New Drugs for Malaria

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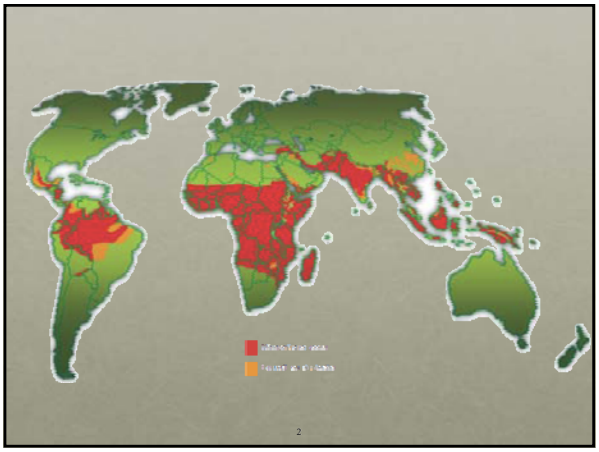
This talk may be politically incorrect or in bad taste.Viewer discretion is advised



Scenario#1 Fever from Kenya

- A 37 year old traveller returns from a one month vacation in rural Kenya with a one week history of fever and looks unwell; no malaria chemoprophylaxis
- Laboratory reports: <1%parasitemia and 100,000 platelets/cumm
- RDT for malaria positive for falciparum malaria
- How would you manage this case?

What to do?

- A. oral quinine plus doxycyline
- B. atovaquone/proguanil
- C. chloroquine plus primaquine
- D. chloroquine alone
- E. artemether /lumefantrine

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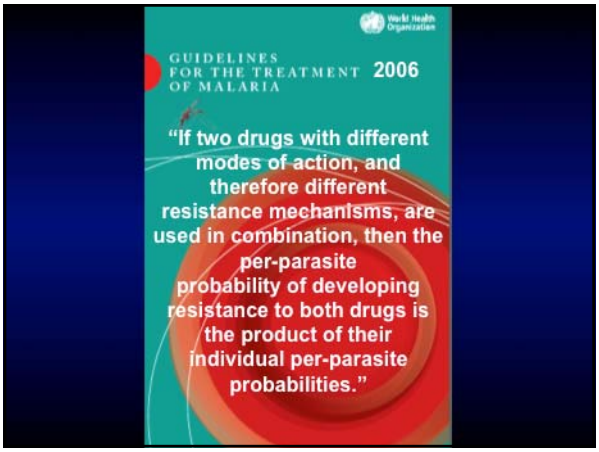

ACT: Artemisisin Combination Therapy

- Artesunate-amodiaquine
- Dyhidroartemesinin -piperaquine
- Artesuante-mefloquine
- Artesunate-pyronaridine
- Artesunate-chlorproguanil-dapsone
- Artemether-lumefantrine

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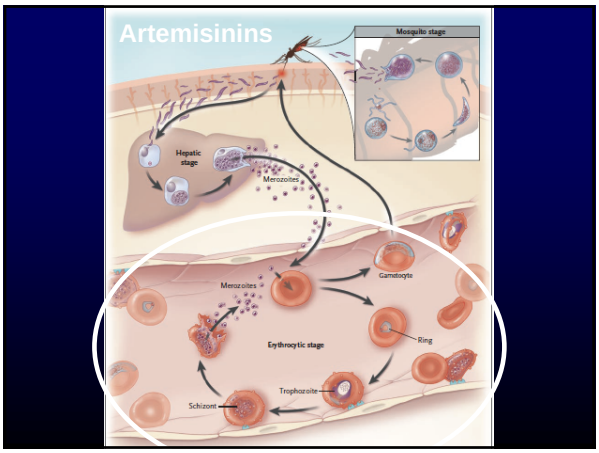

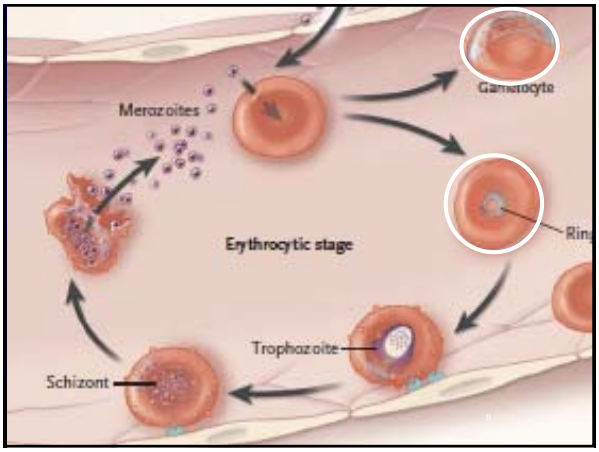

Artemether-lumefantrine

- **Artemether:** rapid acting short 1/2 life 45 min.
- **MOA:** Iron in heme (Fe-protoporphyrin) reduces peroxide bond in artemesinin → reactive oxygen radicals → parasite kill

Artemether-lumefantrine

- **Lumefantrine:** slow acting, long 1/2 life 36 hrs.

MOA: inhibition of hemepolymerase:

1. Hemoglobin breakdown by parasite →

- heme, → heme-heme polymer is which non-toxic

2. inhibition of the polymerase enzyme

free heme → toxic to parasite

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Artemether-lumefantrine dose

On April 8, 2009, Coartem approved by the FDA for the treatment of acute, ***uncomplicated*** malaria in adults and children weighing at least 5kg

Adult dose : 4 tabs stat; then 4 in 8 hours; then, 4 tabs bid for 2 days = total 24 tablets

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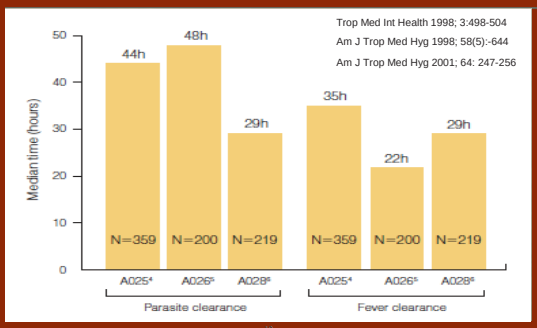
Artemether-lumefantrine parasite/fever clearance time



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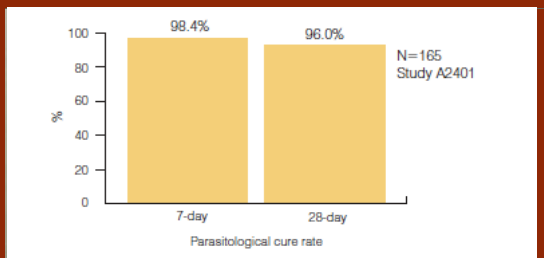
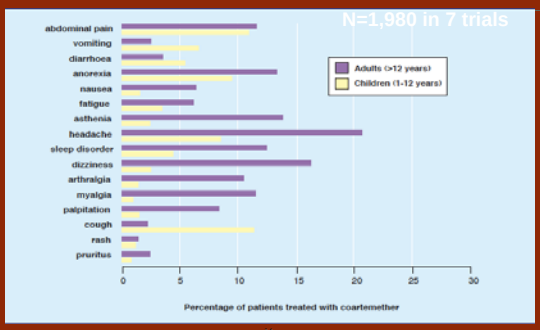
Artemether-lumefantrine efficacy in non-immunes



Am J.Trop Med Hyg. 2008:78:241

Artemether-lumefantrine drug-related adverse events



Am. J. Trop. Med. Hyg., 78(2), 2008, pp. 241–247

Treatment of Acute Uncomplicated Falciparum Malaria with Artemether-Lumefantrine in Non-immune Populations: A Safety, Efficacy, and Pharmacokinetic Study

Christoph Hatz,* Jaime Soto, Hans Dieter Nothdurft, Thomas Zoller, Thomas Weitzel, Louis Loutan, Francois Bricaire, Frederick Gay, Gerd-Dieter Burchard, Kim Andriano, Gilbert Lefèvre, Patricia Ibarra De Palacios, and Blaise Genton

Medical Department, Swiss Tropical Institute, Basel, Switzerland; CIBIC, Centro de Investigaciones Bioclínicas, Bogotá, Colombia; Department of Tropical Medicine and Infectious Diseases, University of Munich, Munich, Germany; University Hospital Charité, Berlin, Germany; Travelmedical, Berlin, Berlin, Germany; Hospital Cantonal, Geneva, Switzerland; Hôpital Bichat-Claude Bernard, Paris

Drug related AEs (mild to moderate) :
29% n=48/165

seemed to be related to malaria. There were few serious adverse events, none of which were considered to be drug-related. No significant effects on ECG or laboratory parameters were observed. In conclusion, the six-dose regimen of artemether-lumefantrine was effective and well tolerated in the treatment of acute uncomplicated falciparum malaria in non-immune patients.

Am. J. Trop. Med. Hyg.,2008 78:241–247

In spite of lumefantrine's similarity to halofantrine:

No serious adverse events attributable to QTc prolongation (e.g. syncope, sudden death) have been reported in clinical trials.

Adverse events: art/lumefantrine vs. atovaquone/proguanil in non-immunes

Drug related AE	Coartem	Malarone
	%(?) n=1,980	% (17) n=103/586
Insomnia	12.5	-
Headache	22	4.0
Vomiting	2.5	<1
Diarrhea	3.0	1.5
Nausea	6.2	-
Anorexia	13.5	1
Abdominal pain	12	3.5
Cough	2.5	0,5

Artemether lumefantrine vs. Atovaquone proguanil

Parameter	Atovaquone proguanil	Artemether lumefantrine
Efficacy "fatty meal"	few treatment failures PCT 4 days FCT 2 days	few treatment failures PCT 2 days FCT 1 day
Safety	well tolerated	more GI upset and headache
Convenience	once daily doses over 3 days	6 doses over 3 days
Cost (USD)	106.79	100,00

Scenario #2 Malicious Malaria from Madagascar

- 66 yr. old man returns from a 3 week trip to Madagascar; non-compliant with malaria prophylaxis
- one week after return: fever, chills, headache for 4 days and is now confused
- RDT+ blood film Pf. > 30% parasitemia and increased creatinine

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Scenario #4 Malicious Malaria from Madagascar

After you change your underwear you call pharmacy for IV quinidine and she says they don't have any.

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What to do?

- A. Use oral quinine with a loading dose
- via an NG tube
- B. Use oral artemether/lumefrantrine
- C Use oral atovaquone/proguanil
- D. Call the CDC to ask for IV artesunate
- E. Pray at the institution of your choice


World Health Organization
GUIDELINES FOR THE TREATMENT OF MALARIA
Mortality rate for treated severe falciparum malaria = 10-40%


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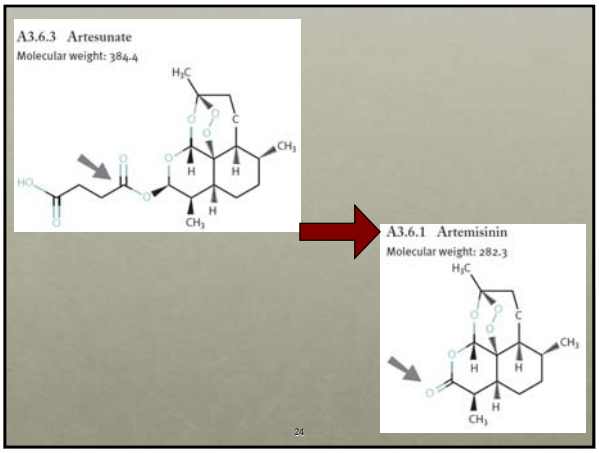
Malaria
Artemesinin Combination Therapy (ACT)
Malaria Home >
Artesunate now available to treat severe malaria in US
Artesunate is in the class of medications known as artemesinins, which are derivatives from the "quinghaosu" or sweet wormwood plant (Artemisia annua).
2.4 mg/kg IV stat, 12 hr , 24hr, then daily …then doxycycline or clindamycin x 7days or Malarone x 3days
Photographer: Emmet J. Judziewicz , University of Wisconsin-Stevens Point and Madison


A3.6.3 Artesunate
Molecular weight: 384.4
A3.6.1 Artemisinin
Molecular weight: 282.3
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Artesunate Treatment

4-dose regimen of IV artesunate is recommended as follows: 2.4 mg/kg IV at 0, 12, 24, and 48 hours (total dose 9.6 mg/kg)

Administered IV push over 1-2 minutes following reconstitution of drug into an established IV filtered line.

Artesunate may be mixed with 5 mL of 5% dextrose or normal saline prior to injection.

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Artesunate Treatment

plus

one of the following follow-on oral agents (to start 4-hours after last dose of IV artesunate:

- atovaquone/proguanil
- doxycycline
- clinamycin

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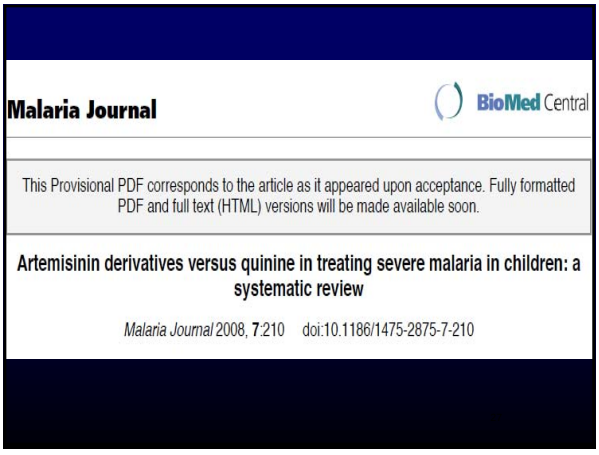


Malaria Journal

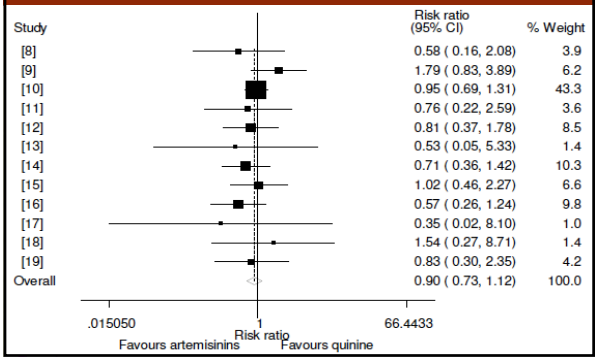
BioMed Central

This Provisional PDF corresponds to the article as it appeared upon acceptance. Fully formatted PDF and full text (HTML) versions will be made available soon.

Artemisinin derivatives versus quinine in treating severe malaria in children: a systematic review

Malaria Journal 2008, **7**:210 doi:10.1186/1475-2875-7-210

Mortality in children with severe malaria treated with quinine vs artemisinins



Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial

*South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group**

Summary

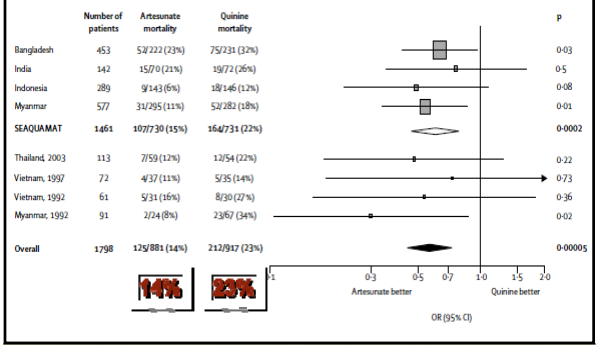
Background In the treatment of severe malaria, intravenous artesunate is more rapidly acting than intravenous quinine in terms of parasite clearance, is safer, and is simpler to administer, but whether it can reduce mortality is uncertain.

Methods We did an open-label randomised controlled trial in patients admitted to hospital with severe falciparum malaria in Bangladesh, India, Indonesia, and Myanmar. We assigned individuals intravenous artesunate 2·4 mg/kg bodyweight given as a bolus (n=730) at 0, 12, and 24 h, and then daily, or intravenous quinine (20 mg salt per kg loading dose infused over 4 h then 10 mg/kg infused over 2–8 h three times a day; n=731). Oral medication was substituted when possible to complete treatment. Our primary endpoint was death from severe malaria, and analysis was by intention to treat.

Findings We assessed all patients randomised for the primary endpoint. Mortality in artesunate recipients was 15% (107 of 730) compared with 22% (164 of 731) in quinine recipients; an absolute reduction of 34·7% (95% CI 18·5–47·6%; p=0·0002). Treatment with artesunate was well tolerated, whereas quinine was associated with hypoglycaemia (relative risk 3·2, 1·3–7·8; p=0·009).

Interpretation Artesunate should become the treatment of choice for severe falciparum malaria in adults.

Forest plot of mortalities comparing IV quinine and artesuante in Tx severe malaria in SE Asia



CDC malaria hotline :criteria

- severe malaria disease
- high levels of malaria parasites in the blood
- inability to take oral medications
- lack of timely access to intravenous quinidine
- quinidine intolerance or contraindications
- quinidine failure

CDC response time to artesunate request

Time from….	Mean
Artesunate request to shipment	2.7 hours
Artesunate arrival to treatment	2.9 hours
Artesunate request to treatment	7.2 hours

CDC

Artemisinin Antimalarials in Pregnancy: A Prospective Treatment Study of 539 Episodes of Multidrug-Resistant *Plasmodium falciparum*

Rose McGready,[1,2,3] Thein Cho,[1] Napaporn Khan Keo,[1] Kyaw Lay Thwai,[1] Leopoldo Villegas,[1,2,4] Sornchai Looareesuwan,[2] Nicholas J. White,[2,3] and François Nosten[1,2,3]

[1]Shoklo Malaria Research Unit, Mae Sot, and [2]Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; [3]Centre for Tropical Medicine, Nuffield Department of Medicine, John Radcliffe Hospital, Headington, Oxford, United Kingdom; and [4]Instituto de Altos Estudios en Salud Pública, Ministerio de Sanidad y Desarrollo Social, Maracay, Venezuela

N=539 ; 44 first trimester

Birth Outcomes: no difference in abortion, stillbirth, congenital abnormality, gestation at pregnancy

about the safety of these valuable antimalarials in pregnancy is needed.

Malar J. 2009 Jul 28;8:172.

A stratified random survey of the proportion of poor quality oral artesunate sold at medicine outlets in the Lao PDR - implications for therapeutic failure and drug resistance.

Sengaloundeth S, Green MD, Fernández FM, Manolin O, Phommavong K, Insixiengmay V, Hampton CY, Nyadong L, Mildenhall DC, Hostetler D, Khounsaknalath L, Vongsack L, Phompida S, Vanisaveth V, Syhakhang L, Newton PN.

Food and Drug Department, Ministry of Health, Government of the Lao PDR, Vientiane, Lao PDR. sivong_sengaloundeth@yahoo.com

- **180 outlets sampled in Laos**
- **25 (14%) sold artesunate**
- **88% sold counterfeit artesunate**

95 %CI 68.8-97.4%) sold counterfeit artesunate, as defined by packaging and chemistry. No artesunate was detected in the counterfeits by any of the chemical analysis techniques and analysis of the packaging demonstrated seven different counterfeit types. There was complete agreement between the Fast Red dye test, HPLC and MS analysis. A wide variety of wrong active ingredients were found by MS. Of great concern, 4/27 (14.8%) fakes contained detectable amounts of artemisinin (0.26-115.7 mg/tablet). CONCLUSION: This random survey confirms results from previous

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Scenario #3

- **An 18 yr old high school student with a controlled seizure disorder, psoriasis, and tetracycline allergy plans a 3 month gap year to rural Guatemala as a volunteer.**

What would you recommend for this bizzaro for malaria prophylaxis?

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What to do?

- A. azithromycin
- B. chloroquine
- C. mefloquine
- D. primaquine
- E. arteether

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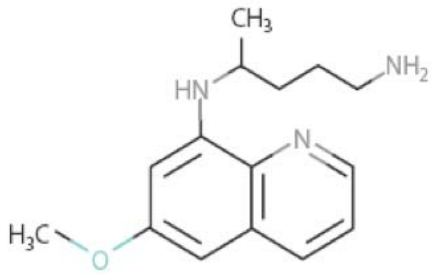
A3.8 Primaquine

8-aminoquinoline

Molecular weight: 259.4



Primaquine

8-aminoquinoline
Rapid absorption peak 1-2 hrs.
Liver metabolism →
carboxyprimaquine
T1/12 3-6 hrs.
Potent oxidizing agent

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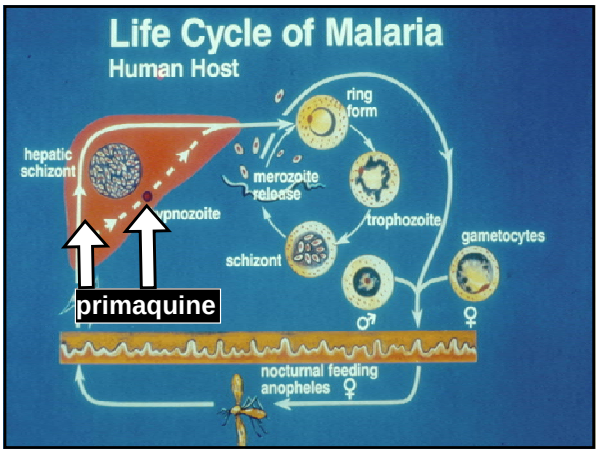

Antimicrob Agents Chemother. 2009 Dec 7. [Epub ahead of print]

Randomized, Double-Blind Study of the Safety, Tolerability and Efficacy of Tafenoquine versus Mefloquine for Malaria Prophylaxis in Non-Immune Subjects.

Nasveld PE, Edstein MD, Reid M, Brennan L, Harris IE, Kitchener SJ, Leggat PA, Pickford P, Kerr C, Ohrt C, Prescott W; the Tafenoquine Study Team.

Phase III trial tafenoquine vs mefloquine
Australian military :tafen. 200/wk vs mef. 250.wk +PART x 6mo.

ADR: 13 vs 12 %; 3 vs 1D/C drug
"Efficacy" equivalent re: vivax relapses post-exposure

Caveat:93% on tafenoquine : mild reversible vortex keratopathy

Summary

- Primaquine is now a drug of choice for prevention of vivax malaria in areas with > 90% *P.vivax*
- IV artesunate available for treatment of severe malaria
- Artemether-lumefantrine a DOC for uncomplicated Pf esp hi parasitemia

References

- 1. Nosten F & White NJ*Artemisinin-Based Combination Treatment of Falciparum Malaria*Am. J. Trop. Med. Hyg.* 2007, 77(Suppl 6),:181–192
- 2. Rosenthal PJ Artesunate for Treatment of Severe Falciparum Malaria N Engl J Med 2008;358:1829-36.
- 3.Hill D.CDC Expert committee report on primaquine AJTMH 2006;76:403