FDA Workshop: Clinical Trial Design Considerations for Malaria Drug Development
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The 5 human *Plasmodium* species

- *P. falciparum*
- *P. vivax*
- *P. ovale*
- *P. malariae*
- *P. knowlesi*

*Anopheles*

*H. sapiens*

*M. fascicularis/nemestrina*
Artemisinins: the best drugs for reducing malaria mortality

SEAQUAMAT
- Asia
  - 4 countries
  - N=1,461
  - (202 children)
  - Δ=35%
- Log-rank p=0.0002

AQUAMAT
- Africa
  - 9 countries
  - N=5,425
  - (all children)
  - Δ=23%
- Log-rank p=0.0022

Dondorp et al. Lancet 2010;
SEAQUAMAT investigators group. Lancet 2005
Broader stage specificity explains superiority of artemisins.
Differences in potency

- **Artesunate best drug to treat severe malaria**

- **Fastest for the artemisinins**

- Detection limit

- **Reduction/48h-cycle**

- **Artesunate**: 48h cycle

- **MQ, PQP, Malarone**: 72h cycle

- **Doxycycline**: 144h cycle

- = artemisinin resistance

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**Courtesy NJ White**
Differences in pharmacokinetics

Plasma concentration (%)

Time after start treatment (weeks)

0% 100%

0 1 2 3 4

A Q P C M

Courtesy NJ White
Artemisinin resistance: a prelude to ACT failure

1. W-Cambodia

**2007-2008**

- Slow clearance

**2012-2013**

- DHA-piperquine efficacy

**2012-2014**

- DHA-piperquine 42-day failures

Dondorp et al.  
*N Eng J Med* 2009

Amaratunga et al.  
*Lancet Infect Dis* 2016

Source CNM Cambodia/ WHO

Map by Richard Maude
The molecular marker for artemisinin resistance: Kelch 13

K13 mutations in the “propeller region” strongly associates with the slow clearing phenotype

multiple SNPs in the propeller region, but: only 1 mutation per clone seems permitted
Regional distribution of Kelch13 Δ propeller 2015

Menard et al.
K580Y mutant found in Myanmar did not spread from Cambodia—it arose independently in Myanmar.
Spread of artemisinin-resistant *Plasmodium falciparum* in Myanmar: a cross-sectional survey of the K13 molecular marker


**Summary**

**Background** Emergence of artemisinin resistance in southeast Asia poses a serious threat to the global control of *Plasmodium falciparum* malaria. Discovery of the K13 marker has transformed approaches to the monitoring of artemisinin resistance, allowing introduction of molecular surveillance in remote areas through analysis of DNA. We aimed to assess the spread of artemisinin-resistant *P falciparum* in Myanmar by determining the relative prevalence of *P falciparum* parasites carrying K13-propeller mutations.

**Methods** We did this cross-sectional survey at malaria treatment centres at 55 sites in ten administrative regions in Myanmar, and in relevant border regions in Thailand and Bangladesh, between January, 2013, and September, 2014. K13 sequences from *P falciparum* infections were obtained mainly by passive case detection. We entered data into two geostatistical models to produce predictive maps of the estimated prevalence of mutations of the K13 propeller region across Myanmar.

**Findings** Overall, 371 (39%) of 940 samples carried a K13-propeller mutation. We recorded 26 different mutations, including nine mutations not described previously in southeast Asia. In seven (70%) of the ten administrative regions of Myanmar, the combined K13-mutation prevalence was more than 20%. Geospatial mapping showed that the overall prevalence of K13 mutations exceeded 10% in much of the east and north of the country. In Homalin, Sagaing Region, 25 km from the Indian border, 21 (47%) of 45 parasite samples carried K13-propeller mutations.

**Interpretation** Artemisinin resistance extends across much of Myanmar. We recorded *P falciparum* parasites carrying K13-propeller mutations at high prevalence next to the northwestern border with India. Appropriate therapeutic regimens should be tested urgently and implemented comprehensively if spread of artemisinin resistance to other regions is to be avoided.

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Figure 4: Geographical extent of predicted artemisinin resistance as determined by the prevalence of K13 propeller mutations (>440 aminoacids)
Artemisinin resistance: selects for partner drug resistance

2. Thai-Myanmar border

**2001-2013**

**1995-2011**

**n = 3814**
Resistance to artemisinins or partner vs ACT failure

- **<10%**
  - AS-MQ *W-Cambodia (2014-now)*
  - AM-Lum *E-Myanmar, Laos*
  - DHA-PQP *Thai-Myanmar border, E-Myanmar*
  - Most endemic countries outside GMS

- **10%-30%**
  - AS-AQ *Indonesia, Myanmar, selected African countries* *
  - AS-SP *Several African countries**, India
  - AS-Pyr *W-Cambodia (2014)*
  - AS-MQ *Thai-Myanmar border, Cambodia (<2010)*

- **>30%**
  - AS-SP *Rwanda, DRC*
  - AS-MQ *Thai-Myanmar border (2011- now)*
  - DHA-PQP *Cambodia (2013-2016)*

*Burkina Faso, Rwanda
** Rwanda, Zambia, DRC
Artemisinin resistance → treatment failure after artesunate-mefloquine, also with little MQ resistance

**Graph Details:***
- **Cure Rate (%)**
- **Days after MAS3**
- **Legend:**
  - WT kelch/1 copy pfmdr1 (N=177)
  - WT kelch/>2 copies pfmdr1 (N=66)
  - Mutant kelch/1 copy pfmdr1 (N=113)
  - Mutant kelch/>2 copies pfmdr1 (N=86)
Antimalarial drug resistance ⇒ ↑ transmission

More drug used → Resistance

More clinical cases

Larger reservoir

Increased transmission

Resistance → Delayed response

Recrudescent infections

Increased gametocyte carriage

Mefloquine: x4.0
Fansidar: x4.1
Chloroquine: x2.9 – x12

Price et al. 1996; Bousema et al 2003

Drakely et al. 2004; Barnes & White 2005
The doom scenario: for artemisinins/ACTs?

Spread of resistance: chloroquine & pyrimethamine

Dondorp et al
Nat Rev Microbiol. 2010

Adapted from Chris Plowe
Options with failing ACTs using existing drugs

1st. Triple therapies (TACT): DHA-PQP-MQ; AM-LUM-AQ: TRAC II

2nd. Arterolane-piperaquine: TRAC II

3rd. 5-day regimen of DHA-PQP or AM-LUM
   Needs trialing & reassurance of safety concerns (QTc-prolongation);
   new problem: PQP resistance.

4th. Drug rotation of DHA-PQP and MAS3,
    guided by prevalence of PfMDR1 copy-number

5th. Sequential use of two different ACTs (e.g. DHA-PQP and MAS3)

6th. Artesunate-pyronaridineline efficacy<90%; cross resistance with PQP??
TACT: DHA-piperaquine + mefloquine

No interaction re QTc time

Possible counter-acting resistance mechanisms

Reasonably matching PK-profiles

Price et al. Lancet 2004
TACT: Artemether-lumefantrine + amodiaquine

Lumefantrine

Artemether-Lumefantrine Treatment failure

PfMDR1 N86Y

PfMDR1 D1246Y

Amodiaquine

Artesunate-amodiaquine

Counter-acting resistance mechanisms

Reasonably matching PK-profiles

Venkatesan et al.
Conclusions: Combination therapy

- Fast acting drug (artemisinin) confers survival advantage
- Partner drug with longer half life permits construction of 3 day regimen
- Combination increases genetic barrier to resistance
- Significantly increases complexity in terms of drug development
Conclusions II: resistance

• Artemisinin resistance now with us:
  - Expanding in SE Asia; not yet in Africa
  - Contributes to treatment failure
  - Selects for partner drug resistance
  - Might increase transmissibility

• Partner drug resistance:
  - Increasing problem in SE Asia (Greater Mekong Subregion)

• Few options left in GMS:
  - Triple combination therapies

• New antimalarials urgently needed!
  - Choice of partner drug no longer trivial...
Global Portfolio of Antimalarials

**Research Lead optimization**
- DHODH: UTSW/UW/Monash
- Open Source Drug Discovery: Univ. Sydney
- Heterocycles: UCT
- Tetraoxanes: LSTM/Liverpool
- dUTPase Inhibitors: Medivir
- Imidazolidinediones: WRAIR
- PF NDH2: Imperial College London
- Pantothenamides: TroplQ/RUMC/Pansynt

**Translational Preclinical**
- 1 project: Novartis
- 2 projects: GSK
- DSM265: UTSW/UW/Monash
- An762: Anacor
- NPC1161B: Mississippi
- JPC2997: Jacobus
- MK4815: Merck
- P218 (Biotec)
- DDD498: Merck-Serono (Dundee)
- PA92: (Drexel/UW/GNF)
- MMV253: (AstraZeneca)
- GSK030: GSK
- DSM421: (UTSW/UW/Monash)
- SJ733: St Jude/Eisai

**Human volunteers**
- MMV048: UCT/TIA
- ACT-451840: Actelion
- CDRI 9778: Ipca
- N-tert butyl Isoquine: LSTM/Liverpool/GSK

**Product development Patient exploratory**
- OZ439/FQ: Sanofi
- Tafenoquine: GSK
- KAE609: Novartis
- CDRI 9778: Ipca
- Dihydroartemisinin-piperazine: Sanofi
- Artemisinin: Sigma-Tau
- Co-trimoxazole: ITM Antwerp
- Methylene Blue/AQ: Heidelberg
- Sar97276: Sanofi
- Artemisone: UHKST
- AQ13: Immtech
- Sevuparin: Dilaforette

**Patient confirmatory**
- DF4537: Actelion
- KAF156: Novartis
- Nafsoquinone: DTI
- Artemether: Lumezantrine
- Dihydroartemisinin-piperazine: Sigma-Tau
- Pyronaridine-artesunate: Shin Poong

**Regulatory review**
- Artemether-lumefantrine: Dispersible Novartis
- Artemether-lumefantrine: Dispensable Novartis
- Artesunate for injection: Gullin
- Pyronaridine-artesunate: Sigma-Tau
- Pyronaridine-artesunate: Shin Poong
- Artesunate-mefloquine: Cipla/DNDi
- SPAQ: Gullin

**Access Post approval**
- Artesunate-mefloquine: Cipla/DNDi
- Pyronaridine-artesunate: Shin Poong
- Artesunate-mefloquine: Cipla/DNDi
Thank you