Multicenter clinical trials of primaquine radical cure

IMPROV & OPRA studies

Kamala Thriemer
Background

P. vivax Life Cycle

Mosquito Stages
- Oocyst
- Release of sporozoites
- Ruptured oocyst
- Mosquito takes a blood meal (injects sporozoites)

Sporogonic Cycle
- Ookinete
- Macrogametocyte
- Microgamete entering macrogamete
- Exflagellated microgametocyte

Human Liver Stages
- Human Blood Stages
- Erythrocytic Cycle
- Mature trophozoite
- Immature trophozoite (ring stage)
- Merozoite release
- Schizont
- Gametocytes

Merozoite release

Human Liver Stages
- Infected liver cell
- Exo-erythrocytic Cycle
- Hypnozoite
- Schizont
- Merozoite release

Human Blood Stages
- Infected liver cell
- Exo-erythrocytic Cycle
- Hypnozoite
- Schizont
- Merozoite release

Gametocytes

Gametocytes d

Gametocytes c

Gametocytes b

Gametocytes a

Gametocytes
Background

- As the incidence of *P. falciparum* decreases, *P. vivax* is becoming the dominant species in Asia.
- Hypnozoites are the main reservoir of *P. vivax* infection.
- The only drug we have to kill the hypnozoite stages is primaquine.
- To prevent *P. vivax* recurrence, anaemia and its associated morbidity relies on a haemolytic drug that is potentially fatal.
- The effectiveness of unsupervised 14 day regimens of *P. vivax* is extremely poor.

![Graph showing incidence of *P. falciparum* and *P. vivax* over time](image)
Risk of death increases with multiple recurrences

**Background**

Cumulative Risk of Death

**Late Mortality**

Incidence $\geq 6$ py

Incidence $< 6$ py

**Cumulative Risk of Death**

$P_V > P_F$

$AHR = 1.26$ [1.10-1.45] $p=0.001$

Data from RSMM Timika
Background

The only drug we have to kill the hypnozoite stages is primaquine.

To prevent *P. vivax* recurrence, anaemia and its associated morbidity and mortality relies on a haemolytic drug that is potentially fatal.

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Luxemburger et al TRSTMH 1999
SMRU Thailand
• Asia-Pacific committed to malaria elimination by 2030 from the region

• Two main factors that will determine the success:
  – Drug resistance, especially artemisinin for P.f.
  – Effective and safe treatment options for radical cure of P.v.
IMPROV
Improving the radical cure of vivax malaria

OPRA
Optimizing the Radical cure of vivax malaria
Background

Ethiopia

- 75% of the country malaria endemic
- >2 million cases 2014
- >200 deaths in 2014
- Seasonal transmission
- 60% *P. falciparum* / 40% *P. vivax*

Current treatment guidelines:

<table>
<thead>
<tr>
<th></th>
<th>Artemether-Lumefantrine</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. falciparum</em> infection</td>
<td></td>
</tr>
<tr>
<td><em>P. vivax</em> in endemic areas</td>
<td>Chloroquine</td>
</tr>
<tr>
<td><em>P. vivax</em> in non-endemic areas</td>
<td>Chloroquine + Primaquine (14d 3.5mg/kg total)</td>
</tr>
<tr>
<td>Clinical malaria (unconfirmed)</td>
<td>Artemether-Lumefantrine</td>
</tr>
</tbody>
</table>
**Aim:** To compare the schizontocidal efficacy of AL and CQ, and the antirelapse efficacy and effectiveness of 14 days low dose primaquine

**Study Design**
- Randomized open label controlled trial with 12m follow up
- Repeated exposure of treatment arm
- 2 Treatment centers (Batu and Bishoftu)

**Inclusion criteria**
- Slide-confirmed Pv mono infection
- Age > 1 year
- Weight ≥ 5.0 kg
- Fever or history of fever

**Exclusion criteria**
- Severe malaria/ malnutrition
- G6PD deficiency (NADP Spot Test)
- Hb < 8 g/dl
- Known hypersensitivity to any of the drugs
- Co-morbid infection or condition
- Pregnant or breastfeeding women
- History or haemolysis
- Regular medication, which may interfere with antimalarial PK
Methods

Randomization

Two step randomization

First randomization

AL  CQ

G6PD normal

AL  AL+PQ  CQ  CQ+PQ

DAY 0

DAY 1/2

Dosing Regimens

Artemether-lumefantrine
Twice daily for three days

Chloroquine
25mg base per kg over 3 days

Primaquine
0.25 mg/kg daily for 14 days (days 2-16)
Methods

Phase 1: weekly visits → Phase 2: monthly visits

- Enrolment → Prim. endpoint → Sec. endpoint
  - 42 days
  - 10 months

Primary endpoints:
- Schizontocidal efficacy at day 28 and day 42

Secondary endpoints:
- Incidence rate and risk over 12 months
- Haematological recovery

Study Period:
- Nov 2012 to Dec 2014
Results

Screened n=1777

Enrolled n=398

CQ n=104
  - LTF n=17
  - Lost n=10
  - Pf n=1
  - APCR D42 n=76

CQ+PQ n=102
  - LTF n=1
  - Lost n=16
  - Pf n=1
  - APCR D42 n=84

AL n=100
  - LTF n=27
  - Lost n=11
  - APCR D42 n=62

AL+PQ n=92
  - LTF n=5
  - Lost n=9
  - APCR D42 n=78
### Late Parasitological Response

- **HR=1.8**
  - [95%CI: 1.0-3.2]
  - \( p=0.059 \)

<table>
<thead>
<tr>
<th></th>
<th>CQ</th>
<th>CQ+PQ</th>
<th>AL</th>
<th>AL+PQ</th>
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<tbody>
<tr>
<td><strong>D28</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>4.0%</td>
<td>0%</td>
<td>12.0%</td>
<td>2.3%</td>
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<tr>
<td></td>
<td>[1.5-10.4]</td>
<td></td>
<td>[6.8-20.6]</td>
<td>[0.6-9.0]</td>
</tr>
<tr>
<td><strong>D42</strong></td>
<td><strong>18.7%</strong></td>
<td>1.2%</td>
<td><strong>29.9%</strong></td>
<td>5.9%</td>
</tr>
<tr>
<td></td>
<td>[12.2-28.0]</td>
<td>[0.2-8.0]</td>
<td>[21.6-40.5]</td>
<td>[2.4-13.5]</td>
</tr>
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</table>
Late Parasitological Response

<table>
<thead>
<tr>
<th></th>
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<th>CQ+PQ</th>
<th>AL</th>
<th>AL+PQ</th>
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<td>D28</td>
<td>4.0%</td>
<td>0%</td>
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<td>[0.2-8.0]</td>
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<td>[2.4-13.5]</td>
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</table>
Early Therapeutic Response

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CQ</td>
<td>64.4</td>
<td>4.8</td>
<td>1.9</td>
</tr>
<tr>
<td>CQ+PQ</td>
<td>55.9</td>
<td>8.8</td>
<td>8.8</td>
</tr>
<tr>
<td>AL</td>
<td>35</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>AL+PQ</td>
<td>27.2</td>
<td>27.2</td>
<td>27.2</td>
</tr>
</tbody>
</table>
Relapse Efficacy

<table>
<thead>
<tr>
<th></th>
<th>CQ</th>
<th>CQ+PQ</th>
<th>AL</th>
<th>AL+PQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>D 322</td>
<td>61.7%</td>
<td>20.5%</td>
<td>72.4%</td>
<td>22.0%</td>
</tr>
<tr>
<td></td>
<td>[51.9-71.1]</td>
<td>[13.0-31.5]</td>
<td>[62.5-81.6]</td>
<td>[14.2-33.1]</td>
</tr>
</tbody>
</table>

HR: 1.3 [0.9-1.9]
p = 0.127
**P. vivax Recurrence**

![Histograms showing recurrence of *P. vivax* infections among patients treated with different combinations of drugs.](image)

- **AL only**
- **CQ only**
- **AL + PQ**
- **CQ + PQ**

The histograms illustrate the number of patients experiencing recurrence over different episodes.
## Incidence Rates

### Episodes per PYO (95%CI)

<table>
<thead>
<tr>
<th></th>
<th>Episodes per PYO (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CQ</td>
<td>2.2 [1.8 – 2.6]</td>
</tr>
<tr>
<td>CQ+PQ</td>
<td>0.4 [0.3 – 0.6]</td>
</tr>
<tr>
<td>AL</td>
<td>2.3 [1.9 – 2.7]</td>
</tr>
<tr>
<td>AL+PQ</td>
<td>0.5 [0.3 – 0.7]</td>
</tr>
</tbody>
</table>

### Rate Ratio (95%CI) and p

<table>
<thead>
<tr>
<th></th>
<th>Rate Ratio (95%CI)</th>
<th>p</th>
<th>Hazard Ratio (95%CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CQ vs CQ+PQ</td>
<td>5.1 [2.9-9.1]</td>
<td>&lt;0.001</td>
<td>5.4 [23.0-9.7]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AL vs AL+PQ</td>
<td>6.4 [3.6-11.3]</td>
<td>&lt;0.001</td>
<td>5.2 [3.0-9.0]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AL+PQ vs CQ+PQ</td>
<td>0.9 [0.6-1.4]</td>
<td>0.530</td>
<td>1.3 [0.9-1.9]</td>
<td>0.172</td>
</tr>
<tr>
<td>AL vs CQ</td>
<td>1.1 [0.5-1.9]</td>
<td>0.964</td>
<td>1.3 [0.5-1.9]</td>
<td>0.523</td>
</tr>
</tbody>
</table>
Effectiveness

CQ

AL

CQ+PQ

AL+PQ

HR = 3.5 [1.4-8.9]  
P = 0.008

HR = 3.9 [1.3-11.4]  
P = 0.004

86.8%  
63.2%  
84.0%  
51.9%
### Haematological Response

<table>
<thead>
<tr>
<th></th>
<th>% Hb change from baseline</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean (95%CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 3</td>
<td>Day 7</td>
<td>Day 14</td>
<td>Day 28</td>
</tr>
<tr>
<td><strong>CQ</strong></td>
<td>-6.3 [-7.7, -4.9]</td>
<td>-1.67 [-3.26, -0.08]</td>
<td>-0.13 [-1.85, 1.59]</td>
<td>3.9 [1.75, 6.17]</td>
</tr>
<tr>
<td><strong>CQ+PQ</strong></td>
<td>-5.9 [-7.3, -4.4]</td>
<td>-0.64 [-2.42, 1.14]</td>
<td>1.8 [-0.53-4.2]</td>
<td>5.84 [3.05, 8.63]</td>
</tr>
<tr>
<td><strong>AL</strong></td>
<td>-5.7 [-7.1, -4.3]</td>
<td>-3.76 [-5.23, -2.29]</td>
<td>-0.89 [-2.6, 0.9]</td>
<td>1.7 [-0.30, 3.71]</td>
</tr>
<tr>
<td><strong>AL+PQ</strong></td>
<td>-7.6 [-10.0, -5.1]</td>
<td>-3.45 [-5.13, -1.78]</td>
<td>-1.5 [-3.5, 0.5]</td>
<td>1.23 [-0.85, 3.3]</td>
</tr>
</tbody>
</table>

*p=0.29*  
*p=0.02*
• Low grade CQ resistance, but fewer recurrences at day 42 than following AL (post treatment prophylaxis)

• Cumulative recurrences at 12 months were greater after AL than CQ, although this didn’t reach significance

• The addition of PQ improved efficacy for both regimens at day 42 and at 12 months

• The fall in Hb was greatest at day 3, and recovery was slower after AL compared to CQ

• Unobserved PQ treatment had 30-40% lower effectiveness than supervised treatment
Research question: Can we deliver the same total dose of primaquine over 7 days instead of 14?

Primary Objective:
Determine whether a 7 day high dose primaquine regimen (total dose of 7mg/kg) is safe and not inferior to the standard 14 day regimen in preventing *P. vivax* relapse in G6PD normal patients.
A multicentre study conducted in 5 (+2) sites:

North and South Sumatra
Afghanistan (2 sites)
Vietnam
Ethiopia (2 sites)
Improving the radical cure of vivax malaria (IMPROV): a study protocol for a multicentre randomised, placebo-controlled comparison of short and long course primaquine regimens

The IMPROV Study Group
Study Design:

- **Double blind placebo controlled study**
- **Schizonticidal treatment:**
  - Chloroquine (Afghan, Viet, Ethiop)
  - DHA-Piperaquine (Indo)
- **Three armed RCT:**
  - Control Arm (PQ placebo for 14 days)
  - Pq 7days (1.0mg/kg/day for 7 days followed by placebo for 7 days)
  - Pq 14 days (0.5mg/kg/day for 14 days)
- **G6PD deficient patients receive weekly primaquine (0.75 mg/kg/week x 8w) - not randomized**
Study Design:
Visit schedule:
  • Daily: day 0-14
  • Weekly: day 21 – 56
  • Monthly: month 3-12
Recurrence:
  – Same treatment as randomized to
  – Repeated activities from Day 0 to day 14 as during first episode
  – Day 15 follows the routine as before episode started
Sample Size

- Assumed incidence rate of 0.2 infection/year in PQ arms
- Non inferiority margin of 0.07 infections/year
- One sided significance level 2.5% & 80% power

-> 1200 subjects in PQ arms (600 per PQ arm)

- Addition of 300 in control arm -> 95% power and 95% Confidence to detect difference at each site (assuming 0.2 infection/year in PQ arms and 0.6/year in control arm)

-> 1875 (750 per treatment arm, 375 in control arm)
Safety monitoring

• Hb measurement on day 0, 3, 7, 14 and on every following visit

• Hemolyses warning signs protocol incl indication when to withhold or stop PQ/placebo

**MANAGEMENT OF ACUTE HAEMOLYSIS**

- Any clinical concern of acute haemolysis (e.g. symptoms of anaemia, dark urine, clinical jaundice or falling haemoglobin) should be trigger the following:
  1. A thorough history and examination
  2. Immediate HemoCue haemoglobin measurement
  3. Hillmen urine colour estimation for haemoglobinuria
  4. Repeat G6PD test if randomised to the G6PD normal arm to confirm correct randomisation
  5. Contact Bangkok coordinating team

**INDICATIONS TO STOP PRIMAQUINE / PLACEBO**

- Patient needs a blood transfusion:
  • Hb < 7 g/dL + symptoms of anaemia limiting daily activities
  • Hb 7-9 g/dL + clinical decompensation due to anaemia

- Continue to assess daily or more frequently and manage as indicated or until resolved.
- Refer to Bangkok Trial Management Team to discuss the need to unblind.
- Continue routine follow up for FULL year from randomisation.

**INDICATIONS TO WITHHELD PRIMAQUINE / PLACEBO**

- Hb < 7 g/dL & daily activities unaffected
- Macroscopic haemoglobinuria (Hillmen ≥ 5)
- Fractional haemoglobin fall ≥ 25% from baseline
- Other significant clinical concern of anaemia or haemolysis

**SAEs NOTIFICATION WITHIN 24 HOURS FOR**

1. Hb < 7 g/dL
2. Referral for blood transfusion
3. Macroscopic haemoglobinuria (Hillmen ≥ 5) + fractional haemoglobin fall ≥ 25% from baseline

**AT FORM TO BE COMPLETED**

1. All patients who have primaquine witheld for any reason

**Daily clinical review and Hb measurement**

- If Hb falls ≥ 1 g/dL over preceding 24 hours:
  - Withhold primaquine/placebo
  - Continue review and repeat Hb daily until the patient can either recommence primaquine/placebo or needs referral for blood transfusion

- If Hb stable or drop over preceding 24 hours is < 1 g/dL:
  - Re-dose with primaquine/placebo (at the discretion of the attending clinician)
  - Review and repeat Hb daily until Hb stable for 5 days.
<table>
<thead>
<tr>
<th></th>
<th>Jalalabad</th>
<th>Laghman</th>
<th>Vietnam</th>
<th>S Sumatra</th>
<th>N Sumatra</th>
<th>Ethiopia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start date</td>
<td>20 Jul 14</td>
<td>3 Sep 14</td>
<td>15 Oct 14</td>
<td>4 May 15</td>
<td>4 May 15</td>
<td>Oct/Nov 16</td>
</tr>
<tr>
<td>Enrolled (G6PDn)</td>
<td>312</td>
<td>120</td>
<td>238</td>
<td>475</td>
<td>340</td>
<td></td>
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<tr>
<td>Enrolled (G6PDd)</td>
<td>6</td>
<td>0</td>
<td>14</td>
<td>6</td>
<td>13</td>
<td></td>
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<tr>
<td>Completed</td>
<td>132</td>
<td>56</td>
<td>122</td>
<td>247</td>
<td>130</td>
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</tr>
</tbody>
</table>
Challenges

- Ethical issues: withholding PQ from control arm
- Placebo, packaging
- Logistics
Other connected studies

• G6PD
  – Point prevalence
  – Variants and phenotypic activity
  – Risk of haemolyses
  – Evaluation of new point of care tests

• Economic evaluation
  – Cost effectiveness etc.
Objective 2 & 3: Study in Timika

Modified Objective: to compare supervised vs unsupervised PQ treatment

- Cluster randomized design
- Nested into the baby-cohort study but recruiting also older children and adult patients
- 6 months follow up
- Planned start in April 2016
IMPROV
Improving the radical cure of vivax malaria

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