Manuscripts for the WHO Evidence Review Group for malaria in pregnancy (MiP-ERG), July 2015

February 2015, Geneva, Switzerland

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Is IST a potential alternative strategy to IPT-SP in areas with low malaria transmission or high SP resistance?

Efficacy

1. ISTp-AL west Africa (low SP resistance)
   - IPTp-SP (3 doses of SP) vs ISTp-AL (ISTp-wAfrica, MAS MiPc)
   - Multicentre 2-arm open-label, individually randomized, non-inferiority trial in 4 west Africa countries with low SP resistance (Burkina Faso, Ghana, The Gambia and Mali)
   - Primary Efficacy Outcome: Efficacy outcomes low birth weight, maternal anaemia and placental infection
   - Sample size: 5,354
   - Timeline: Trial Submitted for publication:
   - Contact Person: Brian Greenwood (LSHTM, UK) and Harry Tagbor (Ghana)

2. ISTp-DP, Malawi (high SP resistance)
   - IPTp-SP vs ISTp-dihydroartemisinin-piperaquine (DP) ("ISTp-Malawi", MA6 MiPc)
   - 3-centre, single country, 2-arm, open-label, individually randomised superiority trial in high SP resistance areas in Southern Malawi comparing
   - Primary efficacy outcome: G1-G2: composite of LBW, pre-term or SGA; G3+ infection at delivery
   - Sample size: 1,872
   - Timeline: Field work completed, database to be closed in Jan 2015; report to WHO June 2015.
   - Publication: Madanitsa M, et al, In preparation. Safety and Efficacy of Intermittent Screening and Treatment (IST) with dihydroartemisinin-piperaquine versus Intermittent Preventive Therapy (IPT) with sulphadoxine-sulphamethoxine for the control of malaria in pregnancy in Malawi: An open-label superiority trial.[2]
   - Contact Person: Feiko ter Kuile (LSHTM, UK) and Mwayi Madanitsa (Malawi)

3. ISTp-DP + IPTp-DP, western Kenya (high SP resistance)
   - IPTp-DP, ISTp-DP, vs IPTp-SP (“STOPMIP Kenya” MA3 MiPc)
   - 4-centre, single country, 3-arm, open-label, individually randomised superiority trial in high SP resistance areas in western Kenya
   - Primary efficacy outcome: All gravidae: infection at delivery
   - Sample size: about 1,377 total
   - Timeline: Field work to be completed in Jan 2015, Database close Feb 15, Report to WHO June 2015
4. ISTp-AQ/AS and ISTp-SP, Ghana
   - IPTp-SP vs ISTp-SP vs ISTp with amodiaquine-artesunate (AS-AS)
   - 6-centre, single country, 3-arm, open-label, individually randomised superiority trial in high SP resistance areas in western Kenya
   - Primary efficacy endpoint: 3rd trimester anaemia, LBW
   - Sample size: 3,333 total
   - Timeline: Published

5. Reviews efficacy and safety ISTp-DP high SP transmission areas
   - Pooled analysis of trials 2 and 3 above
   - Sample size: 3249 total
   - Timeline: Report to be submitted to WHO June 2105
   - Contact person: Julie Gutman (CDC).

Safety and tolerance
1. ISTp-AL: see efficacy trial 1 above
2. DP: Review of DP safety in pregnancy
   Individual participants pooled analysis from ISTp trials in Malawi and Kenya; to be combined with meta-analysis of aggregated safety data of experience with DP in pregnancy
   - Timeline: report to WHO June 2015
   - Contact: Julie Gutman (CDC)
3. Efficacy and safety of DP for the case-management of malaria in pregnancy
   Results from a multi-centre treatment trial of 4 fixed dose ACTs for the case-management of malaria in the 2nd and 3rd trimester of pregnancy (MA1 MiPc). The results are very informative for the use of DP for ISTp as its tolerance and efficacy in clearing existing infections and preventing new infections is compared with the 3 other fixed dose ACTs.
• Timeline: report to WHO June 2015
• Contact: Umberto Dalessandro, MRC The Gambia

Cost-effectiveness analyses of trial data
Cost-effectiveness analysis of trials 1 (west Africa), 2 (Malawi) and 3 (western Kenya) above.
• Timeline: Report to WHO June 2015
• Publication: Hanson K, et al, In preparation. The Cost-effectiveness of Intermittent Screening and Treatment (IST) artmether-lumfantrine or dihydroartemisinin-piperaquine versus Intermittent Preventive Therapy (IPT) with sulphadoxine-pyrimethamine for the control of malaria in pregnancy in Malawi: A meta-analysis. [8]
• Contact: Kara Hanson (as for MA3, 5 and 6 above)

Feasibility and acceptability
Acceptability under trial conditions
1. Ghana: Contact: Jayne Webster
   • Timeline: Published: Smit et al[9,10]
   • Publications:

2. Malawi: Contact: Mwayi Madanitsa
   • Timeline: Submit report to WHO June 2015

3. Kenya: Contact: Jayne Webster (LSHTM, UK) and Jenny Hill (LSTM, UK)
   • Timeline: Submit report to WHO June 2015

Feasibility under real-life conditions
1. Implementation / feasibility study western Kenya in non-trial settings
   • Timeline: Field to be completed in March 2015, Report to WHO June 2015
• Contact person, Jayne Webster (LSHTM, UK) and Jenny Hill (LSTM, UK)

Impact, SP resistance and transmission intensity and threshold maps for potential implementation

Meta-analyses impact of resistance and transmission on IPTp-SP
1. Completion and update of meta-analyses required to obtain a better understanding of the impact of SP resistance and transmission intensity on IPTp effectiveness in terms of relative effect (e.g. % reduction in LBW) and absolute effects (numbers of LBW averted).
   • Timeline: Submit report to WHO in June 2015.
   • Contact: Feiko ter Kuile

Modelling impact and threshold maps for IPTp-SP and ISTp-DP or AL
1. Modelling to combine the data on resistance and transmission maps into a single model to obtain the threshold maps.
   • Timeline: Submit report to WHO in June 2015.
   • Contacts: Patrick Walker (Imperial College London), Matt Cairns (LSHTM).

Artemisinin safety

Aim
Provide update to WHO of the evidence accumulated over the years of the clinical safety of the artemisinin derivatives in the first trimester of pregnancy.

Reviews
Comparison of artemisinin vs. quinine vs. nothing (no malaria) exposure in the first trimester.

   • Description: Update of existing individual participant analysis of 25 years experience at the Thai-Burmese border with different antimalarials used advertantly or inadvertently in the first trimester.[17]
   • Timeline: Report to be submitted to WHO by June 2015
   • Contact person: Francois Nosten

3. Stephanie Dellicour et al, Use of artemisinin derivatives and quinine for the treatment of P. falciparum and vivax malaria in early pregnancy and the association with
spontaneous miscarriages: a pooled analysis of prospective, multi-country observational studies across Africa and Thai-Myanmar border.[18]

- Description: Pooled individual participant analysis of data from:
  i. the ASAP study (a 3-country prospective study in Africa from MIP Consortium)
  ii. the Thai-Burmese border (as above).
  iii. only studies that were able to identify women early in pregnancy and follow prospectively will be included.

- Timeline: Subject to further support from WHO for pooled analysis; Report to WHO by Jun 2015
- Contact: Stephanie Dellicour (LSTM, UK) and Francois Nosten (Thailand)


- Description: Pooled individual participant analysis of data from:
  i. ASAP study (a 3-country prospective study in Africa from MIP Consortium)
  ii. Possibly the WHO register?

- Timeline: Subject to further support from WHO for pooled analysis; Report to WHO by Jun 2015
- Contact: Esperanca Sevene (Mozambique) and Andy Stergachis (University of Washington)


- Description: Meta-analysis of
  i. any available aggregated data on all endpoints (miscarriages, stillbirths, congenital malformations), including from the above reviews
  ii. a listing of number of exposures, i.e., Estimate on how many pregnant women have been exposed to artemisinin in studies and how many had documented outcome

- Timeline: Report to WHO by Jun 2015
- Contact: Andy Stergachis (University of Washington)
References


11. Almond D, Madanitsa M, Paintain L, Mwapasa V, Kalilani L, et al. (In preparation) Provider and user acceptability of intermittent screening and treatment for the control of malaria in pregnancy in Malawi; a qualitative in-depth interview and focus group study


treatment of P. falciparum and P. vivax malaria in the first trimester of pregnancy on the Thai-Myanmar border; a population-based study.


