Online Quiz

Treating *Plasmodium falciparum* Malaria with Artemisinin Derivatives

This quiz is related to a Perspective article (DOI:10.1371/journal.pmed.0020368) and a Research Article (10.1371/journal.pmed.0020330) in the November issue.

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Question 1. Roughly how many episodes of *falciparum* malaria were there in 2002?

- ○ 10 million
- ○ 100 million
- ○ 500 million

Question 2. Roughly how many deaths occur each year as a result of severe *falciparum* malaria?

- ○ 100,000–500,000
- ○ 1–3 million
- ○ 3–5 million

Question 3. For uncomplicated *falciparum* malaria, which of the following best reflects the evidence on empirical treatment (i.e., giving antimalarial drugs to all people with fever without confirming the disease) in stable endemic areas?

- ○ There is good evidence from randomized controlled trials (RCTs) that empirical treatment is more clinically effective and cost effective than treating only cases confirmed by microscopy or rapid diagnostic tests
- ○ There is good evidence from RCTs that empirical treatment is less clinically effective and less cost-effective than treating only cases confirmed by microscopy or rapid diagnostic tests
- ○ There have been no RCTs comparing these two approaches

Question 4. Which of the following is true about artemisinin-based combination therapy?

- ○ Artemisinin-based combination therapy (ACT) is more expensive than chloroquine by a factor of 10–20
- ○ In Africa, there are high rates of *falciparum* resistance to artemisinin derivatives
- ○ The WHO does not recommend ACT as a first-line treatment for *falciparum* malaria

Question 5. Which of the following best reflects the evidence on adding artesunate to amodiaquine, rather than using amodiaquine alone, for treating uncomplicated *falciparum* malaria?

- ○ The combination treatment is associated with a lower rate of parasitological failure (parasitemia detected within a specific time after treatment), but it does not reduce gametocytemia (microscopic evidence of gametes in the blood) compared with amodiaquine alone
- ○ The combination treatment is associated with a lower rate of parasitological failure and with a lower rate of gametocytemia
- ○ The combination therapy is associated with a significantly higher rate of adverse events

Question 6. Which one of the following best reflects the evidence on using artesunate plus SP for treating uncomplicated *falciparum* malaria?

- ○ There is very good evidence that this combination is more effective than SP alone, and that it is more effective than amodiaquine plus SP
- ○ There is no good evidence that artesunate plus SP is more effective than SP alone
- ○ There is very good evidence that artesunate plus SP is more effective than SP alone, but there is little evidence that artesunate plus SP is more effective than amodiaquine plus SP

Question 7. Which of the following best reflects the evidence on ACT for treating uncomplicated *falciparum* malaria?

- ○ Six doses of artemether-lumefantrine given over three days increases treatment cure rates compared with a four-dose regime
- ○ Artesunate plus chlorproguanil-dapsone is more effective than artemether-lumefantrine
- ○ Artemether-lumefantrine is more effective than artesunate-mefloquine

Question 8. The WHO recommends that countries use a combination of drugs to treat *falciparum* malaria once resistance to monotherapies has exceeded which of the following levels?

- ○ Resistance in more than 10% of cases
- ○ Resistance in more than 20% of cases
- ○ Resistance in more than 30% of cases

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Question 9. Which of the following is true about global ACT supply and demand?

- ○ There is a wide variety of different ACTs available for use by countries as a coformulated blister pack
- ○ The WHO estimates that at least 132 million courses of ACT will be needed in 2005
- ○ Although artemisinin compounds are derived from a raw substance extracted from the plant *Artemisia annua*, a synthetic version is now available for clinical use

Question 10. Which of the following best reflects the evidence on using artemether for treating severe, life-threatening *falciparum* malaria in nonpregnant patients?

- ○ Death rates are higher with artemether than with quinine
- ○ Death rates are higher with quinine than with artemether
- ○ Artemether is associated with faster speed of recovery from coma and fever clearance time, and a lower rate of neurological sequelae, than quinine
- ○ There is no significant difference in death rates between artemether and quinine

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Answer 1. 500 million

Robert Snow and colleagues recently estimated that there were 515 million episodes of clinical *P. falciparum* malaria in 2002 (range 300–660 million) [1].

References

1. Snow RW, Guerra CA, Noor AM, Myint HY, Hay SI (2005) The global distribution of clinical episodes of *Plasmodium falciparum* malaria. Nature 434: 214–217.

Answer 2. 1–3 million

A World Health Organization (WHO) expert committee estimated that there are 1.1–2.7 million deaths each year due to severe *falciparum* malaria (http://mosquito.who.int/docs/ecr20_toc.htm).

Answer 3. There have been no RCTs comparing these two approaches

In their systematic review of the literature, Taylor-Robinson and colleagues found no RCTs comparing empirical treatment with treatment of confirmed malaria [1]. The authors pointed out that (1) such empirical treatment used to be common; (2) newer malaria treatments are more expensive, and, therefore, empirical treatment is being questioned; (3) testing everyone will, however, be costly; and (4) treating only people who test positive might delay treatment, and people may default before test results are obtained [1].

References

1. Taylor-Robinson D, Jones K, Garner P (2005) Malaria: Uncomplicated, caused by *Plasmodium falciparum*. Clin Evid 13: 988–1009.

Answer 4. ACT is more expensive than chloroquine by a factor of 10–20

Treating an adult with chloroquine costs about ten cents [1]. Snow and colleagues calculated the cost of ACT as follows: $1.20 for an adult dose of artesunate plus sulfadoxine-pyrimethamine ([SP]; sulfadoxine, 25 milligrams/kilograms of body weight over a one-day period; pyrimethamine, 12.5 milligrams/kilograms of body weight over a one-day period; artesunate, 4 milligrams/kilograms of body weight over a three-day period); $1.30 for an adult dose of artesunate plus amodiaquine (amodiaquine, 25 milligrams/kilograms of body weight over a three-day period; artesunate, 4 milligrams/kilograms of body weight over a three-day period); and $2.40 for an adult dose of artemether-lumefantrine (lumefantrine, 48 milligrams/kilograms of body weight over a three-day period; artemether, 8 milligrams/kilograms of body weight over a three-day period) [2].

The WHO states that to date there has been no documented *falciparum* resistance to artemisinin derivatives [3].

The WHO officially includes ACT as a first-line option for treatment [4]. The organization states that as of 25 October 2005, 53 countries (35 in Africa) have now adopted ACT as first-line treatment [3].

References

1. Barnish G, Bates I, Iboro J (2004) Newer drug combinations for malaria. BMJ 328: 1511–1512.
2. Snow RW, Eckert E, Teklehaimanot A (2003) Estimating the needs for artesunate-based combination therapy for malariacase management in Africa. Trends Parasitol 19: 363–369.
3. World Health Organization (2005) What is the best treatment against malaria. Geneva: World Health Organization. Available: http://www.who.int/features/qa/26/en/. Accessed 24 October 2005.
4. Roll Back Malaria (2005) Facts on ACTs. Geneva: World Health Organization. Available: http://www.rbm.who.int/cmc_upload/0/000/015/364/RBMInfosheet_9.htm. Accessed 24 October 2005.

Answer 5. The combination treatment is associated with a lower rate of parasitological failure and with a lower rate of gametocytemia

A systematic review by Adjuik et al. found lower rates of parasitological failure at day 28 and gametocytemia at day 7 with a three-day course of artesunate plus amodiaquine compared with amodiaquine alone [1]. The review found no significant difference in the rate of serious adverse events between treatments.

References

1. Adjuik M, Babiker A, Garner P, Olliaro P, Taylor W, et al. (2004) Artesunate combinations for treatment of malaria: Meta-analysis. Lancet 363: 9–17.

Answer 6. There is very good evidence that artesunate plus SP is more effective than SP alone, but there is little evidence that artesunate plus SP is more effective than amodiaquine plus SP

The systematic review by Adjuik et al. found that artesunate plus SP reduced the parasitological failure at day 28 and the gametocytemia rate at day 7 compared with SP alone [1].

When Taylor-Robinson and colleagues systematically reviewed the evidence on artesunate plus SP compared with amodiaquine plus SP, they found only one RCT [2], showing that there was no significant difference in treatment failure rates at day 28.

References

1. Adjuik M, Babiker A, Garner P, Olliaro P, Taylor W, et al. (2004) Artesunate combinations for treatment of malaria: Meta-analysis. Lancet 363: 9–17.

Answer 7. Six doses of artemether-lumefantrine given over three days increases treatment cure rates compared with a four-dose regime

One RCT found that six doses of artemether-lumefantrine given over three days increases treatment cure rates compared with a four-dose regime [1].

There have been no trials yet of artesunate plus chlorproguanil-dapsone versus artemether-lumefantrine, while artemether-lumefantrine is probably no more effective than artesunate-mefloquine, although the data are not yet clear (Paul Garner, personal communication).

References
1. Vugt MV, Wilairatana P, Gemperli B, Gathmann I, Phaipun L et al. (1999) Efficacy of six doses of artemether-lumefantrine (benflumetol) in multidrug-resistant *Plasmodium falciparum* malaria. Am J Trop Med Hyg 60: 936–942.
2. Taylor-Robinson D, Jones K, Garner P (2005) Malaria: Uncomplicated, caused by *Plasmodium falciparum*. Clin Evid 2005: 988–1009.

Answer 8. Resistance in more than 10% of cases

The WHO states, "It is critical that countries get ACTs instead of another drug as in most parts of the world falciparum malaria has become resistant to conventional treatment, such as chloroquine, sulfadoxine/pyrimethamine, and other antimalarial medicines used singly. That is why WHO recommends that countries in which the malaria parasite is resistant to single therapies in more than 10% of cases use a combination of drugs" [1].

References
1. World Health Organization (2005) What is the best treatment against malaria. Geneva: World Health Organization. Available: http://www.who.int/features/qa/26/en/. Accessed 24 October 2005.

Answer 9. The WHO estimates that at least 132 million courses of ACT will be needed in 2005

The WHO estimates that a minimum of 132 million courses of ACT will be needed in 2005 [1].

There is only one coformulated ACT, which is artemether-lumefantrine (Coartem) [1]. WHO and Novartis, the manufacturer of artemether-lumefantrine, have entered into a special pricing agreement: Novartis provides the drug at cost price ($ 0.9 and $ 2.4 per child and adult treatment course, respectively) for use in the public sector in malaria-endemic countries [1].

Although researchers are in the process of developing a synthetic version of artemisinin (for example, the Gates Foundation has given a $43 million grant to United States researchers for such development [http://www.berkeley.edu/news/media/releases/2004/12/13_gates.shtml]), this synthetic version is not yet clinically available.

References
1. Roll Back Malaria (2005) Facts on ACTs. Geneva: World Health Organization. Available: http://www.rbm.who.int/cmc_upload/0/000/015/364/RBMInfosheet_9.htm. Accessed 24 October 2005.

Answer 10. There is no significant difference in death rates between artemether and quinine

There is good evidence (from two systematic reviews [1,2] and four subsequent RCTs [3–6]) that there is no significant difference in death rates between artemether and quinine in people with severe malaria. One of the reviews [1] found no significant difference in speed of recovery from coma, fever clearance time, or rate of neurological sequelae.

References
1. Artemether-Quinine Meta-analysis Study Group (2001) A meta-analysis using individual patient data of trials comparing artemether with quinine in the treatment of severe falciparum malaria. Trans R Soc Trop Med Hyg 95: 637–650.
2. McIntosh HM, Olliaro P (2003) Artemisinin derivatives for treating severe malaria. Cochrane Database Syst Rev 2003: CD000527.
3. Faiz MA, Rahman E, Hossain MA, Rahman MR, Yunus EB, et al. (2001) A randomized controlled trial comparing artemether and quinine in the treatment of cerebral malaria in Bangladesh. Indian J Malariol 38: 9–18.
4. Adam I, Idris HM, Mohamed-Ali AA, Aelbasit IA, Elbashir MI (2002) Comparison of intramuscular artemether and intravenous quinine in the treatment of Sudanese children with severe falciparum malaria. East Afr Med J 79: 621–625.
5. Satti GM, Elhassan SH, Ibrahim SA (2002) The efficacy of artemether versus quinine in the treatment of cerebral malaria. J Egypt Soc Parasitol 32: 611–623.
6. Huda SN, Shahab T, Ali SM, Afzal K, Khan HM (2003) A comparative clinical trial of artemether and quinine in children with severe malaria. Indian Pediatr 40: 939–945.

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