Lessons learnt from IPTp with Mefloquine clinical trials in Benin, Gabon, Kenya, Mozambique and Tanzania

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Background

• Increased SP resistance → evaluation of other antimalarials for IPTp needed

• **Mefloquine (MQ)** was considered a good alternative to be evaluated as IPTp

• Developed in the 1970’s by the US army

• MQ belongs to the arylaminoalcohol antimalarials
Background

• Comparative advantages of MQ for IPTp:
  – Long half life (12-17 days at prophylactic doses)
  – Can be given as single dose
  – Acceptable reprotoxicity profile in animal studies
  – Reclassified as pregnancy category B by the US-FDA
  – Recommended for chemoprophylaxis for pregnant women of all GA by the WHO and CDC
  – Well characterized in terms of PK in pregnancy
  – Resistance to MQ is rare in Africa

• Tolerability could be improved by splitting drug administration over 2 days (ter Kuile et al. 1995)
Background

• HIV-infected pregnant women are an special vulnerable group for malaria
• SP is not recommended in women receiving daily cotrimoxazole (CTX) prophylaxis
• CTX has some antimalarial effect
• Evaluation of drugs to be used as IPTp in HIV-infected women receiving CTX is needed

→ MiPPAD (Malaria in Pregnancy Preventive Alternative Drugs) study that included two randomized controlled trials (RCT)
MiPPAD Trial 1:

Safety and Efficacy of Mefloquine as Intermittent Preventive Treatment for malaria in Pregnancy: a randomized multicenter trial in HIV-negative women
Intermittent Preventive Treatment of Malaria in Pregnancy with Mefloquine in HIV-Negative Women: A Multicentre Randomized Controlled Trial

Objectives

Primary:
• To compare the safety, tolerability and efficacy of MQ to SP as IPTp for the prevention of malaria in pregnancy for the mother and her infant

Secondary:
• To compare MQ tolerability given as full dose with a split dose administered over 2 days
Study design

Randomized open-label 3 arms trial to compare 2-dose MQ versus 2-dose SP for IPTp in the prevention of the adverse effects of malaria during pregnancy and to compare MQ tolerability of 2 different MQ administration regimens. Study arms:

- IPTp with SP
- IPTp with MQ given as full dose
- IPTp with MQ given as an split dose
Pregnant women attending ANC

HIV test

HIV negative
n=4749

RCT Open-label, ITNs context
BN, GB, MZB, TZN

SP
MQ full
15mg/kg

MQ split
15 mg/kg/
in 2 days

2 IPTp doses

Delivery

HIV positive
n=1071

RCT double blinded in MZB, TZN and KN

Infants
Follow-up 1 year
## Efficacy results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>SP</th>
<th>MQ</th>
<th>RR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n/N %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence of LBW</td>
<td>177/1398</td>
<td>360/2778</td>
<td>1.02</td>
<td>(0.86, 1.22)</td>
<td>0.801</td>
</tr>
<tr>
<td>Benin</td>
<td>47/349</td>
<td>110/703</td>
<td>1.16</td>
<td>(0.82, 1.64)</td>
<td>0.391</td>
</tr>
<tr>
<td>Gabon</td>
<td>54/331</td>
<td>112/652</td>
<td>1.05</td>
<td>(0.77, 1.44)</td>
<td>0.749</td>
</tr>
<tr>
<td>Mozambique</td>
<td>37/360</td>
<td>66/712</td>
<td>0.90</td>
<td>(0.60, 1.36)</td>
<td>0.621</td>
</tr>
<tr>
<td>Tanzania</td>
<td>39/358</td>
<td>72/711</td>
<td>0.93</td>
<td>(0.63, 1.36)</td>
<td>0.709</td>
</tr>
<tr>
<td>Mean birth weight, m (SD)</td>
<td>3001.5 (517.8)</td>
<td>2997.4 (535.5)</td>
<td>-4.1(^1)</td>
<td>-39.2, 31.1)</td>
<td>0.821</td>
</tr>
<tr>
<td>Maternal parasitemia at delivery (O.M.)</td>
<td>63/1372</td>
<td>88/2737</td>
<td>0.70</td>
<td>(0.51, 0.96)</td>
<td>0.026</td>
</tr>
<tr>
<td>Maternal anemia at delivery (Hb&lt;11 g/dl)</td>
<td>609/1380</td>
<td>1110/2743</td>
<td>0.92</td>
<td>(0.85, 0.99)</td>
<td>0.026</td>
</tr>
<tr>
<td>Maternal Hb at delivery mean (SD)[n]</td>
<td>11.0 (1.6) [1380]</td>
<td>11.1 (1.5) [2743]</td>
<td>0.15(^2)</td>
<td>(0.05, 0.25)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

\(^1\)Proportional difference

July 26, 2016

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# Efficacy results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>SP</th>
<th>MQ</th>
<th>RR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of clinical malaria</td>
<td>96/552.8</td>
<td>130/1106.1</td>
<td>0.67</td>
<td>(0.52, 0.88)</td>
<td>0.004</td>
</tr>
<tr>
<td>Incidence of outpatients visits</td>
<td>850/558.8</td>
<td>1475/1113</td>
<td>0.86</td>
<td>(0.78, 0.95)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hospital Admissions</td>
<td>106/558.8</td>
<td>186/1113.0</td>
<td>0.88</td>
<td>(0.68, 1.14)</td>
<td>0.346</td>
</tr>
</tbody>
</table>

**ITT cohort**  

| 1 Episodes person/year

**Definition of clinical malaria episode:** *P. falciparum* parasitemia of any density plus any signs and/or symptoms suggestive of malaria: fever in the last 24 hours and/or axillary temperature (Tª ≥ 37.5 ºC), and/or pallor and/or arthromyalgias and/or headache and/or history of convulsions.
ITT cohort

Time to first malaria episode

Cumulative Percentage

- SP
- MQ

At risk (ca):
- SP 576
- MQ 164
- (36) 1241
- (35) 2501
- (54) (86)
- 114 242

p-value: 0.004
### Adverse events related to medication

<table>
<thead>
<tr>
<th>After 1st IPTp</th>
<th>N=1559</th>
<th></th>
<th></th>
<th>N=1550</th>
<th></th>
<th></th>
<th>N=1562</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>SP</td>
<td>%</td>
<td>95%CI</td>
<td>n</td>
<td>MQ full</td>
<td>%</td>
<td>95%CI</td>
<td>n</td>
</tr>
<tr>
<td>Vomiting</td>
<td>100</td>
<td>6.41</td>
<td>(5.25; 7.75)</td>
<td>491</td>
<td>31.68</td>
<td>(29.37; 34.06)</td>
<td>471</td>
<td>30.15</td>
<td>(27.88; 32.50)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>115</td>
<td>7.38</td>
<td>(6.13; 8.79)</td>
<td>526</td>
<td>33.94</td>
<td>(31.58; 36.35)</td>
<td>554</td>
<td>35.47</td>
<td>(32.90; 37.90)</td>
</tr>
<tr>
<td>Headache</td>
<td>115</td>
<td>7.38</td>
<td>(6.13; 8.79)</td>
<td>123</td>
<td>7.94</td>
<td>(6.64; 9.39)</td>
<td>131</td>
<td>8.39</td>
<td>(7.06; 9.87)</td>
</tr>
<tr>
<td>Nausea</td>
<td>55</td>
<td>3.53</td>
<td>(2.67; 4.57)</td>
<td>136</td>
<td>8.77</td>
<td>(7.41; 10.29)</td>
<td>152</td>
<td>9.73</td>
<td>(8.31; 11.31)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>14</td>
<td>0.90</td>
<td>(0.49; 1.50)</td>
<td>107</td>
<td>6.90</td>
<td>(5.69; 8.28)</td>
<td>104</td>
<td>6.66</td>
<td>(5.47; 8.01)</td>
</tr>
</tbody>
</table>

**No differences** between groups on frequency of:

- Adverse pregnancy outcomes (miscarriages, stillbirths, congenital malformations, prematurity)
- SAEs
- Maternal and neonatal deaths

**Safety cohort**
Summary of main findings

• No differences in LBW prevalence between groups

• MQ group presented lower rates of
  – Maternal parasitemia at delivery
  – Maternal anemia at delivery
  – Incidence of clinical malaria during pregnancy
  – Incidence of outpatient clinic visits

• No differences in the frequency of adverse pregnancy outcomes (miscarriage, stillbirths, congenital malformations, maternal deaths)

• MQ group presented higher rates of drug related- Adverse Effects
  – Poorer immediate tolerability than the SP group
  – Higher frequency of vomiting and dizziness

• No differences in efficacy, frequency of adverse effects and drug tolerability between MQ full and MQ split groups
Conclusions

• MQ has a **better prophylactic** antimalarial effect than SP

• MQ is a **safe** drug in terms of adverse pregnancy outcomes

• MQ (15 mg/kg) has **worse tolerability** than SP as IPTp

• Splitting the MQ dose does not seem to confer benefits in terms of drug tolerability

• MQ at the **dose** used in this study is **not** an alternative to SP for IPTp
MiPPAD Trial 2:

Mefloquine as Intermittent Preventive Treatment for malaria in Pregnancy in HIV-infected women receiving cotrimoxazole prophylaxis: a randomized double-blind multicenter placebo-controlled trial
Intermittent Preventive Treatment of Malaria in Pregnancy with Mefloquine in HIV-Infected Women Receiving Cotrimoxazole Prophylaxis: A Multicenter Randomized Placebo-Controlled Trial

To evaluate the safety and efficacy of mefloquine (MQ) as intermittent preventive treatment for malaria in pregnancy (IPTp) in HIV-infected women taking daily CTXp and in the context of long lasting insecticide treated nets (LLITNs).
Study design

Randomized double-blind clinical trial to compare the efficacy of MQ as IPTp with placebo-IPTp in HIV-infected pregnant women receiving CTX prophylaxis.
Pregnant women attending ANC

HIV negative  ←  HIV test  →  HIV positive

Trial 2. Double blinded superiority trial, ITNs context
KN, MZB, TZN, n=1071

- Placebo + CTX
- MQ 15 mg/kg + CTX

3 IPTp doses

Delivery

Infants
Follow up 2 months
## Efficacy

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Control</th>
<th></th>
<th>MQ</th>
<th></th>
<th>RR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal parasitemia at delivery (smear or PCR)</td>
<td>37/490</td>
<td>7.6</td>
<td>17/483</td>
<td>3.5</td>
<td>0.47</td>
<td>(0.27; 0.82)</td>
<td>0.008</td>
</tr>
<tr>
<td>Placental infection (Histology, smear or PCR)</td>
<td>34/462</td>
<td>7.4</td>
<td>17/449</td>
<td>3.8</td>
<td>0.52</td>
<td>(0.29; 0.90)</td>
<td>0.021</td>
</tr>
</tbody>
</table>
# Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Control n/PYAR</th>
<th>Mefloquine n/PYAR</th>
<th>Relative Rate</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical malaria</strong></td>
<td>16/189.1</td>
<td>8/182.2</td>
<td>0.52</td>
<td>(0.22; 1.21)</td>
<td>0.128</td>
</tr>
<tr>
<td>Outpatient visits</td>
<td>401/190.2</td>
<td>332/182.8</td>
<td>0.86</td>
<td>(0.72; 1.03)</td>
<td>0.098</td>
</tr>
<tr>
<td><strong>All-cause hospital admissions</strong></td>
<td>68/190.2</td>
<td>41/182.8</td>
<td>0.65</td>
<td>(0.41; 1.03)</td>
<td>0.065</td>
</tr>
<tr>
<td>Non-obstetric admissions</td>
<td>67/190.2</td>
<td>37/182.8</td>
<td>0.59</td>
<td>(0.37; 0.95)</td>
<td>0.031</td>
</tr>
</tbody>
</table>

1 Episodes person/year. ITT analysis adjusted by country.
## Safety

### After 1st IPTp

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo (N=531)</th>
<th>MQ (N=520)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>40</td>
<td>7.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>16</td>
<td>3.0</td>
</tr>
<tr>
<td>Headache</td>
<td>40</td>
<td>7.5</td>
</tr>
<tr>
<td>Nausea</td>
<td>21</td>
<td>4.0</td>
</tr>
</tbody>
</table>

**No differences** between groups on frequency of:

- Adverse pregnancy outcomes (miscarriages, stillbirths, congenital malformations, prematurity)
- SAEs
- Maternal and neonatal deaths
Mother to child transmission of HIV by treatment group (exploratory analysis)

<table>
<thead>
<tr>
<th>Infant HIV PCR results¹</th>
<th>Control</th>
<th></th>
<th>Mefloquine</th>
<th></th>
<th>Risk Ratio (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT [N=855]</td>
<td>Positive</td>
<td>19</td>
<td>36</td>
<td>1.95</td>
<td>(1.12; 3.39)</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>416</td>
<td>384</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATP [N=754]</td>
<td>Positive</td>
<td>15</td>
<td>29</td>
<td>2.04</td>
<td>(1.08; 3.85)</td>
<td>0.028</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>378</td>
<td>332</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹Median age 5.9 weeks (Interquartile Range 1.7). ITT analysis adjusted by country. ATP analysis adjusted by baseline variables: country, literacy, gestational age, gravidity, anemia, MUAC, CD4 counts and viral load. Interaction MQ x Country = p-value 0.642 for ITT cohort, and 0.860 for ATP cohort.
### Risk factors for MTCT of HIV

<table>
<thead>
<tr>
<th></th>
<th>ITT Risk Ratio</th>
<th>95% CI</th>
<th>p-value</th>
<th>ATP Risk Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mefloquine vs Control</td>
<td>2.05</td>
<td>1.16; 3.63</td>
<td>0.014</td>
<td>2.17</td>
<td>1.12; 4.19</td>
<td>0.021</td>
</tr>
<tr>
<td><strong>Viral load at delivery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(copies/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>400-999 vs &lt;400</td>
<td>4.80</td>
<td>1.38; 16.65</td>
<td>0.013</td>
<td>3.32</td>
<td>0.88; 12.50</td>
<td>0.075</td>
</tr>
<tr>
<td>1000-9999 vs &lt;400</td>
<td>3.59</td>
<td>1.39; 9.29</td>
<td>0.008</td>
<td>3.75</td>
<td>1.43; 9.87</td>
<td>0.007</td>
</tr>
<tr>
<td>&gt;9999 vs &lt;400</td>
<td>5.82</td>
<td>2.01; 16.84</td>
<td>0.001</td>
<td>3.62</td>
<td>1.14; 11.51</td>
<td>0.029</td>
</tr>
<tr>
<td>No data vs &lt;400</td>
<td>2.78</td>
<td>0.80; 9.74</td>
<td>0.109</td>
<td>1.22</td>
<td>0.16; 9.20</td>
<td>0.847</td>
</tr>
<tr>
<td><strong>Clinical malaria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>episodes in pregnancy&lt;sup&gt;2&lt;/sup&gt;</td>
<td>3.05</td>
<td>1.35; 6.92</td>
<td>0.008</td>
<td>4.76</td>
<td>2.01; 11.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Maternal compliance to PMTCT or ART guidelines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete&lt;sup&gt;3&lt;/sup&gt; vs Complete&lt;sup&gt;4&lt;/sup&gt;</td>
<td>1.94</td>
<td>1.06; 3.57</td>
<td>0.031</td>
<td>1.96</td>
<td>0.98; 3.92</td>
<td>0.056</td>
</tr>
<tr>
<td>Nothing&lt;sup&gt;5&lt;/sup&gt; vs Complete</td>
<td>2.86</td>
<td>1.43; 5.74</td>
<td>0.003</td>
<td>3.01</td>
<td>1.22; 7.37</td>
<td>0.016</td>
</tr>
</tbody>
</table>

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<sup>1</sup>Median age of infants was 5.9 weeks (IQR 1.7) at the time of the HIV PCR test. Analysis adjusted by baseline variables: country, literacy, gestational age, gravidity, anemia, MUAC, CD4 counts and viral load. PMTCT: Prevention of Mother to Child Transmission. ART: Antiretroviral therapy. <sup>2</sup>At least one episode of clinical malaria during study follow-up in pregnancy. <sup>3</sup>Incomplete: received partially PMTCT (either antenatal, intrapartum or postpartum) or ART. <sup>4</sup>Complete: received PMTCT (antenatal, intrapartum, and postpartum) or ART according to national guidelines. <sup>5</sup>The mother did not receive either PMTCT or ART.
Summary of main findings

• In IPTp-MQ group, **reduced** rate of:
  – Maternal **parasitemia** at delivery
  – Placental infection
  – Hospital admissions

• **No differences** on frequency of adverse pregnancy outcome

• No maternal SAEs related to medication

• In IPTp-MQ group, **higher**:
  – Frequency of **vomiting and dizziness**
  – HIV **viral loads** at delivery
  – Rates of **MTCT of HIV**
Conclusions

• The **addition** of an **effective antimalarial** drug to daily **CTX** prophylaxis in **HIV-infected women** can have a beneficial effect by:
  – Halving the risk of maternal **parasitemia** at delivery
  – Reducing the incidence of hospital **admissions**

• Poor tolerability of MQ (15mg/kg) → search for alternative antimalarials

• The increased MTCT of HIV calls for the need of **specifically designed studies** to fully understand the effects of antimalarials and ARVs co-administration

• There is an **urgent** need to address the **prevention** of malaria in **HIV-infected pregnant women** who are one of the most **vulnerable** group to the infection in malaria endemic areas in **Africa**
MiPPAD investigators

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• John J. Aponte
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• Abraham Katana

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• Michael Ramharter

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• Achille Massougbodji
• Smaïla Ouédragou

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• Arsénio Nhacolo
• María Rupérez
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- Daniel Iñíguez
- Montserrat Pi

**Safety Monitoring Team**
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- Laia Sánchez
- Alberto L. García-Basteiro
- Sergi Sanz

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