Update of artemisinin resistance and its containment efforts

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World Health Organization

GLOBAL MALARIA PROGRAMME
Artemisinin Resistance in *Plasmodium falciparum* Malaria

Arjen M. Dondorp, M.D., François Nosten, M.D., Poravuth Yi, M.D., Debashish Das, M.D., Aung Phae Phyo, M.D., Joel Tarning, Ph.D., Khin Maung Lwin, M.D., Frederic Arrey, M.D., Warunee Hanpithakpong, Ph.D., Sue J. Lee, Ph.D., Pascal Ringwald, M.D., Kamolrat Silamut, Ph.D., Mallika Imwong, Ph.D., Kesinee Chotivanich, Ph.D., Pharith Lim, M.D., Trent Herdman, Ph.D., Sen Sam An, Shunmay Yeung, Ph.D., Pratap Singhasivanon, M.D., Nicholas P.J. Day, D.M., Niklas Lindegardh, Ph.D., Duong Socheat, M.D., and Nicholas J. White, F.R.S.
Parasite Clearance

\((p=0.0001 \text{ for } \Delta \text{ slopes between sites})\)

Dondorp, NEJM, 2009
Treatment failures with monotherapies

- Parasite clearance time
- Gametocyte carriage
- Treatment failures

Detection limit

WEEKS
Clinical trials of artemisinin and its derivatives in the treatment of malaria in China

Guo-Qiao Li, Xing-Bo Guo, Lin-Chun Fu, Hua-Xiang Jian and Xin-Hua Wang  Sanya Tropical Medicine Institute, Guangzhou College of Traditional Chinese Medicine, Guangzhou, People’s Republic of China

**Introduction**

Since 1979, several different formulations of artemisinin suppositories. The relation between course of treatment and recrudescence of malaria.

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

*Recrudescence rates are shown as no. of recrudescences/no. treated (with percentages in parentheses).*

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**GLOBAL MALARIA PROGRAMME**
PCT and treatment failure with artemisinin

Artemisinin monotherapy (sensitive parasites)

Artemisinin monotherapy (reduced sensitivity)

Gametocytal carriage?

Treatment failure

Treatment failures (3-5 %)

Detection limit

WEEKS

0 1 2 3 4

0 10^2 10^4 10^6 10^8 10^10 10^12
ACT treatment failures, Cambodia (2001–2011)

Artemether-lumefantrine             (D28)
Artesunate-mefloquine               (D42)
Dihydroartemisinin-piperaquine  (D42)

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Relate between Day 3 positivity rate and initial parasitemia

Stepniewska K, J Infect Dis 2010

Parasite clearance data from 18,699 falciparum malaria patients with fully artemisinin sensitive parasites, treated with an artemisinin derivative

Relation between Day 3 positivity rate and initial parasitemia

Proportion (%) positive on Day 3

Parasitaemia at enrolment (/uL)

3%

Parasite clearance data from 18,699 falciparum malaria patients with fully artemisinin sensitive parasites, treated with an artemisinin derivative
Day 3 positivity rate after ACT treatment, Cambodia (2001–2011)

- **Battambang**
  - 2001: 20%
  - 2002: 30%
  - 2004: 10%
  - 2005: 20%
  - 2007: 30%

- **Pailin**
  - 2002: 10%
  - 2004: 20%
  - 2009: 30%
  - 2010: 40%
  - 2011: 50%

- **Oder Meanchey**
  - 2003: 10%

- **Preah Vihear**
  - 2005: 0%
  - 2006: 0%
  - 2008: 10%
  - 2010: 20%

- **Ratanakiri**
  - 2003: 0%
  - 2005: 10%
  - 2006: 20%
  - 2008: 30%
  - 2010: 30%

- **Kratie**
  - 2001: 10%
  - 2003: 20%
  - 2006: 30%

- **Pursat**
  - 2002: 10%
  - 2004: 20%
  - 2005: 30%
  - 2007: 40%
  - 2009: 50%
  - 2011: 60%

- **Kampong Speu**
  - 2003: 30%

- **Kampot**
  - 2008: 30%

**Graphs**

- **Artemether-lumefantrine**
- **Artesunate-mefloquine**
- **Dihydroartemisinin-piperaquine**

**Legend**

- **artemisinin resistance containment project zone 1**
ACT efficacy in Pailin, Cambodia (2002-2011)

- Artesunate-mefloquine
  - 2002: 14.3%
  - 2004: 9.9%
  - 2008: 8.9%
  - 2011: 0.0%

- Dihydroartemisinin-piperaquine
  - 2009: 26.4%
  - 2010: 7.9%
  - 2011: 24.1%

- D3: $n=70$
- D28 TF: $n=8$
- D42 TF: $n=76$
PCT in Pailin with artemunate 6 and 8 mg/kg/d
<table>
<thead>
<tr>
<th>Province</th>
<th>Year</th>
<th>N</th>
<th>D2</th>
<th>D3</th>
<th>D7</th>
<th>PCT (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trat</td>
<td>2003</td>
<td>44</td>
<td>14 (31%)</td>
<td>7 (15.9%)</td>
<td>2 (4.5%)</td>
<td>2.0</td>
</tr>
<tr>
<td>Trat</td>
<td>2004</td>
<td>15</td>
<td>2 (13.3%)</td>
<td>2 (13.3%)</td>
<td>0</td>
<td>2.1</td>
</tr>
<tr>
<td>Trat</td>
<td>2005</td>
<td>22</td>
<td>7 (31.8%)</td>
<td>2 (9%)</td>
<td>1 (4.5%)</td>
<td>2.3</td>
</tr>
<tr>
<td>Trat</td>
<td>2006</td>
<td>32</td>
<td>10 (31.2%)</td>
<td>7 (21.8%)</td>
<td>0</td>
<td>3.3</td>
</tr>
<tr>
<td>Trat</td>
<td>2007</td>
<td>31</td>
<td>14 (45.1%)</td>
<td>5 (16.1%)</td>
<td>0</td>
<td>3.7</td>
</tr>
</tbody>
</table>

Courtesy Wichai Satimai & Saowanit Vijaykadga, 2008
Parasite clearance with AS+MQ in Mae Sot

Carrara, PLoS One, 2009
Definition of artemisinin resistance

- WHO is using working definition as below:
  - an increase in parasite clearance time, as evidenced by greater than 10% of cases with parasites detectable on day 3 following treatment with an ACT (suspected resistance); or
  - a treatment failure as evidenced by presence of parasites at day 3 and either persistence of parasites on day 7 or recrudescence after day 7 of parasites within 28/42 days, after treatment with an oral artemisinin-based monotherapy, with adequate blood concentration (confirmed resistance)
Limits of current definitions

- The parasite clearance time is prone to be affected by several confounding factors (known and unknown) such as splenectomy, haemoglobin abnormalities and reduced immunity.

- The proportion of patients who are parasitaemic after 3 days of treatment is a suitable though imperfect tool to detect suspected artemisinin resistance but is highly dependent on:
  - the initial parasitemia
  - immunity of the patients
  - the skills of the microscopists
  - D3 ≠ 72 hours
  - Artemisinin monotherapies ≠ ACTs ≠ among ACTs
Evaluation of therapeutic efficacy study results

Day 3: % patients parasitemic

Day 28 or 42: % treatment failure

Interpretation

Response

< 10%

< 10%

No evidence of resistance to artemisinin or partner drug

No change in treatment policy required

≥ 10%

Partner drug is failing

Change ACT

≥ 10%

< 10%

Suspected resistance to artemisinin

Confirm resistance to artemisinin No change in treatment policy required

≥ 10%

< 10% but increasing over time

Suspected resistance to artemisinin & Partner drug is failing

Evaluate alternative treatment options

≥ 10% or

Evaluate alternative treatment options

≥ 10%
Artemisinin resistance containment areas

Confirmed artemisinin resistance according to WHO working definition
### GPARC recommended action by tier

<table>
<thead>
<tr>
<th>Tier III</th>
<th>Tier II</th>
<th>Tier I</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Good Control</strong></td>
<td><strong>Intensified and accelerated control</strong></td>
<td><strong>Intensified and accelerated control to universal coverage</strong></td>
</tr>
<tr>
<td><strong>More routine monitoring</strong></td>
<td><strong>Intensified monitoring, especially around foci</strong></td>
<td><strong>Intensified monitoring, especially around foci</strong></td>
</tr>
<tr>
<td><strong>Eliminate mono-therapies and poor-quality drugs</strong></td>
<td><strong>Actively eliminate mono-therapies and poor-quality drugs</strong></td>
<td><strong>Aggressively eliminate monotherapies and poor-quality drugs</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Lower transmission; focus on mobile and migrant populations</strong></td>
<td><strong>Lower transmission; focus on mobile and migrant populations</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Consider ACD, MSAT, FSAT or MDA</strong></td>
</tr>
</tbody>
</table>
Oral artemisinin-based monotherapies
Cases diagnosed in Pailin province

Number of *P. falciparum* cases diagnosed by microscopy and RDT at health facilities in Pailin province, Cambodia, May 2008 – May 2012

ARCE interventions begin

<table>
<thead>
<tr>
<th>Month</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAY</td>
<td>23</td>
<td>74</td>
<td>12</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>JUN</td>
<td>30</td>
<td>60</td>
<td>26</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>JUL</td>
<td>43</td>
<td>43</td>
<td>21</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>AUG</td>
<td>63</td>
<td>102</td>
<td>14</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>SEP</td>
<td>135</td>
<td>139</td>
<td>18</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>OCT</td>
<td>121</td>
<td>121</td>
<td>8</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>NOV</td>
<td>103</td>
<td>103</td>
<td>17</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>DEC</td>
<td></td>
<td></td>
<td>12</td>
<td>5</td>
<td>14</td>
</tr>
</tbody>
</table>

- Health facilities
- Village Malaria Workers

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## Consequences of artemisinin resistance

<table>
<thead>
<tr>
<th>FACTS</th>
<th>IMPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>(ACPR) Clinical and parasitological cure of ACTs - not compromised</td>
<td>➢ Change in parasite sensitivity not reflected in therapeutic efficacy results</td>
</tr>
<tr>
<td>Clinical resolution (fever clearance time – prolonged slightly)</td>
<td>➢ May lead to dissatisfied patients and incorrect treatment practices</td>
</tr>
<tr>
<td>Parasite clearance time – prolonged</td>
<td>➢ Could potentially increased risk of mortality associated with severe malaria (which is treated with AS monotherapy)</td>
</tr>
<tr>
<td>Infectivity to mosquitoes – <em>Needs more data</em></td>
<td>➢ Increased risk of transmission of less sensitive parasites – <em>Needs more research</em></td>
</tr>
<tr>
<td>Total parasite biomass over period of infection – increased</td>
<td>➢ More parasites exposed to partner medicine alone</td>
</tr>
<tr>
<td></td>
<td>➢ Likely to increased frequency of parasite de novo mutations – which favour parasite survival</td>
</tr>
</tbody>
</table>
Thank you for your attention