Update on tolerance/resistance and therapeutic efficacy of artemisinin in South East Asia

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World Health Organization
Artemisinin Resistance in *Plasmodium falciparum* Malaria

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What is antimalarial drug resistance?

- Ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject (WHO, 1973).

- Therapeutic efficacy is used as an 'alert' to drug resistance but not all treatment failures are due to resistance. Treatment failure can be due to:
  - Pharmacokinetic (low absorption, increased metabolism, etc.)
  - Immunity (HIV, pregnancy, etc.)
  - Confirmed resistance

- Therefore the following tools are needed to confirm resistance:
  - Pharmocokinetic data
  - in vitro sensitivity
  - molecular markers
Clinical trials of artemisinin and its derivatives in the treatment of malaria in China

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Introduction

Since 1979, several different formulations of artemisinin have been used to treat malaria. The relation between course of treatment and recrudescence of malaria is shown in the table below.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Treatment course</th>
<th>3 d</th>
<th>5 d</th>
<th>7 d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artemisinin suppositories</td>
<td></td>
<td>50/113 (44%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Artesunate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tablets</td>
<td></td>
<td>30/56 (54%)</td>
<td>7/144 (5%)</td>
<td></td>
</tr>
<tr>
<td>Intramuscular</td>
<td></td>
<td>13/25 (52%)</td>
<td>9/82 (10%)</td>
<td>1/40 (2.5%)</td>
</tr>
<tr>
<td>Intravenous</td>
<td></td>
<td>44/89 (49%)</td>
<td>2/36 (6%)</td>
<td></td>
</tr>
<tr>
<td>Artemether tablets</td>
<td></td>
<td>14/30 (47%)</td>
<td>5/97 (5%)</td>
<td>2/41 (5%)</td>
</tr>
<tr>
<td>Dihydroartemisinin tablets</td>
<td></td>
<td>12/25 (48%)</td>
<td>3/50 (6%)</td>
<td>4/205 (2%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>163/338 (48%)</td>
<td>24/373 (6%)</td>
<td>9/322 (3%)</td>
</tr>
</tbody>
</table>

"Recrudescence rates are shown as no. of recrudescences/no. treated (with percentages in parentheses)."
Proportion of patients with treatment failure (day 28)

- **Odder Meanchey**
- **Preah Vihear**
- **Battambang**
- **Pailin**
- **Ratanakiri**
- **Pursat**
- **Kampong Speu**
- **Kampot**

*Graphs showing the proportion of patients with treatment failure over different years in various provinces. The graph keys indicate different drug combinations used for treatment.*
Proportion of patients positive on (day 3)

Odder Meanchey

Preah Vihear

Battambang

Ratanakiri

Pailin

Kratie

Pursat

Kampong Speu

Kampot

Artesunate-mefloquine
Artemether-lumefantrine
Dihydroartemisinin-piperaquine

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Parasite Clearance

(p=0.0001 for \( \Delta \) slopes between sites)

Dondorp, NEJM, 2009
PCR-adjusted efficacy of MAS3 in Mae Sot

Carrara, PLoS One, 2009
Parasite clearance with MAS3 in Mae Sot

Carrara, PLoS One, 2009
PCT in Pailin with artesunate 6 and 8 mg/kg/d

N=40
Mechanism of artemisinin resistance?

48 hours

Artemisinin

Quinine
Parasite clearance data from 18,699 falciparum malaria patients with fully artemisinin sensitive parasites, treated with an artemisinin derivative.
Definition of artemisinin resistance

- Absence of consensus on the definition

- WHO is using the following working definitions:
  - **suspected resistance**: increase in parasite clearance time, as evidenced by over 10% of cases with parasites detectable on day 3 following treatment with an ACT;
  - **confirmed resistance**: treatment failure, as evidenced by persistence of parasites at day 7 or the presence of parasites at day 3 and recrudescence within 28/42 days, after full treatment of oral artemisinin-based monotherapy with adequate blood concentration.
WHO strategy for dealing with antimalarial drug resistance
(adopted by the RBM Board. Dec 2009)

- Contain drug resistance
- Confirm drug resistance
- Monitor therapeutic efficacy
- Avoid emergence of resistance
- Develop new drugs
Structure of the containment project

International Task Force

National Task Force
Cambodia

National Task Force
Thailand

HQ

Mahidol-Oxford Tropical Medicine Research Unit
Mahidol University

SEARO

Bureau of Vector Borne Disease,
Ministry of Public Health
Thailand

Center of Excellence for Biomedical and Public Health Informatics (BIOPHICS)
Geographic Information Unit (GIU)
Faculty of Tropical Medicine
Mahidol University

WPRO

Malaria Consortium

National Center for Parasitology,
Entomology and Malaria Control in Cambodia

Institut Pasteur du Cambodge
Objectives of containment project

- To eliminate artemisinin tolerant parasites by detecting all malaria cases in target areas and ensuring effective treatment and gametocyte clearance

- To decrease drug pressure for selection of artemisinin resistant malaria parasites (including monotherapy ban)

- To prevent transmission of artemisinin tolerant malaria parasites by vector control and personal protection

- To limit the spread of artemisinin tolerant malaria parasites by mobile/migrant populations

- To support containment/elimination of artemisinin resistant parasites through comprehensive behavior change communication (BCC), community mobilization and advocacy

- To undertake basic and operational research to fill knowledge gaps and ensure that strategies applied are evidence-based

- To provide effective management, surveillance and coordination to enable rapid and high quality implementation of the strategy
Day 3 positivity rate > 10%
<table>
<thead>
<tr>
<th>FACTS</th>
<th>IMPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical and parasitological cure of ACTs - not compromised</td>
<td>Change in parasite sensitivity not reflected in routine therapeutic efficacy results</td>
</tr>
<tr>
<td>Fever clearance time – prolonged slightly</td>
<td>Incorrect treatment practices</td>
</tr>
<tr>
<td>Parasite clearance time – prolonged</td>
<td>Potentially increased risk of mortality of severe malaria which is treated with AS monotherapy</td>
</tr>
<tr>
<td>Increased gametocyte rate</td>
<td>Increased transmission of less sensitive parasites</td>
</tr>
<tr>
<td>Unknown infectivity to mosquitoes</td>
<td>Likely to increase transmission</td>
</tr>
<tr>
<td>Unknown impact on parasite biomass over period of infection</td>
<td>More parasites exposed to partner medicine</td>
</tr>
<tr>
<td></td>
<td>Increased number of de novo mutations – promoting parasite survival</td>
</tr>
</tbody>
</table>
Artemisinin resistance or tolerance? an irrelevant debate

- *P. falciparum* has changed sensitivity to artemisinins

- Implications are:
  - Prolonged morbidity and increased risk of mortality
  - Increased risk of transmission of resistant parasites
  - Increase risk of losing partner medicines

Malaria control and elimination efforts could be seriously compromised

**IMMEDIATE AND EFFECTIVE ACTION IS WARRANTED**
Thank you
for your kind attention