Artesunate combinations for treatment of malaria: meta analysis

CRD summary
This meta-analysis of individual patient level data from randomised controlled trials investigated the hypothesis that the addition of artemisinin derivatives to existing drug regimens for malaria can reduce treatment failure and transmission potential. It concluded that the addition of 3 days' artesunate to standard antimalarial treatments substantially reduces treatment failure, recrudescence and gametocyte carriage. The overall conclusions appear reliable. However, the magnitude of the effect remains uncertain.

Authors’ objectives
To determine whether the addition of artemisinin derivatives to existing drug regimens for malaria can reduce treatment failure and transmission potential.

Searching
Studies sponsored by the World Health Organization and the Special Programme in Research and Training in Tropical Diseases (WHO/TDR) were included in the review. In addition, MEDLINE and the Cochrane CENTRAL Register were searched. The authors of relevant studies were contacted and invited to join the International Artemisinin Study Group.

Study selection

Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) were eligible for inclusion in the review (6,004 people randomised; 5,632 people analysed at day 14).

Specific interventions included in the review
Studies that compared artesunate plus a standard antimalarial drug with the standard drug alone were eligible for inclusion. The standard malarial drugs used in the included studies were chloroquine, amodiaquine, sulfadoxine-pyrimethamine and mefloquine. Each of these drugs had been studied in a different country or area of a country from the others; mefloquine had been studied only in Thailand. The dose of artesunate was generally 4 mg/day for up to 3 days; the exception was one trial in which a lower dose of 2 mg/day was given after the first day.

Participants included in the review
Studies of people with acute, uncomplicated Plasmodium falciparum malaria were eligible for inclusion. The populations in the included studies were from Burkino Faso, Ivory Coast, Sao Tome and Principe, Gabon, Kenya, Senegal, Gambia, Malawi, Uganda, Peru and Thailand. The proportion of males in the primary studies was around 50%. All the Africa-based studies comprised populations of young children (mean age range: 1.4 to 8.1 years). In the studies from Thailand the mean age of the populations was higher (15.9 to 18.6 years), and in the one study from Peru the mean age of the study population was 29 years.

Outcomes assessed in the review
The primary outcome for the review was parasitological failure rates by days 14 and 28. Failure rate at day 14 was defined as:

the development of severe malaria or danger signs of severe disease;

parasitaemia at 48 hours equal to or more than the parasite count at day 0;

parasitaemia on day 3 equal to or more than 25% of the parasite count at day 0, and fever or parasitaemia on day 4 equal to or more than 25% of the parasite count at day 0;
parasitaemia on day 7;
initial parasite clearance by day 7 followed by recurrence by day 14;
an adverse event requiring withdrawal;
use of further antimalarial drugs between days 0 and 14.

Recurrent parasitaemia was divided into recrudescence of original infection or reinfection by a new malarial parasite. The secondary outcomes included parasitological failures by day 28 irrespective of type of infection, time to parasite clearance, time to fever clearance, gametocyte carriage, and adverse events.

How were decisions on the relevance of primary studies made? The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Trial quality was assessed on the basis of adequacy of random allocation, inclusion of all randomised patients in the analysis, completeness of follow-up and comparability of the baseline characteristics. The authors also reported on blinding and allocation concealment. For the WHO/TDR-sponsored trials, a single protocol had been used and every trial was assessed with internal checks to identify missing and outlying data. Other included studies were checked for discrepancies, either with published data or by contact with trial investigators. Participants were excluded from the analysis if they were found to have been included in a primary study in error. The authors did not provide details of how the validity checks were performed, or how many reviewers performed them.

Data extraction
Individual patient data (IPD) were obtained from the original trial investigators. The difference between the number of observed failures in the artesinate combination group and the expected number of failures and the variance of this difference was calculated for each trial. The log odds ratio (OR) and 95% confidence intervals (CI) for treatment failure of combination treatment versus standard therapy alone was also calculated for each trial.

Methods of synthesis
How were the studies combined? For binary outcomes, the Peto-Mantel-Haenszel method was used: the individual trial differences between observed and expected failures (O-E) and their variances (V) were summed to obtain a summary of O-E and V across all trials. The value of (O-E)^2/V was then referred to the chi-squared distribution with one degree of freedom. A summary OR was calculated with a weighted average of trial-specific log ORs, with weights inversely proportional to their variance. All analyses were stratified by the background treatment given. A substantial number of polymerase chain reaction results were missing, and these data were excluded from the primary 28-day analysis. However, two sensitivity analyses were conducted, one that assumed that all participants with missing data were treatment failures, the other that all were treatment successes. For time to event outcomes, life table methods stratified by individual trials were used and the results were reported as rate ratios.

How were differences between studies investigated? Meta-regression was used to explore the possible effects of pre-specified factors.

Results of the review
Sixteen RCTs were included; all provided IPD (5,948 randomised).

Failure rate at 14 days (15 trials, n=4,504).

The addition of 3 days of arsenate to standard antimalarial therapy was associated with a statistically significant reduction in the day 14 failure rate compared with placebo (OR 0.20, 95% CI: 0.17, 0.25). There was, however,
statistically significant heterogeneity between the studies. Some of the heterogeneity was explained by variability in the background antimalarial used: the effect of artesunate on failure rate at 14 days was better when combined with mefloquine (OR 0.04) and worse when combined with amodiaquine (OR 0.41). Participant age, intensity of malarial transmission and packed cell volume did not affect the effect size of artesunate.

Failure rate at 28 days.

There was a statistically significant beneficial effect of artesunate on the failure rate at 28 days, compared with placebo, when reinfections were either excluded (10 trials, n=2,908; OR 0.23, 95% CI: 0.19, 0.28) or included (14 trials, n=4,332; OR 0.30, 95% CI: 0.26, 0.35). The sensitivity analysis showed similar results regardless of whether missing data were counted as treatment failures or successes.

Parasite clearance (n=3,517).

Parasite clearance was statistically significantly faster with artesunate than with placebo (rate ratio 1.96, 95% CI: 1.85, 2.12).

Gametocyte count.

In participants with no gametocytes at baseline, artesunate significantly reduced the gametocyte count at 7, 14 and 28 days.

The results for other secondary outcomes were reported in the review.

**Authors' conclusions**

The addition of 3 days' artesunate to standard antimalarial treatments substantially reduced treatment failure, recrudescence and gametocyte carriage.

**CRD commentary**

This review was based on 16 trials, three of which were based on a single protocol. The search for relevant studies was restricted to two databases, but researchers in the field were invited to join the study group, thus reducing the potential for missed studies. Some details of the review procedures, such as how the validity checks were performed, were not given. The use of IPD rather than summary data increased the robustness of the analysis, especially as sensitivity analyses found that missing data did not alter the results.

The included trials were in many ways clinically heterogeneous and the pooled result for the primary outcome was subject to significant heterogeneity. Therefore, too much emphasis should not be placed upon the actual effect size. However, the authors' investigation of heterogeneity was thorough and it appears that there is no simple explanation for differences between the effect sizes across trials. Importantly, the review demonstrated that in the drug combinations, countries and populations studied, the direction of effect was consistent, with all but one study reporting favourable results for artesunate. Thus, the conclusion pertaining to the addition of artesunate to standard antimalarial treatment can be taken to be reliable, although the magnitude of the effect remains uncertain.

**Implications of the review for practice and research**

Practice: The authors stated that the addition of artesunate to an effective antimalarial (i.e. where resistance to that antimalarial is as yet low) represents the optimal use of the drug.

Research: The authors stated that additional research into specific strategies to enhance the use of and adherence to 3-day combination regimens, and their short- and long-term benefits, is needed.

**Bibliographic details**


PubMedID
14723987

Other publications of related interest
This additional published commentary may also be of interest. Fanning MM. Review: artesunate added to standard drug treatment reduces treatment failure in malaria. Evid Based Med 2005;9:150.

Indexing Status
Subject indexing assigned by NLM

MeSH
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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.