

## MEDICINES FOR MALARIA VENTURE (MMV)

### Strategy for the selection and early development of combination drugs for the treatment of uncomplicated *P. falciparum* malaria

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#### List of abbreviations

ACT	artemisinin-based combination therapy	PK	pharmacokinetic
CDA	chlorproguanil-dapsone-artesunate	PRR	parasite reduction ratio
COG	cost of goods	R&D	research and development
IPT	intermittent preventative treatment	WHO	World Health Organisation
MIC	minimum inhibitory concentration	o.d.	once daily
MPC	minimum parasitocidal concentration	b.i.d.	twice daily
NCE	new chemical entity	t.i.d.	three times daily
PCR	polymerase chain reaction	WWARN	WorldWide Antimalarial Resistance Network
PD	pharmacodynamic		

## Objectives

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1. Revisit the MMV 2005 position paper: ‘Strategic consultation: selection of partners for antimalarial drug combinations’ in the context of new information and future challenges in antimalarial therapy.
2. Discuss decision-making strategies for the development of antimalarial drug combinations.

## Summary of key points

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1. Antimalarial combination therapy is required for the oral treatment of uncomplicated *P. falciparum* malaria and *P. vivax* malaria in adults and children; symptomatic malaria in pregnant women; intermittent preventative treatment (IPT) in pregnant women and children; and use in epidemics.
2. Different indications and patient groups will require different target product profiles.
3. Antimalarial combinations require optimised dosing regimens, rationally developed in both adults and children, to maximise outcomes and minimise the potential for the development and spread of resistance.
4. New antimalarial combination therapies should provide an overall advantage in their risk:benefit profile relative to other available therapies in terms of:
  - Potential for resistance development based on pharmacokinetic/pharmacodynamic (PK/PD) considerations.
  - No cross-resistance between partners or with deployed antimalarials.
  - Safety and tolerability, including in children and ideally pregnancy.
  - Speed and duration of parasitocidal activity.
  - Speed of malaria symptom resolution.
  - Gametocytocidal activity.
  - Hypnozoitocidal activity.
  - Duration of post-treatment prophylaxis.
  - Activity against both *Plasmodium falciparum* and *Plasmodium vivax*.
  - Acceptability and dosing convenience (3 days or less; o.d. versus b.i.d.).
  - Affordability (<US\$1 per adult treatment).
5. The utility of new antimalarial combinations will need to be revisited should artemisinin resistance become more widespread or high-level artemisinin resistance emerge.

## Requirements for partner selection

### Revisiting the MMV 2005 position paper

Since the 2005 MMV position paper ‘Selection of partners for antimalarial drug combinations’, there have been two major changes in the management of malaria.

1. Renewed focus on malaria eradication.
2. Emergence of artemisinin resistance, and the implications for antimalarial therapy:
  - Increased doses of artemisinin-based combination therapy (ACT) may be required (e.g. b.i.d. and/or 5-day dosing) in areas of emerging resistance.
  - Combination therapies effective against artemisinin-resistant parasites are needed.

### Selection of partners for antimalarial drug combinations 2010

The statements of the 2005 MMV position paper were revised as follows:

Issues and questions	Recommendation
1. What is the driving force behind the need for combinations?	Combination therapy aims to maximise outcomes and minimise the potential for the development and spread of resistance. New antimalarial combination therapies should provide an overall advantage in their risk:benefit profile relative to other available therapies in terms of: Potential for resistance development based on PK/PD considerations; no cross-resistance between partners or with deployed antimalarials; safety and tolerability, including in children and ideally pregnancy; speed and duration of parasitocidal activity; speed of malaria symptom resolution; gametocytocidal activity; duration of prophylaxis; activity against both <i>P. falciparum</i> and <i>P. vivax</i> ; acceptability and dosing convenience (3 days or less; o.d. versus b.i.d.); affordability (<US\$1 per adult treatment).
2. Which antimalarial indications need combination products?	<b>Combination therapy:</b> Oral treatment of uncomplicated <i>P. falciparum</i> malaria and <i>P. vivax</i> malaria in adults and children; treatment of symptomatic malaria in pregnant women; use in epidemics.
3. Should combinations be fixed or loose?	Fixed dose, co-formulated combinations are preferable, to maximise patient compliance and prevent inappropriate use of the individual components.
4. Should concerns about cost of goods (COG) constrain partner consideration?	COG is not a justification for monotherapy, but remains a relevant consideration in partner selection. The US\$1 landed cost in country for an adult course of therapy remains a useful benchmark.
5. When in the development process should partner selection be done?	As early as possible in preclinical studies to avoid delaying progression to clinical studies. See also Question 13.
6. How many partner drugs should be included in the proposed combination?	Combinations of two drugs are most feasible in terms of research and development (R&D) costs, safety, COG and tablet size. Combinations of more than two drugs should only be considered if they provide considerable benefits to the final product in a cost-effective manner.
7. How many combinations for each malaria indication should be developed for each new chemical entity (NCE)?	Endoperoxides may be developed in multiple combinations. For other compounds, a preferred combination should be developed initially, but others may be considered subsequently.

8. Which molecules can be considered for combination with an MMV NCE?	Any antimalarial in development or deployed should be considered. Some deployed antimalarials may not be available at the required GMP manufacturing standard.
9. What are the minimal antimalarial activities needed for the proposed partners?	<p><b>Fast-acting drugs:</b> Parasite clearance by Day 7, plus evaluation of the parasite reduction ratio (PRR) in comparison with artemisinins. NB: artemisinins are exceptionally active; a % of artemisinin activity will need to be agreed.</p> <p><b>Slow-acting drugs:</b> 100% cure by Day 7 and &gt;90% cure by Day 28 (PCR corrected).</p>
10. What are the appropriate PK characteristics of the partners?	The appropriate PK characteristics will depend on the objectives of therapy; the overall risk: benefit is a consideration (see Question 1). As a minimum, a $\leq 3$ -day dosing schedule is required for combination therapy, with at least one drug present at therapeutic levels for 3–4 intraerythrocytic cycles.
11. Should the biological targets for the combination partners be different?	Partner drugs should have a low potential for resistance development. Cross resistance can arise through common biological targets, and from common drug uptake mechanisms. Cross-resistant molecules should not be combined.
12. Must a new antimalarial combination include an endoperoxide?	No. As long as the risk/benefit profile for the particular indication/ patient group is satisfactory (see Question 1).
13. What data should be generated on potential combinations to drive selection and dose optimisation?	<p><b>In vitro:</b> Drug–drug interaction studies can be disregarded unless there is &gt;5-fold antagonism or synergy. Resistance development and cross-screening are early selection tools.</p> <p><b>In vivo:</b> Resistance induction in animal models is useful to predict the potential for resistance development in clinical use. Animal models of efficacy are unreliable, Phase I trials are needed to determine efficacy.</p> <p><b>Phase I:</b> Evaluation of all partners separately to obtain safety data.</p> <p><b>Phase II dose ranging:</b> Dose-optimisation needs to be achieved for both partners. PK data are required for children and adults as the optimum dosing regimen may be different. Any PK/ PD interaction between the components needs to be determined.</p> <ul style="list-style-type: none"> <li>• Rapid-acting drugs: The slope of the parasite clearance–time graph versus dose in non-immune adults can be examined. The optimum dose in children should also be calculated using paediatric PK data.</li> <li>• Slow-acting drugs: Dose optimisation requires under-treatment, i.e. there must be treatment failures. There are ethical concerns for under-treating patients with <i>P. falciparum</i> malaria. It may be possible to do dose-ranging studies of this type in <i>P. vivax</i> malaria as failures are more acceptable.</li> </ul> <p><b>Phase II combination therapy:</b> Dose optimisation of the individual components may allow comparison of just two doses of the combination therapy in Phase II. If dose-finding can be done rationally for the components, then a ‘proof of concept study’ is not required.</p> <p><b>Phase III dose validation:</b> Analysis of failures versus drug levels allows validation of the dosing regimen in Phase III.</p>

## **Discussion of the 2010 recommendations**

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### ***1. What is the driving force behind the need for combinations?***

Slowing of resistance development is an important, but not the exclusive, objective of antimalarial combination therapy. Combination therapy aims to maximise outcomes and minimise the potential for the development and spread of resistance.

#### **Therapy must be optimised**

**If there is parasite elimination (in the individual patient) then resistance cannot be selected.** The aim of optimal therapy (drug/dose/duration) is to eliminate parasites in the majority of patients treated. Sub-optimal therapy drives resistance development and spread.

#### **Is there an ideal combination?**

There is unlikely to be one 'ideal' combination that satisfies all requirements. New antimalarial combination therapies should provide an overall advantage in their risk: benefit profile relative to other available therapies in terms of:

- Potential for resistance development based on PK/PD considerations.
- No cross-resistance between partners or with deployed antimalarials.
- Safety and tolerability, including in children and ideally pregnancy.
- Speed and duration of parasitocidal activity.
- Speed of malaria symptom resolution.
- Gametocytocidal activity.
- Hypnozoitocidal activity
- Duration of post-treatment prophylaxis.
- Activity against both *P. falciparum* and *P. vivax*.
- Acceptability and dosing convenience (3 days or less; o.d. versus b.i.d.).
- Affordability (<US\$1 per adult treatment).

For example, as no single-dose antimalarial therapy is available, a new single-dose combination therapy with 100% Day-7 and >90% Day-28 efficacy, but with no prophylactic effect would have utility.

#### **Artemisinin resistance**

The relative utility of new antimalarial combinations will depend on the spread and degree (low-level or high-level) of artemisinin resistance.

### ***2. Which antimalarial indications need combination products rather than monotherapy?***

#### **Combination therapy**

Combination therapies for different indications will require different target product profiles.

- Oral treatment of uncomplicated *P. falciparum* malaria and *P. vivax* malaria in adults and children. Combination therapy should ideally be active against both *P. falciparum* and *P. vivax*. These pathogens are often not differentiated in the clinical situation, and a significant proportion of patients may have co-infection.

- Treatment of symptomatic malaria in pregnant women.  
In pregnancy, only those drugs that have comprehensive safety information can be used. In practice, this means existing medicines; it takes 10–20 years to get safety data in pregnancy.
- Intermittent preventative treatment in pregnant women and children. Combination therapy is necessary, because even though parasite densities are smaller, at around  $10^8$  per person, this is still sufficient to allow the spread of resistant strains, especially given the large numbers of patients potentially treated.
- Use in epidemics.

#### **Sequential therapy**

Severe malaria should be treated with two agents, but not necessarily in combination.

#### **Monotherapy**

Prevention of *P. vivax* relapse.

### ***3. Should combinations be fixed or loose?***

The 2005 statement was still valid.

### ***4. Should concerns about cost of goods (COG) constrain partner consideration?***

The US\$1 landed cost in country per adult treatment remains a useful benchmark. However, should the effectiveness of ACT be compromised, this may need to be revised.

### ***5. When in the development process should partner selection be done?***

As early as possible to avoid development delay. See also Question 13.

### ***6. How many partner drugs should be included in the proposed combination?***

The 2005 statement was still valid. Tablet size is also a consideration in including more than two drugs.

### ***7. How many combinations for each malaria indication should be developed for each new chemical entity (NCE)?***

The 2005 statement was still valid.

### ***8. Which molecules can be considered for combination with an MMV NCE?***

The 2005 statement was still valid.

**9. What are the minimal antimalarial activities needed for the proposed partners?**

Using a 7-day 100% cure and a Day-28 >90% cure rate (PCR-corrected) for EACH partner may exclude drugs that have useful properties.

Minimum criteria for any antimalarial:

- A PRR of >10, ideally more than  $10^3$  kills per cycle.

For clinical studies, partner drugs can be evaluated based on their PK/PD profile using the dosing regimen that will be used in the combination:

**Fast-acting drugs:** Parasite clearance by Day 7, plus evaluation of the PRR in comparison with artemisinin.

- NW has data on 30,000 patients with daily parasite counts and some with more frequent counts. These data could be used to develop a composite parasite count–time graph for artemisinins against which new drugs could be compared.
- Comparison criteria should not be too stringent so as not to exclude potentially valuable drugs; artemisinins are exceptionally active and it will be difficult to achieve this activity with other drug classes.

**Slow-acting drugs:** Should achieve 100% cure by Day 7 and >90% cure by Day 28 (PCR-corrected).

**10. What are the appropriate PK characteristics of the partners?**

Appropriate PK will depend on the objectives of therapy; the risk: benefit of the combination is the important consideration (see Question 1).

- As a minimum, a  $\leq 3$ -day dosing schedule is required for combination therapy, with at least one drug present at therapeutic levels for 3–4 intraerythrocytic cycles.

**Resistance:** For more on the implications of PK on resistance development and spread see:

- Effective half-life refers to the half-life of drug concentrations above the minimum inhibitory concentration (MIC). From the perspective of delaying the emergence and spread of resistance, it is reasonable to consider a short effective half-life ‘best’. However a long effective half-life may not be ‘bad’, particularly if resistance has not yet emerged.

Resistance may not be the most important factor:

- A long effective half-life is required to achieve short-course therapy ( $\leq 3$ -day dosing), for IPT, and parasite elimination.
- Prophylaxis resulting from a long effective half-life is of benefit to the patient and from a public health perspective.

**11. Should the biological targets for the combination partners differ?**

The 2005 statement was still valid.

**12. Must a new antimalarial combination include an endoperoxide?**

- No. As long as the risk: benefit profile is satisfactory (see Question 1).

### 13. What data should be generated on potential combinations to drive selection and dose optimisation?

#### In vitro

- Results from *in vitro* drug–drug interaction studies can be disregarded unless there is >5-fold antagonism or synergy.
- *In vitro* resistance development and cross-screening can be used early in the selection process. Potential combinations should elicit different pathogen resistance mechanisms and be active against strains resistant to the other potential partners. Consistent methodology is required.
- Test new antimalarials against parasite strains resistant to currently deployed antimalarials, particularly artemisinins.

#### In vivo

- Resistance induction in animal models is useful to predict the potential for resistance development in clinical use. If resistance cannot be induced, this is a positive sign. Rapid resistance induction would stop further drug development.
- Animal models of synergy *in vitro* are invalidated. More relevant data obtained are from Phase I studies. Clinical

#### **Phase I**

All partners need to be evaluated separately in Phase I to obtain safety data.

#### **Phase II dose ranging**

Dose-optimisation needs to be achieved for **BOTH** partners.

- Phase II dose ranging data is required for individual drugs and in combination.
- PK data are required for both children and adults; the optimum dosing regimen may be different in children versus adults.
- Any PK/PD interaction between the components needs to be determined.

**Rapid-acting drugs:** For peroxides and agents capable of rapid ring-stage clearance, the slope of the parasite clearance–time graph versus drug dose can be examined. This should be done in non-immune adults. The need for frequent sampling means that these data cannot be generated in children, but the optimum dose in children can be calculated from paediatric PK data.

**Slow-acting drugs:** For agents with slower parasiticidal activity, the parasite clearance–time slope is messier and difficult to use for dose-ranging. In these cases, patients must be under-treated to find the minimum effective dose, i.e. there must be treatment failures. In tandem with safety/tolerability data this provides the therapeutic window allowing rational decisions regarding dose, duration of dose and frequency of dose. There are ethical concerns for under-treating patients with *P. falciparum* malaria. It may be possible to do dose-ranging studies of this type in *P. vivax* malaria as failures are more acceptable. Quantitative PCR may be useful if it can be validated.

#### **Phase II combination therapy**

Rational dose finding based on PK/PD data for the individual components may allow comparison of just two doses of the combination therapy in Phase II. This is in contrast to performing fractional design (2x2 or 3x3) studies which can be quite complex to construct and analyse.

- Few well designed dose finding studies have been conducted for antimalarials. Developing the protocol templates for rational dose finding is challenging, and may require validation while ‘in process’.

**Impact of immunity:** An induced infection model in asymptomatic adult Africans is an unacceptable trial model. High immunity in these patients would provide an inadequate test of antimalarial effectiveness and invalid dose–response data.

**Phase III dose validation**

Except in cases where it would not be ethical, drug concentrations should be obtained from all patients during the clinical programme. In phase III, this allows all failures to be analysed: are failures because of low drug concentrations or other reasons? Comparing drug levels with outcomes also allows further validation of the dosing regimen.

**Participants list**

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**Chair:** David McGibney

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