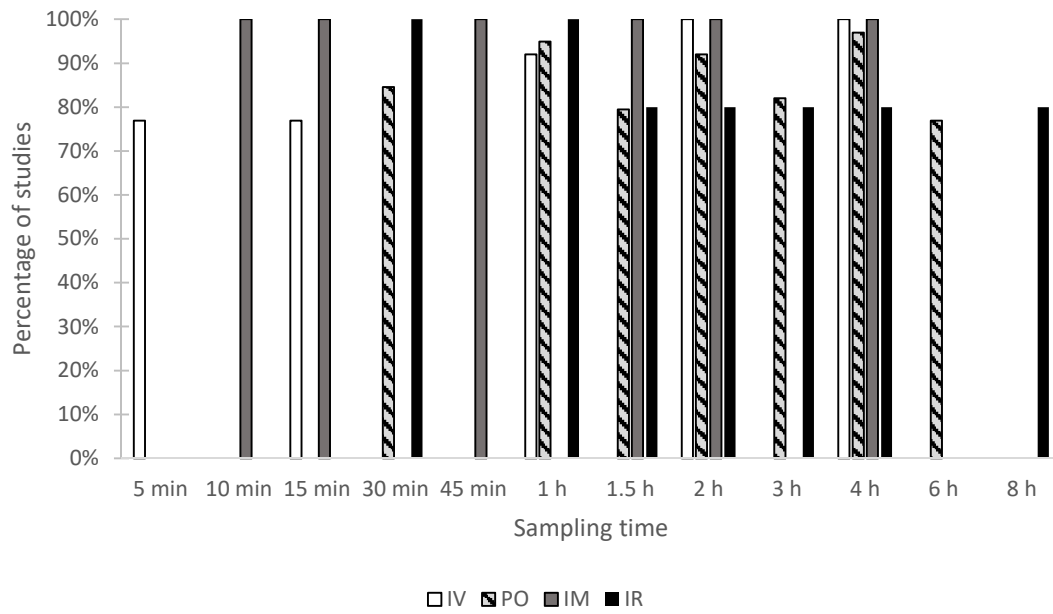
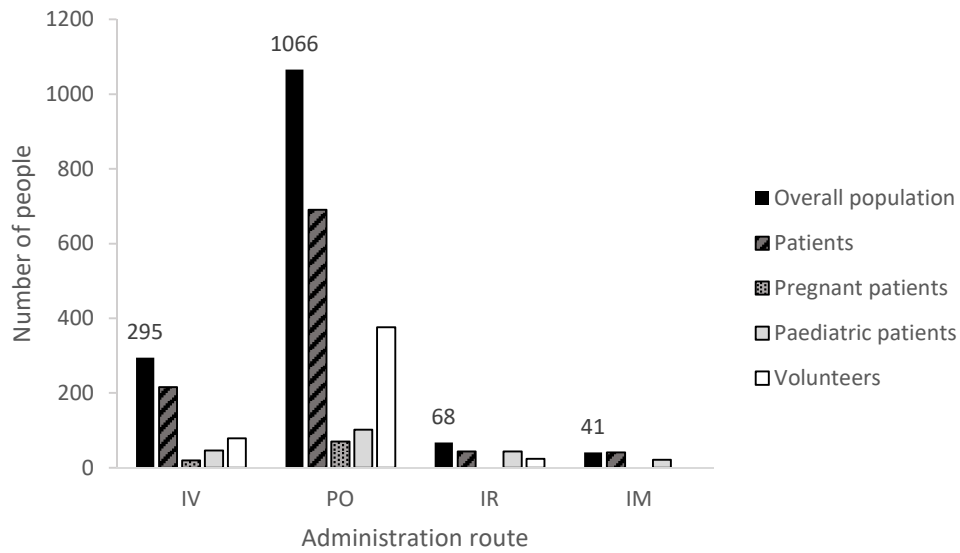


Figure 3. Description of the most frequent blood sampling times by administration route.



A sampling time was considered as frequent when it was described in at least 75% of the studies of an administration route. 48 studies out of 50 (96%) reported having sampled blood before dosing. IV=intravenous; PO=*per os*; IR=intrarectal; IM=intramuscular

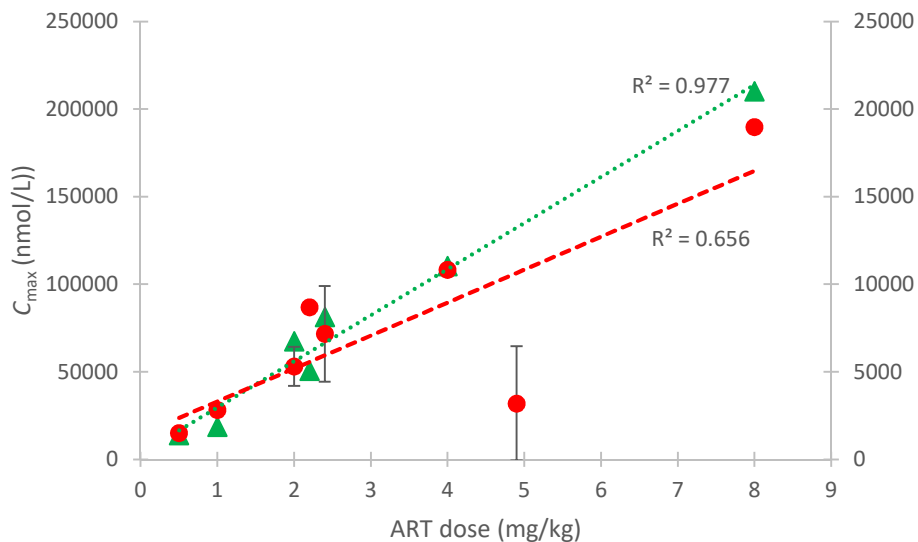
Figure 4. Distribution of the population of study by administration route.



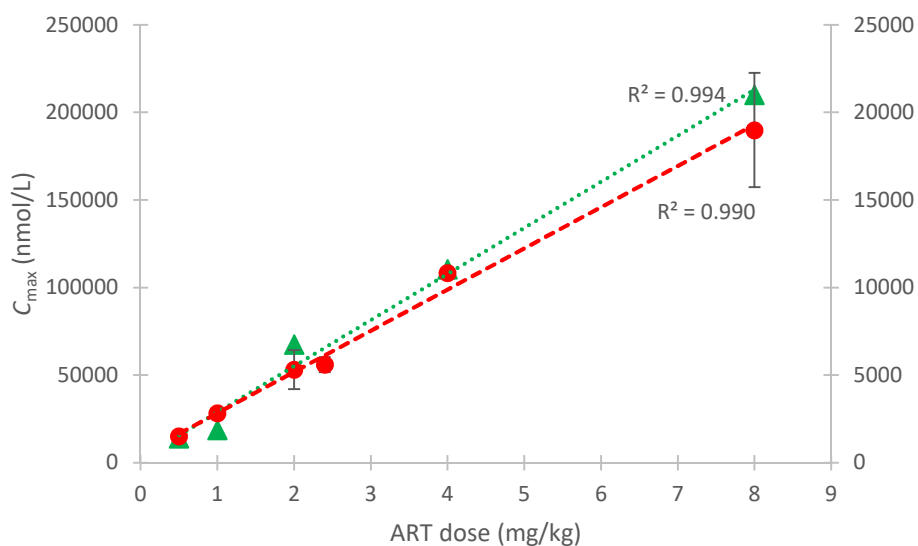
There were 112 cases of severe *falciparum* malaria (IV: 82; IM: 30), 856 cases of non-severe *falciparum* malaria (IV: 122; PO: 679; IM: 11; IR: 44) and 23 cases of *vivax* malaria (IV: 12; PO: 11). IV=intravenous; PO=*per os*; IR=intrarectal; IM=intramuscular

Figure 5. Correlation analysis between C_{\max} (nmol/L) and dose (mg/kg) after ART IV administration in the whole population and in volunteers.

a)



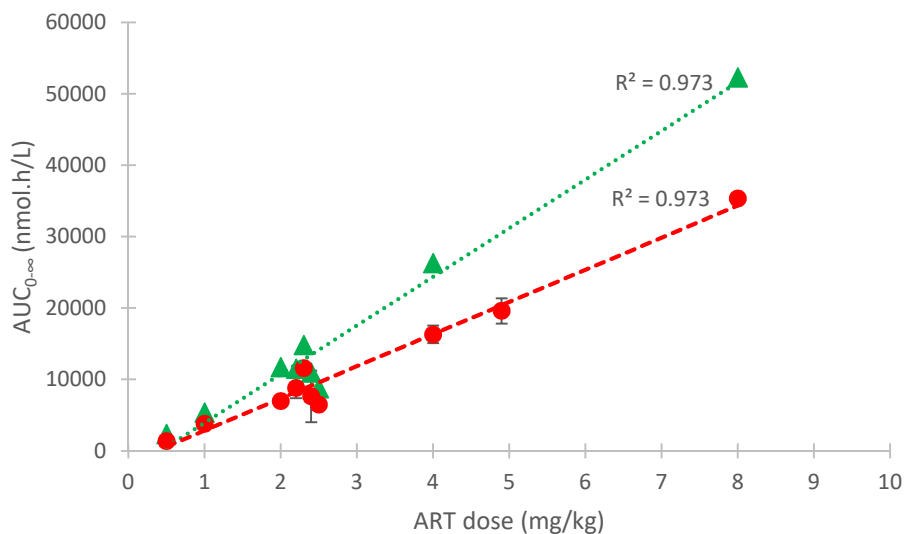
b)



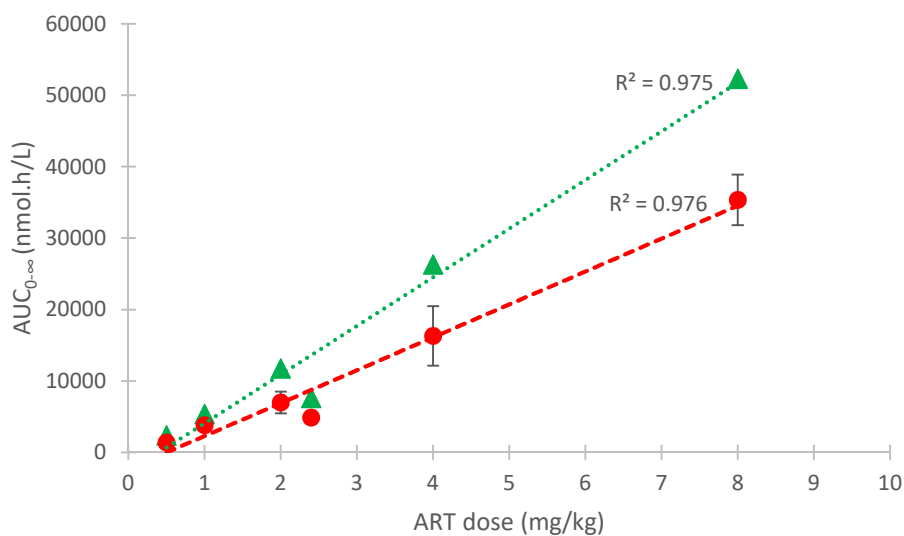
Comparison between DHA C_{\max} (red curve) and the sum of ART C_{\max} and DHA C_{\max} (green curve). Figure (a) presents the results of the correlation analysis in the whole population and figure (b) the results of the correlation analysis in volunteers. C_{\max} were converted from ng/ml to nmol/L using the respective molecular weights of ART (384.421 g/mol) and DHA (284.35 g/mol). C_{\max} =maximal plasmatic concentration; ART=artesunate; IV=intravenous; DHA=dihydroartemisinin

Figure 6. Correlation analysis between $AUC_{0-\infty}$ (nmol.h/L) and dose (mg/kg) after ART IV administration in the whole population and in volunteers.

a)



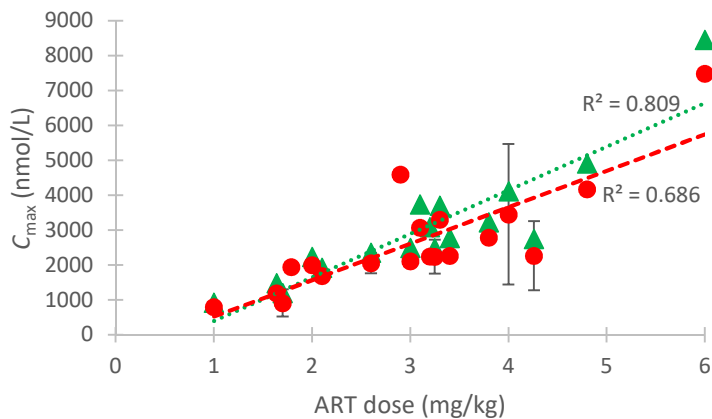
b)



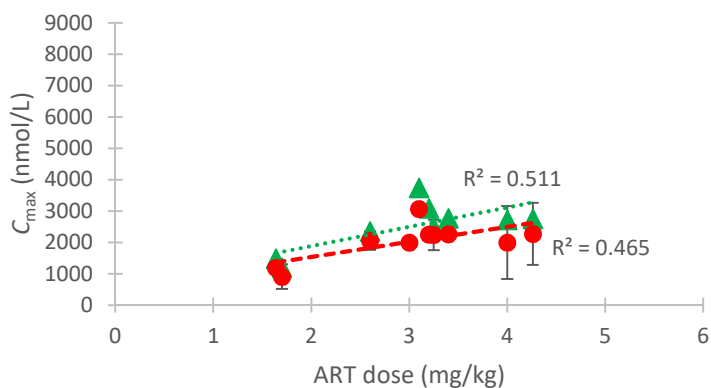
Comparison between DHA $AUC_{0-\infty}$ (red curve) and the sum of ART $AUC_{0-\infty}$ and DHA $AUC_{0-\infty}$ (green curve). Figure (a) presents the results of the correlation analysis in the whole population and figure (b) the results of the correlation analysis in volunteers. $AUC_{0-\infty}$ were converted from ng.h/ml to nmol.h/L using the respective molecular weights of ART (384.421 g/mol) and DHA (284.35 g/mol). AUC=area under the concentration-time curve; ART=artesunate; IV=intravenous; DHA=dihydroartemisinin

Figure 7. Correlation analysis between C_{\max} (nmol/L) and dose (mg/kg) after ART PO administration in the whole population, in volunteers, and in patients.

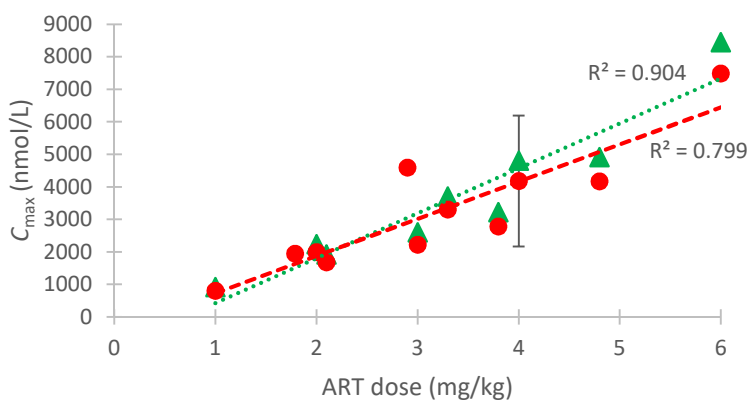
a)



b)



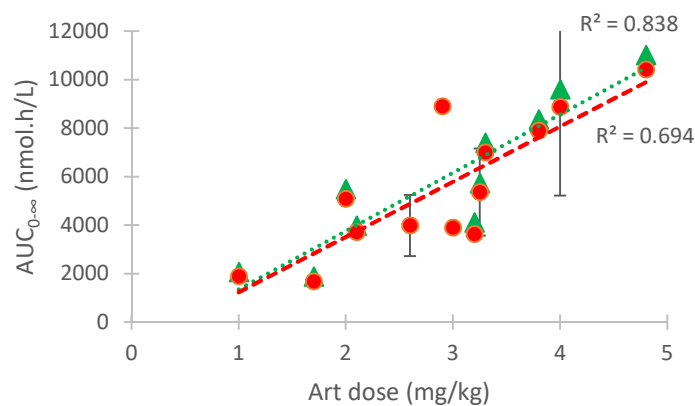
c)



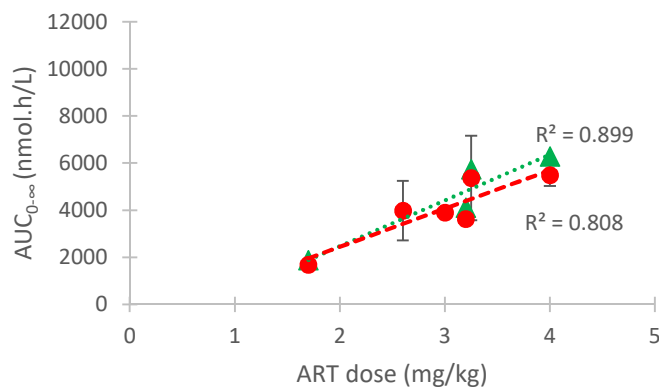
Comparison between DHA C_{\max} (red curve) and the sum of ART C_{\max} and DHA C_{\max} (green curve). Figure (a) presents the results of the correlation analysis in the whole population, figure (b) the results of the correlation analysis in volunteers, and figure (c) the results of the correlation analysis in patients. C_{\max} were converted from ng/ml to nmol/L using the respective molecular weights of ART (384.421 g/mol) and DHA (284.35 g/mol). C_{\max} =maximal plasmatic concentration; ART=artesunate; PO=*per os*; DHA=dihydroartemisinin

Figure 8. Correlation analysis between $AUC_{0-\infty}$ (nmol.h/L) and dose (mg/kg) after ART PO administration in the whole population, in volunteers, and in patients.

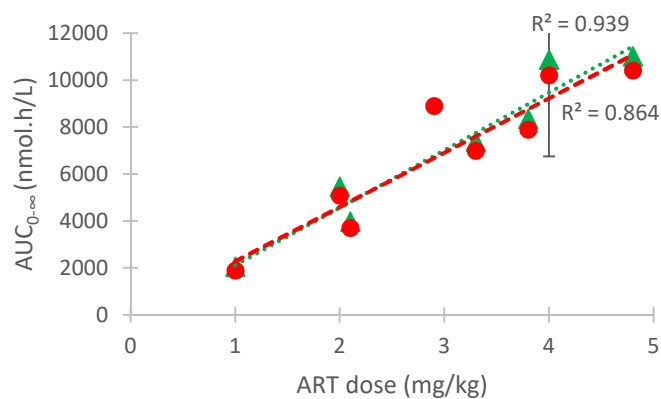
a)



b)

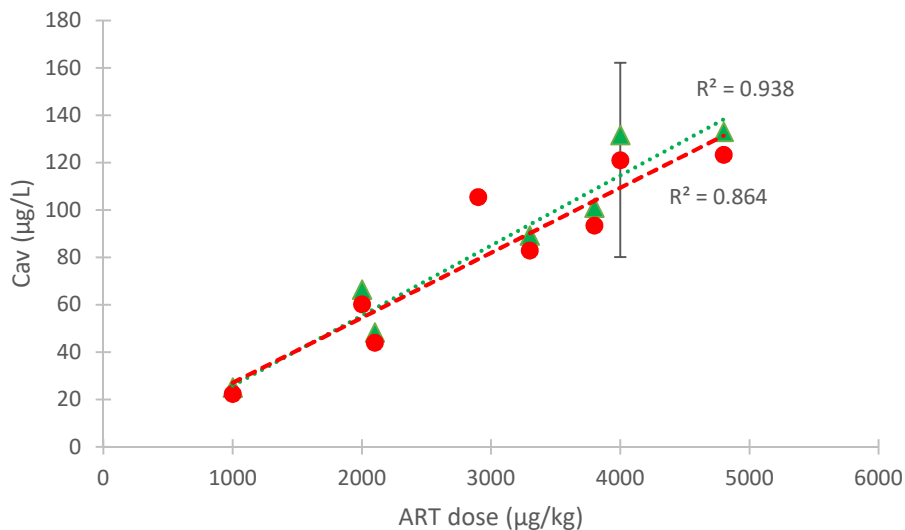


c)



Comparison between DHA $AUC_{0-\infty}$ (red curve) and the sum of ART $AUC_{0-\infty}$ and DHA $AUC_{0-\infty}$ (green curve). Figure (a) presents the results of the correlation analysis in the whole population, figure (b) the results of the correlation analysis in volunteers, and figure (c) the results of the correlation analysis in patients. $AUC_{0-\infty}$ were converted from ng.h/ml to nmol.h/L using the respective molecular weights of ART (384.421 g/mol) and DHA (284.35 g/mol). AUC=area under the concentration-time curve; ART=artesunate; PO=*per os*; DHA=dihydroartemisinin

Figure 9. Correlation analysis between Cav (DHA and the sum of ART and DHA, in $\mu\text{g/L}$) and dose ($\mu\text{g/kg}$) after ART PO administration in patients.



Comparison between DHA Cav (red curve) and the sum of ART Cav and DHA Cav (green curve). Cav were first calculated for ART and DHA separately with the formula previously described in the material and methods section. Then, for each given dose of ART administered *per os*, ART and DHA respective Cav were summed. Cav=concentration over time; DHA=dihydroartemisinin; ART=artesunate; PO=*per os*