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

Yobouet Ines Kouakou[a], Michel Tod[b], Gilles Leboucher[b], Adeline Lavoignat[a], Guillaume Bonnot[a], Anne-Lise Bienvenu[a,b,*,1], Stephane Picot[a,c,1]

[a] ICBMS CNRS 5246, SMITh, Malaria Research Unit, Campus Lyon-Tech La Doua, Lyon University, Lyon, France
[b] Groupement Hospitalier Nord, Service Pharmacie, Hospices Civils de Lyon, Lyon, France
[c] Groupement Hospitalier Nord, Institut de Parasitologie et Mycologie Médicale, Hospices Civils de Lyon, Lyon, France

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ABSTRACT

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 (Cav) 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 Cav/EC_{50} ratio for IV route provides evidence that IV ART will remain efficient even in the case of increased resistance level, whereas for the 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.

Introduction

Significant progress has 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 are 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; Ouji et al., 2018). This threat is particularly alarming as the use of ACTs, considered 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,b). The drug regimens remained as low as possible to obtain antimalarial effects leading to oral doses as low

* Corresponding author at: Groupement Hospitalier Nord, Service Pharmacie, Hospices Civils de Lyon, 103 Grande Rue de la Croix-Rousse, F-69004, Lyon, France.
E-mail address: anne-lise.bienvenu@chu-lyon.fr (A.-L. Bienvenu).
[1] Joint last authors.

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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 an 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 was proven 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 was stressed a decade ago (Barnes et al., 2008). The PK and PD properties of ART were extensively described but some degree of uncertainty 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 focus on the impact of resistance on pharmacodynamic 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 search for studies published before January 2019 was performed using three databases: MEDLINE, Web of Science (WoS) and Scopus. Keys words of interest were “artesunate” and “pharmacokinetic”. Search details are as follows: ("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 pharmacokineticsm[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 limitations 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 were extracted from the included studies by one author (YIK) and an independent sampling of those data was done by another author (AL) to ensure 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 statuses (adults, pregnant women, children) were mixed in the 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 but 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 (Cav, μg/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 μg/L) of DHA (Das et al., 2017). It was assumed that the ART EC_{50} was equivalent to DHA EC_{50}. Cav were calculated using the formula: $Cav = \frac{AUC0-\infty \ (for\ a\ single\ dose\ of\ ART)}{24\ (PO)\ or\ 8\ (IV)}$ (note that $AUC_{0-\infty}$ after a single dose is equal to AUC over a dosing interval at steady-state). Cav and Cav/EC_{50} were calculated separately for ART and DHA and sums of the Cav and Cav/EC_{50} (ART + DHA) were then calculated). A correlation analysis between DHA Cav and ART + DHA Cav and ART dose was performed. Variability of dose-independent PK parameters ($t_{1/2}$, T_{max}, Vd, 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 significance level of $p \leq 0.050$.

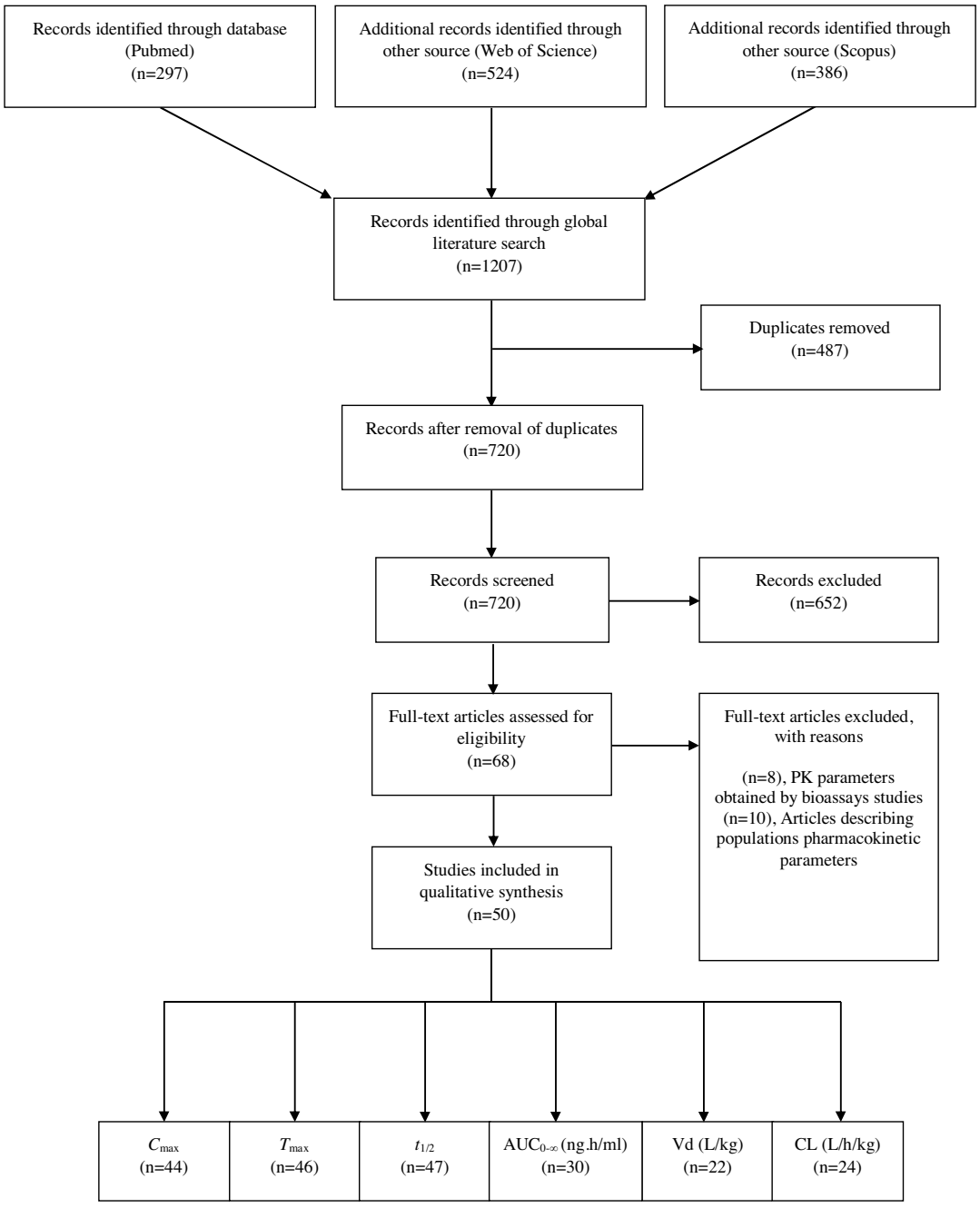
Results

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



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; Vd=volume of distribution; CL=clearance

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; Vd = volume of distribution; CL = clearance.

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 *falciparum* malaria (Gabon) Rectal administration of a single 50 mg ART suppository twice a day (4 h interval)
Navaratnam et al. (1998)	IR, Oral	n = 12	12 healthy adults (Malaysia) Either rectal of oral administration of a single 200 mg dose or artesunate (crossover study)
Batty et al. (1998a)	IV, Oral	n = 12	12 adults with *Plasmodium vivax* 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 *falciparum* 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 *Plasmodium falciparum* 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) /byt IV bolus followed by adequate treatment to ensure healing
Krishna et al. (2001)	IV, IR	n = 34	34 children with moderate *falciparum* 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) etT_{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 *falciparum* malaria, 150 mg ART (Oral)
Teja-Isavadharm et al. (2001)	Oral	n = 12	G1: 6 adult men with uncomplicated *falciparum* 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 falciparum 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 falciparum 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 *falciparum* malaria (Gabon) 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 *falciparum* malaria (Vietnam) 2.4 mg/kg ART (stat) followed by 1.2 mg/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 *falciparum* malaria (Thailand) 2.4 mg/kg at T_0 (stat) followed by 1.2 mg/kg et T_{12h} and 1.2 mg/kg once every 24 h
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 *falciparum* 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 *falciparum* 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 *falciparum* malaria receiving coformulation 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 *falciparum* 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)

Table 1 (*Continued*)

Articles (ref)	Route of administration	Population treated (n)	Treatment regimen
Sinou et al. (2009)	Oral	n = 13	13 adults with acute uncomplicated *falciparum* 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 *falciparum* malaria (Malawi and Gambia) 1 (n = 30), 2 (n = 29) or 4 mg/kg (n = 27) ART once a day for 3 days coadministered with dapsone and chlorproguanil
Mwesigwa et al. (2010)	Oral	n = 21	21 children with uncomplicated *falciparum* malaria (Uganda) 4 mg/kg ART twice a day for 3 days coadministered with amodiaquine
Krudsood et al. (2010)	Oral	n = 50	50 adults with uncomplicated *falciparum* 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 *falciparum* 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 *falciparum* 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 *falciparum* 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 < 65 kg and 240 mg when ≥ 65 kg
Saunders et al. (2012)	Oral	n = 143	143 adults with uncomplicated *falciparum* 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 *falciparum* 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 *falciparum* 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 *falciparum* 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 100/270 mg per tablet (Artesun® ; ASAQ Wintrop®) Study in 4 periods (separated by washout periods): On each period, 200 mg ART administered as 2 cp of Artesun® or ASAQ Wintrop® (crossover study)
Jittamala et al. (2015)	Oral	n = 17	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.

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 follows: 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

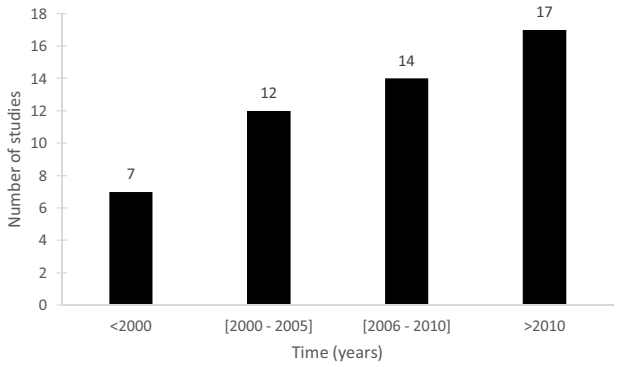


Figure 2. Publication time-slate of the studies included in the present review.

(28%, 14/50), there were no indications of 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 infrequently 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), chloproguanil-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 the IR route, and three, the 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 more 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 more reduced ($p = 0.022$) in volunteers (1.67 ± 0.56 L/h/kg) than in patients (2.40 ± 0.59 L/h/kg).

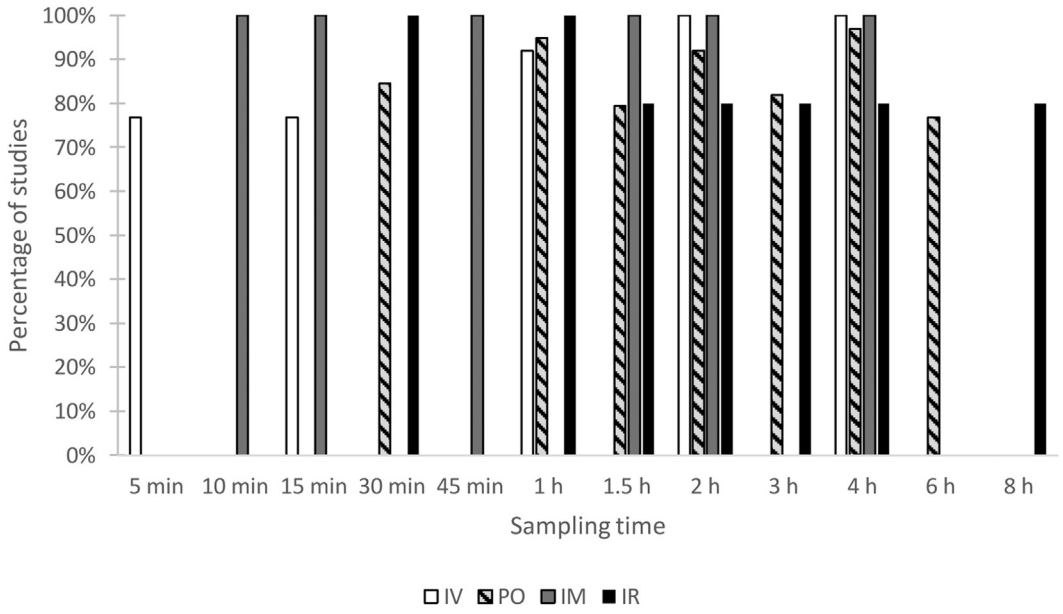


Figure 3. Description of the most frequent blood sampling times by administration route.
A sampling time was considered as frequent when it was described in at least 75% of the studies of an administration route. 48 studies out of 50 (96%) reported having sampled blood before dosing. IV = intravenous; PO = *per os*; IR = intrarectal; IM = intramuscular.

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}	$t_{1/2}$	$AUC_{0-\infty}$	Vd or Vd/F	CL or CL/F
IV	120 mg$^{\mu}$	120–240 mg$^{\mu}$	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$^{\alpha}$	1/13$^{\alpha}$	4/13$^{\alpha}$	3/13$^{\alpha}$	4/13$^{\alpha}$	4/13$^{\alpha}$
				DHA:	DHA:	DHA:	DHA:	DHA:	DHA:
				5/13†	4/13†	8/13†	8/13†	7/13†	6/13†
				8/13$^{\alpha}$	7/13$^{\alpha}$	5/13$^{\alpha}$	4/13$^{\alpha}$	4/13$^{\alpha}$	5/13$^{\alpha}$
PO	100–300 mg$^{*\mu}$	100–200 mg$^{*\mu}$	NA	ART:	ART:	ART:	ART:	ART:	ART:
	100–200 mg$^{\S\mu}$	200 mg$^{\S\mu}$	NA	17/38†	14/38†	13/38†	8/38†	3/38†	4/38†
				8/38$^{\alpha}$	14/38$^{\alpha}$	9/38$^{\alpha}$	3/38$^{\alpha}$	4/38$^{\alpha}$	5/38$^{\alpha}$
	4 mg/kg$^{*¥}$	2–6 mg/kg$^{*¥}$	NA	DHA:	DHA:	DHA:	DHA:	DHA:	DHA:
	4 mg/kg$^{\S¥}$	1–4 mg/kg$^{\S¥}$	2–4.8 mg/kg$^{\S¥}$	19/38†	15/38†	23/38†	12/38†	2/38†	2/38†
				11/38$^{\alpha}$	19/38$^{\alpha}$	14/38$^{\alpha}$	6/38$^{\alpha}$	4/38$^{\alpha}$	5/38$^{\alpha}$
IR	200 mg$^{\mu}$	NA	50 mg$^{\mu}$	ART:	ART:	ART	ART	ART	ART
	NA	NA	9.3–20 mg/kg$^{¥}$	2/5†	2/5†	NA	NA	NA	NA
				1/5$^{\alpha}$	1/5$^{\alpha}$	1/5$^{\alpha}$	1/5$^{\alpha}$	NA	NA
				DHA:	DHA:	DHA	DHA	DHA	DHA
				2/5†	3/5†	NA	NA	NA	NA
				2/5$^{\alpha}$	2/5$^{\alpha}$	2/5$^{\alpha}$	2/5$^{\alpha}$	1/5$^{\alpha}$	1/5$^{\alpha}$
IM	NA	120 mg$^{\mu}$	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$^{\alpha}$	2/3$^{\alpha}$	2/3$^{\alpha}$	2/3$^{\alpha}$	2/3$^{\alpha}$	2/3$^{\alpha}$
				DHA	DHA	DHA	DHA:	DHA:	DHA:
				NA	NA	1/3†	1/3†	1/3†	1/3†
				3/3$^{\alpha}$	3/3$^{\alpha}$	2/3$^{\alpha}$	2/3$^{\alpha}$	2/3$^{\alpha}$	2/3$^{\alpha}$

ART = artesunate; DHA = dihydroartemisinin; PK = pharmacokinetic; IV = intravenous; PO = *per os*; IR = intrarectal; 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); $^{\mu}$ ART dose given in mg in the studies; ¥ ART dose given in mg/kg in the studies; † mean data type; $^{\alpha}$ median data type.

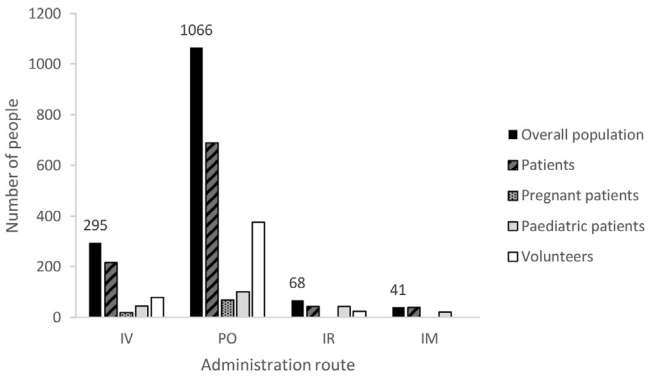


Figure 4. Distribution of the population of study by administration route.
There were 112 cases of severe *falciparum* malaria (IV: 82; IM: 30), 856 cases of non-severe *falciparum* malaria (IV: 122; PO: 679; IM: 11; IR: 44) and 23 cases of *vivax* malaria (IV: 12; PO: 11). IV = intravenous; PO = *per os*; IR = intrarectal; IM = intramuscular.

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 Cav and Cav/EC_{50} were calculated for patients after oral administration of ART (Table 3). The correlation analysis demonstrated that Cav 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

Table 3
Pharmacokinetic parameters per administration route.

PK parameters Range (CV)	ART/DHA	Administration route			
		IV	PO	IR	IM
C_{max} (ng/ml)	ART (mean data)	4,797–83,340	48.9–451	90–448.5	NA
	ART dose range (mg/kg)	*0.5–8*	*1–6*	*1.79 –3.2*	NA
	DHA (mean data)	428–6,056	180.4–2,129	180–385.6	NA
	ART dose range (mg/kg)	*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
	ART dose range (mg/kg)	*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
	ART dose range (mg/kg)	*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
	ART dose range (mg/kg)	*0.5–8*	*1–4.8*	NA	NA
	DHA (mean data)	385–10,410	433.2–3,837	NA	NA
	ART dose range (mg/kg)	*0.5–8*	*1–4.8*	NA	NA
	ART (median data)	49–1,042	*62.9–217*	692–1,076	535–856
	ART dose range (mg/kg)	*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
	ART dose range (mg/kg)	*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
	ART dose range (μg/kg)	*2,200–2,500*	*1,000–4,800*	NA	NA
	ART + DHA (mean data)	340.13–566.00	25.11–133.04	NA	NA
	ART dose range (μg/kg)	*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
	ART dose range (μg/kg)	*2,200–2,500*	*1,000–4,800*	NA	NA
	ART + DHA (mean data)	34.29–57.06	2.53–13.41	NA	NA
	ART dose range (μg/kg)	*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); EC_{50} = 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/EC_{50}: provided as a range with the corresponding ART dose range (in μg/kg).

compiled, giving us an overview of 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 (Pariente 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 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

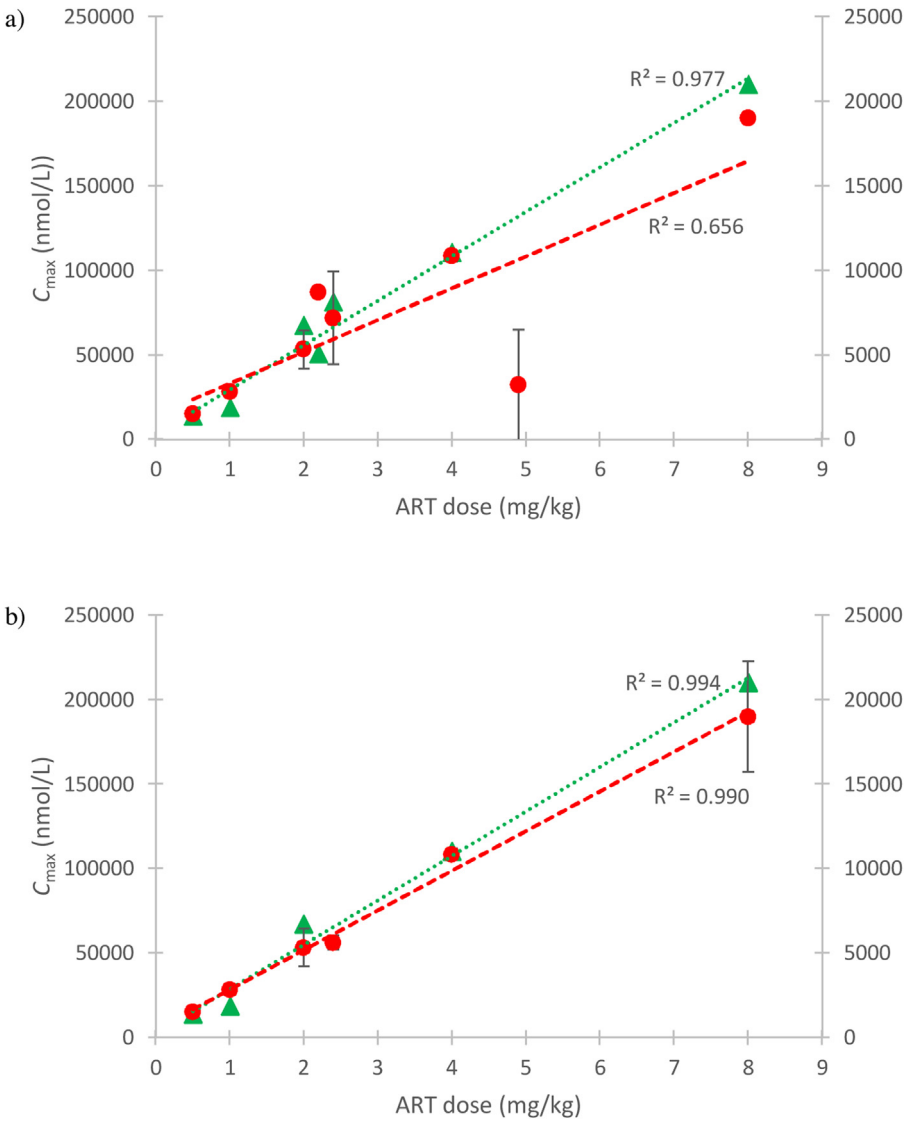


Figure 5. Correlation analysis between C_{max} (nmol/L) and dose (mg/kg) after ART IV administration in the whole population and in volunteers.
Comparison between DHA C_{max} (red curve) and the sum of ART C_{max} and DHA C_{max} (green curve). Figure (a) presents the results of the correlation analysis 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.

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 artemisinins 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 Cav 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 the 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

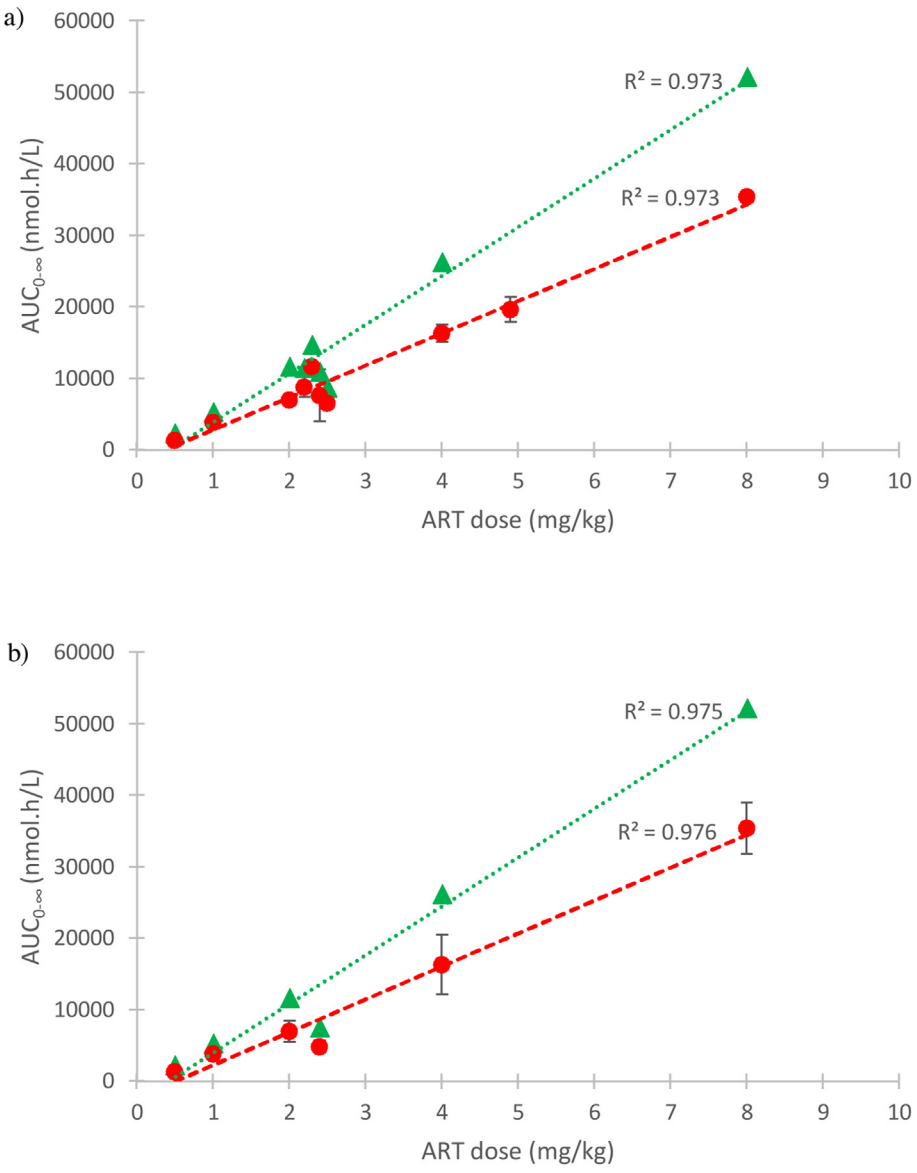


Figure 6. Correlation analysis between $AUC_{0-\infty}$ (nmol h/L) and dose (mg/kg) after ART IV administration in the whole population and in volunteers.
Comparison between DHA $AUC_{0-\infty}$ (red curve) and the sum of ART $AUC_{0-\infty}$ and DHA $AUC_{0-\infty}$ (green curve). Figure (a) presents 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.

relationship between ART dose and some PK parameters for IV and oral routes. DHA and ART + DHA Cav increased with dose escalation of ART after oral administration, as demonstrated by correlation analyses. Intravenous route led to Cav values of 340 to 566 μg/L, well above *in vivo* EC_{50} value (9.92 μg/L) (Das et al., 2017). The oral route led to Cav values of 22 to 123 μg/L. Thus, the ratio Cav/EC_{50} is much higher for the intravenous route (34 to 57) than for the 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 the intravenous route but will be limited for the oral route. Assuming a concentration dependent parasite killing (Das et al., 2017), an increase in Cav may have an impact on parasite clearance time. Besides Cav, 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 min for intravenous ART and 7 to 24 min for DHA, leading to excellent efficacy provided the C_{max} is higher than the minimum parasiticidal 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 promoted through antimalarial

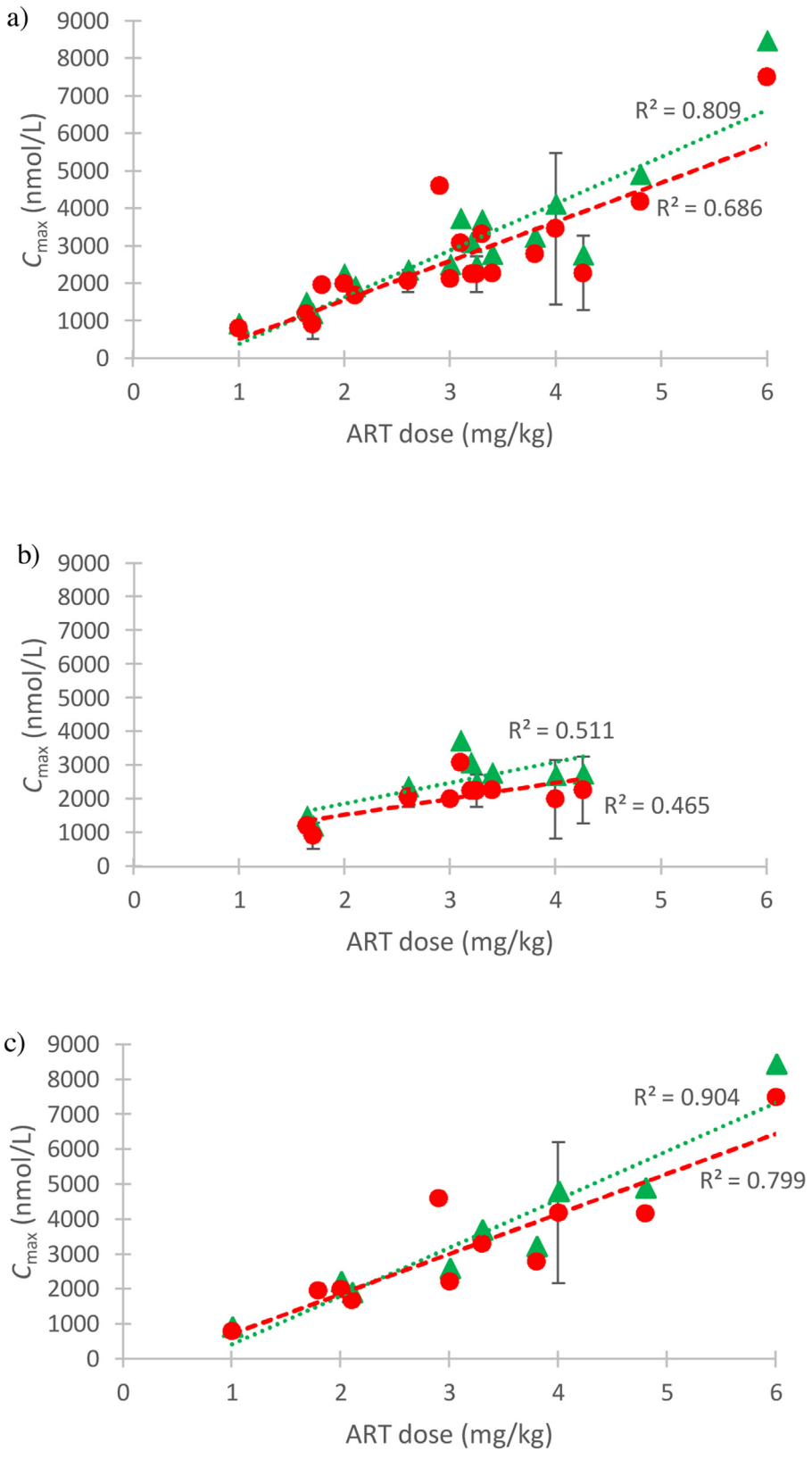


Figure 7. Correlation analysis between C_{max} (nmol/L) and dose (mg/kg) after ART PO administration in the whole population, in volunteers, and in patients. Comparison between DHA C_{max} (red curve) and the sum of ART C_{max} and DHA C_{max} (green curve). Figure (a) presents the results of the correlation 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.

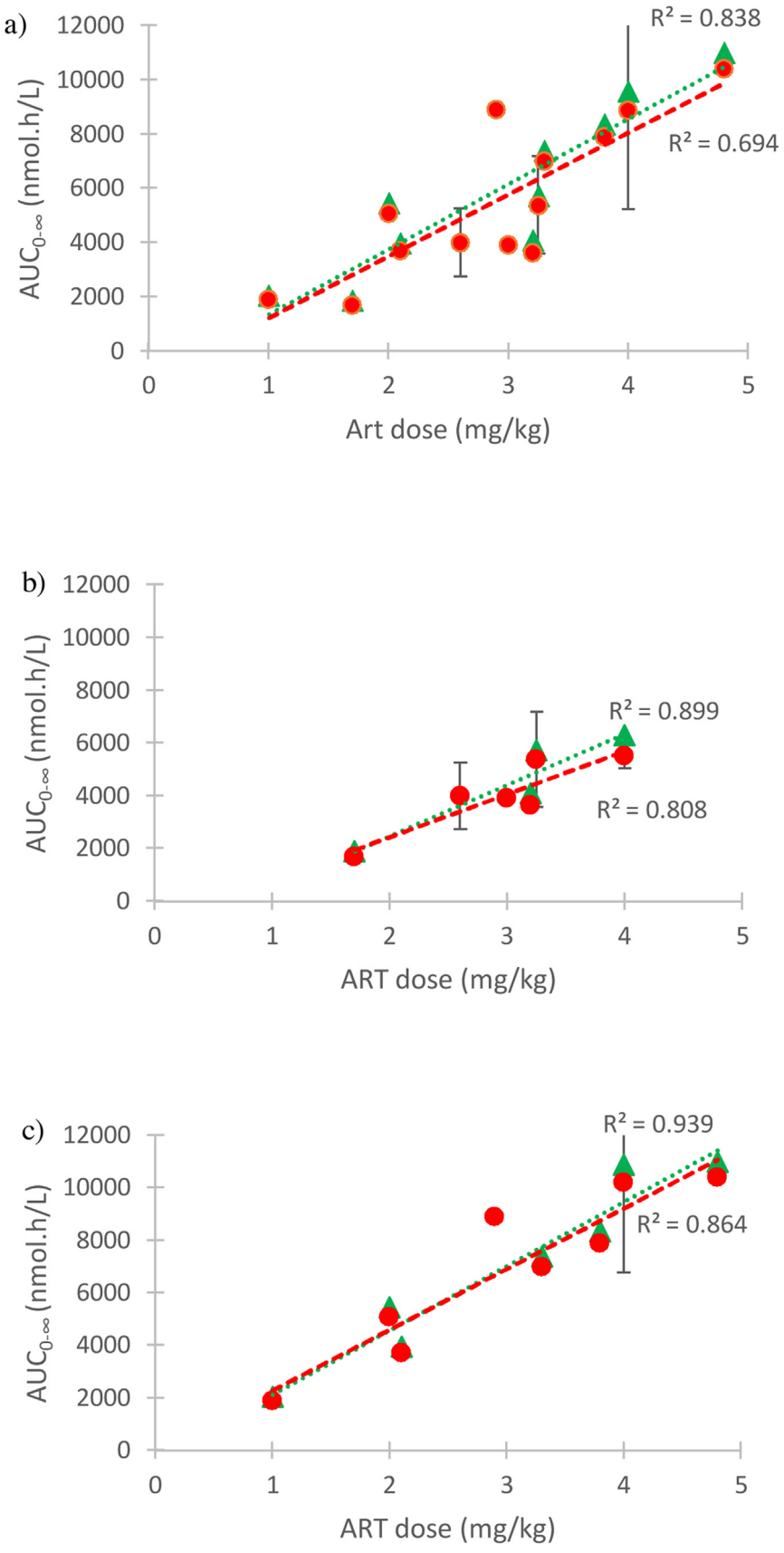


Figure 8. Correlation analysis between $AUC_{0-\infty}$ (nmol h/L) and dose (mg/kg) after ART PO administration in the whole population, in volunteers, and in patients. Comparison between DHA $AUC_{0-\infty}$ (red curve) and the sum of ART $AUC_{0-\infty}$ and DHA $AUC_{0-\infty}$ (green curve). Figure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

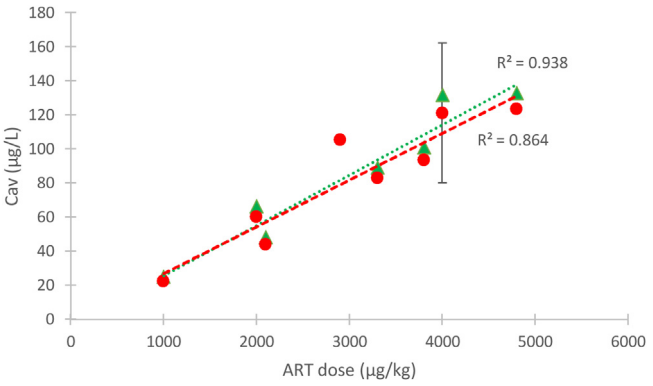


Figure 9. Correlation analysis between Cav (DHA and the sum of ART and DHA, in µg/L) and dose (µg/kg) after ART PO administration in patients.
Comparison between DHA Cav (red curve) and the sum of ART Cav and DHA Cav (green curve). Cav were first calculated for ART and DHA separately with the formula 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*.

stewardship programs, whose 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.

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Conflict of interest

None.

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