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Safety and Effectiveness of Intravenous Artesunate for Treatment of Severe Malaria in the United States—April 2019 Through December 2020

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Abstract

Background.—Severe malaria can be deadly and requires treatment with intravenous artesunate (IVAS). The Centers for Disease Control and Prevention provided IVAS starting 1 April 2019 for all patients with severe malaria in the United States. This study describes the safety and effectiveness of IVAS in these patients.

Methods.—Patients meeting criteria for severe malaria April 2019–December 2020 who received IVAS were included. Demographic, clinical, laboratory, adverse event, and outcome information were collected. Clinical presentation, time to reach 1% and 0% parasitemia, adverse events, and death were described using proportions, medians, interquartile range (IQR), and tests of significance for differences in proportions.

Results.—Of 280 patients included, the majority were male (61.4%), Black (75.0%), with a median age of 35 years (IQR: 15.8–53.9). Most had *Plasmodium falciparum* (83.6%) with median parasitemia of 8.0% (IQR: 4.6–13.2). Of 170 patients with information, 159 (93.5%) reached ≤1% parasitemia by the third IVAS dose with a median time of 17.6 hours (IQR: 10.8–28.8), and 0% parasitemia in a median of 37.2 hours (IQR 27.2–55.2). Patients with parasite densities >10% and those requiring adjunct therapy had significantly higher parasite clearance times. Adverse events associated with IVAS were reported in 4.8% (n = 13 of 271). Eight patients had post-artesunate delayed hemolysis that resolved. There were 5 (1.8%) deaths, all attributable to severe malaria.

Conclusions.—IVAS is a safe and effective drug for the treatment of severe malaria in the United States; timely administration can be lifesaving.

Keywords

effectiveness; intravenous artesunate; safety; severe malaria; United States

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Malaria is caused by a parasite that infects red blood cells 6 days to months after a bite by an infective *Anopheles* mosquito. The disease is endemic in 87 countries worldwide [1]. With a case-fatality rate approaching 100% for untreated severe disease, globally malaria kills more than 400 000 people annually [1]. Commensurate with an increase in global travel, the annual number of reported malaria cases in the United States between 1987 and 2017 more than doubled from 932 to 2161 cases [2]. The proportion of malaria cases that progressed to severe malaria also increased from 3.8% in 2007 to 14.4% in 2017 [2, 3], reflecting increased travel to Africa where *Plasmodium falciparum*, the species most likely to cause severe malaria, predominates [4]. In 2017, there were 312 cases of severe malaria in the United States and 7 deaths [2].

Severe malaria must be treated immediately with intravenous (IV) antimalarials to prevent poor outcomes including death [5]. IV quinidine, a derivative of quinine released in the United States as an antiarrhythmic, was the only Food and Drug Administration (FDA)-approved IV drug for treatment of severe malaria for decades, despite its association with potentially severe adverse effects [6]. An alternative treatment, IV artesunate (IVAS), was shown in 2 seminal studies to have fewer adverse effects, decrease parasite clearance time, and reduce mortality from severe malaria when compared with IV quinine [7, 8]. IVAS has been the WHO recommended treatment for severe malaria worldwide since 2010 [9].

Starting on 1 April 2019 when IV quinidine became unavailable in the United States, and IVAS became the first-line drug for treatment of severe malaria in the United States but was not yet approved by the FDA, the Centers for Disease Control and Prevention (CDC) launched the National Artesunate for Severe Malaria Program, making IVAS available from CDC under an investigational new drug (IND) protocol for all patients with severe malaria nationwide [10]. To ensure adequate supply, CDC requested additional IVAS stock from its US supplier, United States Army Medical Materiel Development Activity, and purchased supplemental product from an international manufacturer, Guilin Pharmaceuticals. Both products were thought to be equally safe and efficacious and were impartially distributed. Patients with severe malaria treated with IVAS are described here, including treatment outcomes and adverse events associated with this drug.

METHODS

Inclusion Criteria

Patients with malaria in the United States that meet certain criteria (Box 1) are eligible to receive IVAS under the IND protocol. Although these criteria included patients with uncomplicated malaria unable to tolerate oral medications, this descriptive study focuses only on the subset of patients with severe malaria (Box 1) receiving IVAS from April 2019 through December 2020.

Treatment and Follow-up

Clinicians caring for patients with severe malaria called CDC to obtain IVAS. CDC staff confirmed that criteria were met, and IVAS was released from sites across the country where drug was prepositioned. Dosing for IVAS was 2.4 mg/kg/dose for patients ≥ 20 kg and 3.0

mg/kg/dose for patients <20 kg given at time 0, 12, 24, and 48 hours for a total of 4 doses. Starting on 21 October 2019, IVAS dosing was changed to a 3-dose regimen (at 0, 12, and 24 hours) to align with WHO recommendations [6]. Additionally, starting from 26 May 2020, based on unpublished FDA pharmacokinetic simulations showing comparable efficacy with the use of 2.4 mg/kg dosing regardless of age, weight-based dosing was updated to the 2.4 mg/kg for all patients (WHO policy continues to recommend 3.0 mg/kg/dose for patients <20 kg). Clinicians were advised to treat patients in intensive care units and to provide supportive care as needed. Additionally, clinicians were asked to treat the patient with an oral antimalarial drug while waiting for IVAS to arrive. After completion of the IVAS doses, and if parasitemia was ≤1% and the patient was able to tolerate oral medication, an oral antimalarial regimen was given within 4–24 hours. If parasitemia was >1% after the recommended IVAS doses or the patient was unable to tolerate oral medications, IVAS could be continued daily for up to 7 days.

Clinicians were advised to repeat malaria smears every 12–24 hours until 2 consecutive blood smears were negative. All malaria smears were performed and read by the treating hospitals, and CDC provided diagnostic assistance when requested. During and after treatment, clinicians were required to report any serious adverse events to CDC within 24 hours. All reported adverse events were investigated and their relationship to IVAS was determined by CDC Principal Investigators.

Clinicians were also asked to monitor patients receiving IVAS weekly for up to 4 weeks after treatment for evidence of post-artesunate delayed hemolysis (PADH), a known adverse event of IVAS. Weekly laboratory evaluation for PADH included hemoglobin, reticulocyte count, haptoglobin, lactate dehydrogenase (LDH), and total bilirubin. PADH was defined as a nonrecurring event characterized by a 10% or greater decrease in hemoglobin levels in the setting of a haptoglobin level <0.1 g/L and an increase of LDH levels to >390 U/L, or an increase of ≥10% over baseline, at least 7 days after initiation of parenteral artesunate [11]. An event was considered as suspected PADH when there was a ≥10% decrease in hemoglobin concentration and either LDH *or* haptoglobin met criteria for diagnosis, but the other value was missing, or had not yet met the threshold.

At the end of hospitalization, clinicians reported outcomes including completion of treatment with survival, death (including cause), and lost to follow-up.

Data Collection and Management

Treating clinicians used standardized forms to collect information on patient demographics, eligibility criteria, laboratory values, antimalarial drugs taken, IVAS dosing, outcomes, and adverse events. Collection of information on antimalarial drugs given to patients while waiting for arrival of artesunate was initiated in October 2019. Data were submitted to CDC and entered into a Microsoft Access® Database.

Data Analysis

Patient demographics, clinical presentation, and antimalarial treatment received are described using proportions and medians with interquartile range (IQR) for categorical and continuous variables, respectively.

Drug effectiveness was assessed based on the number of IVAS doses and time from the initial IVAS dose required to reach ≤1% parasitemia, and complete parasite clearance (ie, first negative smear). Drug safety was described in terms of type and frequency of adverse events reported.

Additional analyses were conducted to determine if there were differences in the following categories (i) demographic and clinical presentations based on the drug manufacturer, (ii) time to negative blood smear based on admission parasitemia and use of adjunct therapy, and (iii) presence of PADH based on admission parasitemia. Categorical variables were compared using χ^2 and Fischer exact tests, and continuous variables were compared using Kruskal-Wallis tests with *P*-values < .05 considered statistically significant. Data analysis was performed using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina, USA).

Ethical Approval

An expanded access IND protocol, IND #76 725 was approved by the FDA. IND #76 725 covered CDC protocols for 2 products: CDC Institutional Review Board (IRB) #5032 for IV artesunate produced by Walter Reed Army Institute of Research (WRAIR) and CDC IRB #7171 for the product produced by Guilin Pharmaceutical. Both protocols were approved by CDC's IRB. Patients provided written informed consent before IVAS administration.

RESULTS

Patient Demographics

From April 2019 through December 2020, CDC released IVAS for 280 patients with a confirmed diagnosis of severe malaria. (Figure 1). Figure 2 depicts the states where IVAS was released for treatment of these 280 patients. Demographics are summarized in Table 1.

Clinical Presentation

Malaria was confirmed by microscopy for all patients by their treating hospitals. Clinical presentation is summarized in Table 1. Parasitemia was reported for 278 patients with a median of 8.0% (IQR: 4.6–13.2) and a range of 0.1%–69.0%. Patients were infected with primarily *P. falciparum* malaria (n = 234, 83.6%). The median number of clinical criteria reported was 2 (IQR: 1–3). The most frequently reported criteria for requiring IVAS was parasitemia ≥5% (n = 210, 75.0%), followed by acute kidney injury (n = 90, 32.1%) and signs of cerebral malaria (n = 82, 29.3%). Jaundice was also reported in 83 (29.6%) patients. For 73 patients (26.1%), parasitemia ≥ 5% was the only severe malaria criterion reported. For the 278 patients with parasitemia available, 70 (25.2%) had a parasitemia of <5% and 1 or more severe malaria criterion.

Treatment Regimen

Of 280 patients, 133 (47.5%) patients were treated with Guilin product, and 147 (52.5%) patients received the WRAIR product. There were no significant differences in demographics and clinical presentation between the two groups of patients treated with either drug product. Based on the protocol recommendations at the time of treatment, 154 (55.0%) patients were prescribed a 4-dose IVAS regimen and 126 (45.0%) a 3-dose regimen;

262 (93.6%) received all recommended doses. Of 154 patients on the 4-dose regimen, 14 discontinued IVAS (Table 2), and 1 patient received 4 extra doses due to continued inability to take and absorb oral medications. Of the 126 patients on the 3-dose regimen, 4 discontinued IVAS (Table 2), and 22 received additional doses. Reasons for additional doses included parasitemia level > 1% (n = 10), worsening clinical status (n = 4), and inability to take oral antimalarials (n = 8). Of the 126 patients with information collected, 113 (89.7%) received antimalarial drugs while awaiting arrival of artesunate (Table 3).

Among 262 patients who received all recommended number of IVAS doses per protocol, 245 (93.5%) received oral antimalarials after IVAS. Twelve (4.6%) patients received other antimalarials concurrently with IVAS administration. Atovaquone-proguanil was the most frequently prescribed post-IVAS drug (n = 123, 50.2%), followed by artemether-lumefantrine (n = 96, 39.2%) and doxycycline (n = 11, 4.5%); a few patients were treated with clindamycin (n = 3, 1.2%), clindamycin + quinine (n = 2, 0.8%), and other less frequently used drug combinations that are not recommended (n = 10). Timing of post-IVAS antimalarials was available for 212 patients. A total of 176 (83.0%) patients were started on oral antimalarials between 4 and 24 hours of the last IVAS dose; the median time from last IVAS dose to the first dose of oral antimalarial was 10.4 hours (IQR: 5.3–16.1).

Time to Clearance

The median number of IVAS doses needed to achieve a ≤1% parasitemia was 2 (IQR: 1–3) (n = 170); this equated to a median time of 17.6 hours (IQR: 10.8–28.8) (n = 167) from first IVAS dose. Of 170 patients with information, for 159 (93.5%) patients, ≤1% parasitemia was reached by the third IVAS dose (Table 4). Of the 167 patients with information, time to ≥1% parasitemia was significantly different between those with ≤10% parasitemia (n = 91) versus >10% (n = 76) parasitemia [14.5 hours (IQR: 10.3–25.9) versus 22.0 hours (IQR: 13.0–33.0), respectively, $P = .003$]. For 155 patients with data on timing of first IVAS dose and negative blood smear, the median time from first IVAS dose to complete parasitemia clearance was 37.2 hours (IQR: 27.2–55.2).

The median complete parasitemia clearance time was significantly different between those with parasitemia ≤10% at admission (n = 97) versus those with parasitemia >10% at admission (n = 58); 34.3 hours (IQR: 26.5–51.1) and 45.1 hours (IQR: 31.8–62.3), respectively ($P = .01$). There was no statistically significant difference in clearance times between those patients who did and did not receive oral therapy prior to IVAS and between patients who received the Guilin versus WRAIR products.

Adjunct Treatment

For 279 patients with data, a total of 117 (41.9%) patients received at least one adjunctive treatment. (Table 5). The median complete parasite clearance time from first IVAS dose was 42.6 hours (IQR: 32.0–60.7) for patients receiving adjunct treatment (n = 76) and 32.1 hours (IQR: 26.5–45.7) for those who did not receive adjunct treatment (n = 79) (P-value = .007). Patients who received adjunct therapy had a statistically significant higher number of severe malaria criteria met (median 2 [IQR: 1–2] vs 3 [IQR: 2–4]) but had similar parasitemia levels compared to those that did not receive adjunct therapy (median 8.0% vs 8.1%).

Adverse Events

For 271 patients with data, 34 adverse events were reported for 32 (11.8%) patients, with 2 patients experiencing more than 1 event. Upon investigation, 14 (41.2%) reported events among 13 patients were associated with IVAS administration. The most common adverse event was PADH occurring in 8 patients (3.0% of all patients receiving IVAS, 61.5% of patients with adverse events associated with IVAS). Four cases of suspected PADH were also reported. There was no difference in risk among those with a baseline parasitemia of ≤10% versus >10% parasitemia, or between Guilin versus WRAIR product. Most cases of PADH were mild and self-limiting; 4 patients with PADH (50.0%) and two with suspected PADH (50.0%) required blood transfusions, but all patients with PADH and suspected PADH recovered without additional sequalae. The final patient with an adverse event associated with IVAS developed rash, neutropenia (nadir 400/mm^3), and chills after treatment with IVAS and was started on levofloxacin prophylaxis and recovered without sequelae.

Outcome

All (98.2%) but 5 patients recovered from their severe malaria episode; the remaining 5 died. All 5 deaths were attributed to complications from severe malaria, including brain herniation, cerebral edema, ischemic stroke related to cerebral malaria, and multisystem organ failure. Parasitemia ranged from 6 to 77%; only 1 patient had taken chemoprophylaxis; 4 presented with impaired consciousness. Three pregnant women, all in their third trimester, survived, completing treatment without adverse events.

DISCUSSION

IVAS was an effective and safe drug for treatment of severe malaria in the United States in our analysis. This study describes one of the largest cohorts of severe malaria cases treated with IVAS in a nonendemic country [12–14]. All cases of severe malaria treated with IVAS in the United States during the study period are included in our analysis because during that time, CDC was the only source of IVAS in the country.

Prompt administration of IVAS is a lifesaving therapy. All but 5 patients (98.2%) treated with IVAS survived; all deaths were attributed to complications of severe malaria. Although a direct comparison to patients treated with quinidine was not done in this study, the observed mortality rate in our cohort (1.8%) appears lower than for patients with severe malaria treated with quinidine (3.0%) in the United States between the years 2012 and 2017 [2, 15–19].

Our findings support the CDC and WHO guidance of using a 3-dose IVAS regimen to rapidly drop parasitemia levels, followed by an oral antimalarial regimen to clear remaining parasites [6, 20]. Most patients only required two doses of IVAS to lower parasitemia to ≤1%, with nearly all patients (93.5%) below this parasitemia threshold after the third dose. Following IVAS with an oral antimalarial allowed for complete parasite clearance, which was achieved in less than 56 hours from first IVAS dose for all surviving patients.

Predictably, sicker patients (ie, higher baseline parasitemia and/or requiring adjunct therapy) took longer to attain a negative smear.

IVAS is generally a safe and well tolerated drug; in our study, the most commonly reported adverse event was PADH. PADH is a recognized adverse reaction to artesunate that can occur up to a month after treatment [21]. The prevalence of PADH in our cohort was less frequently reported than in other studies (3% in our study vs up to 33% in others) [12, 22, 23]. This difference may be due to variations in the definition of PADH and the limited available literature on this phenomenon. This low prevalence in the current study could also be due to underreporting or loss to follow-up. While clinicians were requested to do weekly labs to assess for PADH, only abnormal results indicating an adverse event were required to be reported. Therefore, a nonresponse to PADH follow-up could be lack of PADH, lack of detection due to weekly labs not being done, or patients lost to follow-up after discharge. Others have observed that a parasitemia of 10% is associated with increased risk for and severity of PADH [6, 24–26]. We did not observe an increased risk for PADH in those with >10% parasitemia compared to those with ≤10% parasitemia, but our number of patients with PADH were few. Although all cases of PADH resolved without sequelae, it is notable that 50% of patients with PADH or suspected PADH required blood transfusion. Weekly monitoring for the four weeks after IVAS treatment may help facilitate identification and management of PADH.

Although CDC recommends artemether-lumefantrine as the first choice oral antimalarial while awaiting arrival of and after IVAS treatment [20], atovaquone-proguanil was more frequently prescribed in our cohort. CDC recommends artemether-lumefantrine as the first-line oral antimalarial in accordance with WHO recommendations, and for its superior pharmacokinetic properties [6, 20]. The artemether component reaches peak concentration at 2 hours and median parasite clearance time is about 29 hours compared to 65 hours for atovaquone-proguanil [27, 28]. Atovaquone-proguanil may have been more easily accessible and readily available than artemether-lumefantrine at the treating hospitals and is an acceptable alternative for treatment. However, maintaining artemether-lumefantrine in stock allows for drug to be available for timely treatment of uncomplicated malaria, provides an effective drug while awaiting arrival of IVAS and as post-IVAS oral treatment for those with severe malaria.

The presentation of severe malaria in this cohort has implications for diagnosis. Notably, about one-quarter of cases had parasitemia ≥5% as the only criterion for severe malaria, and one-quarter had other severe criteria despite a parasitemia <5%. Microscopy findings including parasitemia should be used with clinical and other laboratory findings when assessing for severity.

Our study has limitations. Misclassification bias is possible as no central validation of malaria microscopy results took place. Without other FDA-approved IV antimalarial drugs available during the study period, a comparison group was not available. Other limitations include lack of data for initial antimalarial prescription and missing microscopy data that led to smaller sample sizes for some analyses. However, as CDC was the sole provider of IVAS in the country at that time, all patients treated with IVAS are accounted for in the analysis.

Hospitals need to be prepared to diagnose and treat malaria. While Figure 2 shows only where severe cases have occurred during the time period of study, annual malaria surveillance has demonstrated that cases occur in every state [2]. Severe malaria is effectively and safely treated with IVAS. With IVAS now being FDA approved and commercially available, hospital stocking of IVAS will expedite treatment of severe malaria. If IVAS is not in stock, patients should be started on an oral antimalarial while waiting for IVAS to arrive. As artemether-lumefantrine is the first-line drug for interim treatment while waiting for IVAS, post-IVAS treatment, and for treatment of uncomplicated malaria, it should also be stocked. Timely treatment also requires timely diagnosis. A pre-established workup plan of the febrile returned traveler includes on-site, timely, and quality malaria microscopy with an aim to diagnose patients with malaria as soon as possible, within 24 hours of seeking care, so that treatment can be started promptly. Finally, the importance of preventing malaria warrants greater emphasis. Prescription and careful adherence to malaria chemoprophylaxis course remains an underutilized but critically important prevention strategy to reduce the occurrence of severe malaria and the overall malaria burden in the United States [2].

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Disclaimer.

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

References

1. World Health Organization. World malaria report 2020: 20 years of global progress and challenges. Geneva: World Health Organization, 2020.
2. Mace KE, Lucchi NW, Tan KR. Malaria surveillance - United States, 2017. MMWR Surveill Summ 2021; 70:1–35.
3. Mali SS, Steele S, Slutsker L, Arguin PM. Malaria surveillance - United States, 2007. MMWR Surveill Summ 2009; 58:1–16.
4. National Travel and Tourism Office. International air travel statistics (I-92 data), 1996–2019. Available at: https://travel.trade.gov/research/monthly/departures/index.asp. Accessed 7 April 2021.
5. Hess KM, Goad JA, Arguin PM. Intravenous artesunate for the treatment of severe malaria. Ann Pharmacother 2010; 44:1250–8. [PubMed: 20551300]
6. World Health Organization. Guidelines for the treatment of malaria. 3rd ed. Geneva: World Health Organization, 2015.
7. Dondorp A, Nosten F, Stepniewska K, Day N, White N; South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. Lancet 2005; 366:717–25. [PubMed: 16125588]
8. Dondorp AM, Fanello CI, Hendriksen IC, et al. ; AQUAMAT group. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. Lancet 2010; 376:1647–57. [PubMed: 21062666]
9. World Health Orgranization. Guidelines for the treatment of malaria. 2nd ed. Geneva: World Health Organization, 2010.

10. Centers for Disease Control and Prevention. Availability of intravenous artesunate for treatment of severe malaria in the United States. Available at: https://www.cdc.gov/malaria/new_info/2019/artesunate_2019.html. Accessed 7 April 2021.
11. Paczkowski MM, Landman KL, Arguin PM. Update on cases of delayed hemolysis after parenteral artesunate therapy for malaria - United States, 2008 and 2013. MMWR Morb Mortal Wkly Rep 2014; 63:753–5. [PubMed: 25166926]
12. Kreeftmeijer-Vegter AR, van Genderen PJ, Visser LG, et al. Treatment outcome of intravenous artesunate in patients with severe malaria in the Netherlands and Belgium. Malar J 2012; 11:102. [PubMed: 22462806]
13. El Ket N, Kendjo E, Thellier M, et al. Propensity score analysis of artesunate versus quinine for severe imported *Plasmodium falciparum* malaria in France. Clin Infect Dis 2020; 70:280–7. [PubMed: 30874798]
14. Kurth F, Develoux M, Mechain M, et al. Severe malaria in Europe: an 8-year multi-centre observational study. Malar J 2017; 16:57. [PubMed: 28143519]
15. Cullen KA, Arguin PM, Centers for Disease C, Prevention. Malaria surveillance - United States, 2012. MMWR Surveill Summ 2014; 63:1–22.
16. Cullen KA, Mace KE, Arguin PM, Centers for Disease C, Prevention. Malaria Surveillance - United States, 2013. MMWR Surveill Summ 2016; 65:1–22.
17. Mace KE, Arguin PM. Malaria surveillance - United States, 2014. MMWR Surveill Summ 2017; 66:1–24.
18. Mace KE, Arguin PM, Lucchi NW, Tan KR. Malaria surveillance - United States, 2016. MMWR Surveill Summ 2019; 68:1–35.
19. Mace KE, Arguin PM, Tan KR. Malaria surveillance - United States, 2015. MMWR Surveill Summ 2018; 67:1–28.
20. Centers for Disease Control and Prevention. Malaria treatment (United States). Available at: https://www.cdc.gov/malaria/diagnosis_treatment/treatment.html. Accessed 7 April 2021.
21. Jauréguiberry S, Ndour PA, Roussel C, et al. ; French Artesunate Working Group. Postartesunate delayed hemolysis is a predictable event related to the lifesaving effect of artemisinins. Blood 2014; 124:167–75. [PubMed: 24859359]
22. Kurth F, Develoux M, Mechain M, et al. ; TropNet Severe Malaria Investigator Group. Intravenous artesunate reduces parasite clearance time, duration of intensive care, and hospital treatment in patients with severe malaria in Europe: the TropNet Severe Malaria Study. Clin Infect Dis 2015; 61:1441–4. [PubMed: 26187021]
23. Bélard S, Brand J, Schulze-Sturm U, et al. Intravenous artesunate for imported severe malaria in children treated in four tertiary care centers in Germany: a retrospective study. Pediatr Infect Dis J 2019; 38:e295–300. [PubMed: 31626041]
24. Rolling T, Schmiedel S, Wichmann D, Wittkopf D, Burchard GD, Cramer JP. Post-treatment haemolysis in severe imported malaria after intravenous artesunate: case report of three patients with hyperparasitaemia. Malar J 2012; 11:169. [PubMed: 22594446]
25. Rehman K, Lötsch F, Kremsner PG, Ramharter M. Haemolysis associated with the treatment of malaria with artemisinin derivatives: a systematic review of current evidence. Int J Infect Dis 2014; 29:268–73. [PubMed: 25448338]
26. Briggs MA, Arguin PM. Published reports of delayed hemolytic anemia after treatment with artesunate for severe malaria—worldwide, 2010–2012. MMWR Morb Mortal Wkly Rep 2013; 62:5–8. [PubMed: 23302816]
27. Looareesuwan S, Viravan C, Webster HK, Kyle DE, Hutchinson DB, Canfield CJ. Clinical studies of atovaquone, alone or in combination with other antimalarial drugs, for treatment of acute uncomplicated malaria in Thailand. Am J Trop Med Hyg 1996; 54:62–6. [PubMed: 8651372]
28. Lefèvre G, Looareesuwan S, Treeprasertsuk S, et al. A clinical and pharmacokinetic trial of six doses of artemether-lumefantrine for multidrug-resistant *Plasmodium falciparum* malaria in Thailand. Am J Trop Med Hyg 2001; 64:247–56. [PubMed: 11463111]

BOX 1:

Eligibility criteria for treatment with intravenous artesunate.

- Malaria confirmation by microscopy. In exceptional cases and after discussion with a CDC Malaria Branch clinician, microscopic diagnosis might be waived for a patient with strong clinical suspicion of malaria for whom a timely, reliable microscopic diagnosis is not available; AND
- Parenteral treatment required due to 1 or more of the following reasons:
  - Severe malaria based on at least 1 of the following:
    - High parasitemia (≥5%)
    - Impaired consciousness
    - Seizures
    - Circulatory collapse/shock
    - Pulmonary edema or acute respiratory distress syndrome (ARDS)
    - Acidosis
    - Acute kidney injury
    - Abnormal bleeding or disseminated intravascular coagulation (DIC)
    - Jaundice (must be accompanied by at least 1 other sign)
    - Severe anemia (Hb <7 g/dL)
  - Inability to take oral medications despite attempt after an oral antiemetic

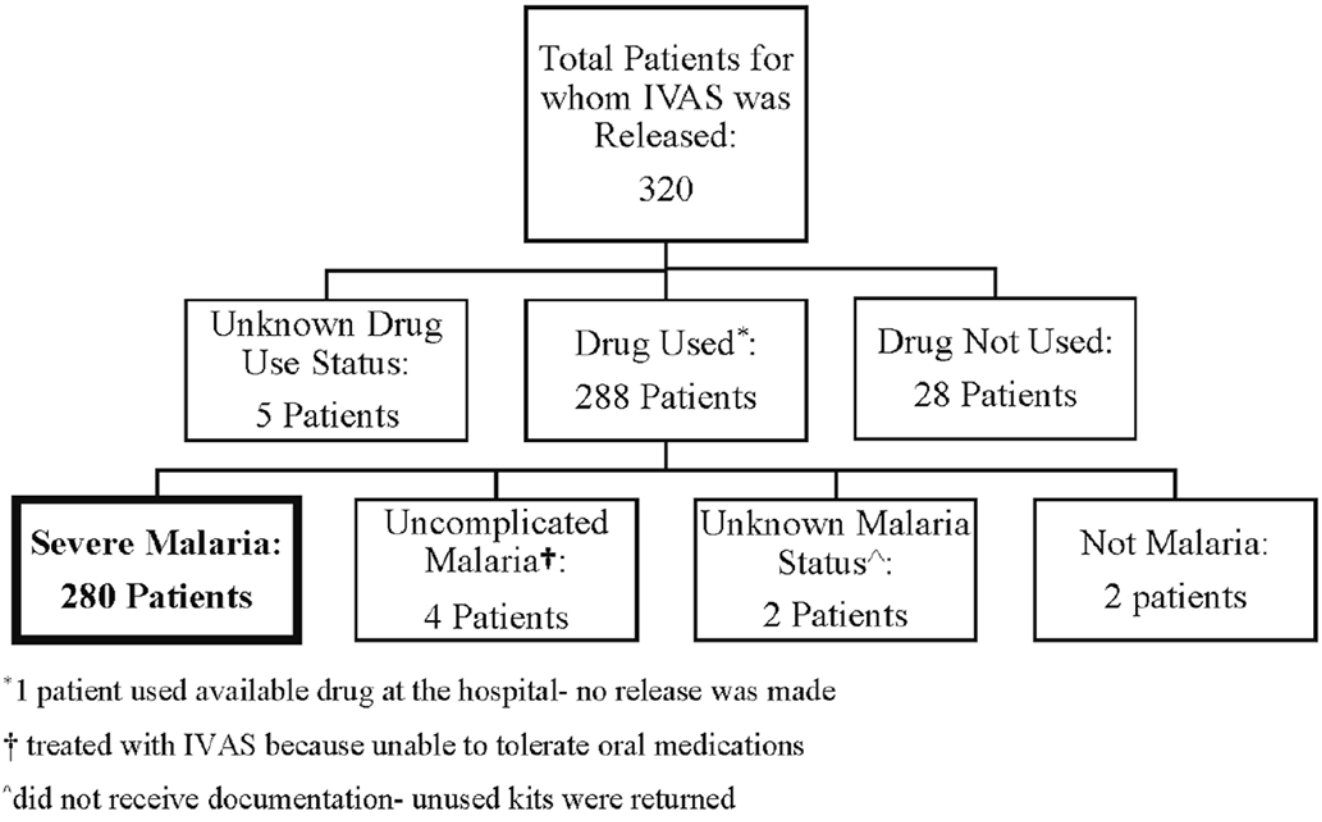

Figure 1.
Overall releases and use of intravenous artesunate (IVAS) in patients from 1 April 2019 to 31 December 2020.

Figure 2.

States where cases of severe malaria were treated with intravenous artesunate (IVAS) (1 April 2019 to 31 December 2020).

Table 1.

Demographic and Clinical Characteristics of Patients Receiving Intravenous Artesunate (IVAS) for Malaria Treatment, According to IVAS Drug Manufacturer, United States, 2019–2020

Characteristic	All Patients (N = 280) No. (%) or Median (IQR)	WRAIR (N = 147) No. (%) or Median (IQR)	Guilin (N = 133) No. (%) or Median (IQR)
Age (years)	35.2 (15.8–53.9)	34.4 (12.9–55.9)	35.7 (179–53.0)
Children (≤18 years)	80 (28.6)	46 (31.3)	34 (25.6)
Sex, male	172 (61.4)	89 (60.5)	83 (62.4)
Weight (kg)	73.0 (55.1–88.0)	71.1 (50.0–87.0)	74.9 (58.0–88.6)
Pregnancy status	3 (1.1)	2 (1.4)	1 (0.8)
Race/Ethnicity			
Black	210 (75.0)	116(78.9)	94 (70.7)
White	50 (19.7)	21 (14.3)	29 (21.8)
Asian	9 (2.8)	6 (4.1)	3 (2.3)
Other/unknown	11 (2.8)	4 (2.7)	7 (5.3)
Ethnicity, Non-Latino	275 (98.2)	145 (98.6)	130 (97.4)
Malaria criteria[a]			
Inability to take oral medication	44 (15.7)	20 (13.6)	24 (18.1)
Parasitemia ≥5%	210 (75.0)	109 (74.2)	101 (75.9)
Impaired consciousness	82 (29.3)	40 (27.2)	42 (31.6)
Seizures	8 (2.9)	6 (4.1)	2 (1.5)
Circulatory collapse/shock	46 (16.4)	21 (14.3)	25 (18.8)

Characteristic	All Patients (N = 280) No. (%) or Median (IQR)	WRAIR (N = 147) No. (%) or Median (IQR)	Guilin (N = 133) No. (%) or Median (IQR)
Pulmonary edema or ARDS	24 (8.6)	15 (10.2)	9 (6.8)
Acidosis	58 (20.7)	33 (22.5)	25 (18.8)
Acute kidney injury	90 (32.1)	47 (32.0)	43 (32.3)
Abnormal bleeding or DIC	23 (8.2)	14 (9.5)	9 (6.8)
Severe anemia	31 (11.1)	13 (8.8)	18 (13.5)
Jaundice	83 (29.6)	47 (32.0)	36 (27.1)
Parasite species			
P. falciparum	234 (83.6)	129 (87.8)	105 (79.0)
P. vivax	8 (2.9)	2 (1.4)	6 (4.5)
P. malariae	1 (0.4)	0 (0.0)	1 (0.8)
Mixed	4 (1.4)	1 (0.7)	3 (2.3)
P. falciparum and P. malariae	2	1	1
P. falciparum and P. vivax	1	0	1
P. vivax and P. ovale	1	0	1
Unknown	33 (11.8)	15 (10.2)	18 (13.5)
Parasite density[b]	N = 278	N = 145	N = 133
At admission (%)	8.0 (4.6–13.2)	70 (4.2–13.0)	8.6 (4.8–13.3)

Abbreviations: ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation; IQR, interquartile range; WRAIR, Walter Reed Army Institute of Research.

[a] Criteria are not mutually exclusive. Patients can present with more than one criterion. No significant differences using χ^2 or Fisher's or Kruskal-Wallis test.

[b] Percent of peripheral erythrocytes infected.

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Table 2.

Reasons for Discontinuing Intravenous Artesunate (IVAS) Prematurely

	4-dose Regimen	3-dose Regimen
Reason for Discontinuation	**Frequency (N = 14)**	**Frequency (N = 4)**
Clinical improvement	4	3
Death	1	1
No reason provided	5	0
Other[a]	4	0

[a]Left against medical advice (1), administration issues (1), error in clinical advice (2).

Table 3.

Antimalarial Drugs Taken While Waiting for Intravenous Artesunate (IVAS) (N = 113)

Antimalarial Drug	Frequency (%)
Atovaquone-proguanil (AP)	53 (46.9)
Coartem	35 (31.0)
Quinine + doxycycline	9 (8.0)
Other[a]	16 (14.1)

[a]AP + doxycycline (3); Coartem + AP (3); Coartem + doxycycline (2); quinine + clindamycin (1); mefloquine + doxycycline (1); doxycycline + clindamycin (1); AP + doxycycline + clindamycin (1); mefloquine (1); doxycycline (1); chloroquine (1); hydroxychloroquine (1).

Table 4.

Number of Intravenous Artesunate (IVAS) Doses Before Reaching ≤1% Parasitemia Level (N = 170)

Number of IVAS Doses Administered	Frequency (%)	Cumulative Frequency (%)
1	53 (31.2)	53 (31.2)
2	55 (32.4)	108 (63.5)
3	51 (30)	159 (93.5)
4	10 (5.9)	169 (99.4)
5	1 (0.59)	170 (100)

Table 5.

Adjunct Therapies

Type	Frequency (%)
Blood product transfusions	77 (27.6)
Vasopressors	39 (14.0)
Dialysis	25 (9.0)
Respiratory support	24 (8.6)
Fluid support	7 (7.7)
Exchange transfusion	4 (1.4)
Other[a]	3 (1.2)

[a]Antiepileptic and insulin (1), antiemetic (1), supportive care, unspecified (1).