Intermittent screening and treatment (IST) or intermittent preventive treatment (IPT) with dihydroartemisinin-piperaquine versus IPT with sulphadoxine-pyrimethamine for the control of malaria in pregnancy in western Kenya:

A randomized controlled superiority trial

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Summary

Background

Annually, over 32 million pregnancies are at risk of malaria infection and its adverse consequences in Africa. The intermittent preventive therapy with sulphadoxine-pyrimethamine (IPTp-SP) strategy recommended by WHO, is threatened by high levels of parasite resistance. We evaluated the efficacy and safety of two alternative strategies: intermittent screening with malaria rapid diagnostic tests (RDTs) and treatment of RDT-positive women with dihydroartemisinin-piperaquine (ISTp-DP), and IPT with dihydroartemisinin-piperaquine (IPTp-DP).

Methods

We conducted an open-label three-arm randomized superiority trial at four sites with high malaria transmission and SP resistance in Kenya. HIV-negative pregnant women of 16-32 weeks gestation were randomly assigned using computer-generated randomization codes to receive ISTp-DP, IPTp-DP or IPTp-SP 3 to 4 times during pregnancy at least 1 month apart. Study participants, study clinic nurses, and the study coordinator were aware of the treatment allocation; study investigators, delivery unit nurses and the laboratory staff remained masked to the treatment assignment. The primary outcome was malaria infection at delivery (composite of peripheral or placental parasitaemia detected by placental histology, microscopy or RDT).

Findings

Between August 2012 and June 2014, 1546 women were randomized to ISTp-DP (n=515), IPTp-DP (n=516) and IPTp-SP (n=515), and 1368 (88.5%) contributed to the primary analysis. The prevalence of malaria infection at delivery was lower in the IPTp-DP than IPTp-SP arm: 15/457 (3.3%) vs 47/459 (10.2%); Relative Risk (RR)=0.32 (95% CI 0.18-0.56);p<0.0001, but not in the ISTp-DP arm: 57/452 (12.6%); RR=1.23 (0.86-1.77);p=0.26. Compared to IPTp-SP, IPTp-DP was also associated with lower incidence rates (IR) of malaria infection during pregnancy (54.4 vs 192.0 events/100 person-years with IPTp-SP, incidence rate ratio [IRR] 0.28 [0.22-0.36],p<0.0001) and clinical malaria during pregnancy (6.1 vs 37.9, IRR=0.16 [0.08-0.33], p<0.0001), whereas ISTp-DP was associated with a higher incidence of malaria infection (IR=232.0, IRR=1.21 [1.03-1.41],p=0.02) and clinical malaria (IR=53.4, IRR=1.41 [1.00-1.98],p=0.05). There were no significant differences in adverse newborn morbidity (composite of small-for-gestational age, low birth-weight or preterm birth) between study arms, however the mean birth-weight was 87grams higher (95% CI 24-150;p=0.01) in the IPTp-SP compared to IPTp-DP arm. Stillbirths (4/452 [0.9%] vs 16/453 [3.5%], RR=0.25 [0.08-0.74];p=0.01) and infant mortality by 6-8 weeks (4/452 [0.9%] vs 13/453 [2.9%], RR=0.31 [0.10-0.94];p=0.04) were lower in the IPTp-DP arm compared to IPTp-SP.

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79 Interpretation

80 At the current levels of RDT sensitivity, ISTp is not a suitable alternative to IPTp-SP in the
81 context of high SP resistance and malaria transmission. However, DP is a promising alternative
82 drug to replace SP for IPTp. The efficacy, operational feasibility and cost-effectiveness of IPTp-
83 DP should be investigated further.

84

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87

88 Trial Registration

89 Clinicaltrials.gov Identifier: NCT01669941

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90

91 **Introduction**

92 In sub-Saharan Africa, over 32 million pregnancies occur annually in malaria endemic areas and
93 in the absence of pregnancy-specific interventions, 12 million women delivering live babies
94 (45% of all liveborn deliveries) would be exposed to malaria infection which would be
95 responsible for an estimated 900,000 low birth weight deliveries due to preterm labour and
96 intrauterine growth retardation.¹⁻³ The World Health Organization (WHO) recommends the use
97 of long-lasting insecticide treated nets (LLINs) throughout pregnancy and intermittent preventive
98 therapy (IPT) with sulphadoxine-pyrimethamine (SP) in the second and third trimesters in
99 malaria endemic areas in sub-Saharan Africa.⁴ IPTp with SP has been shown to be very effective
100 in reducing the adverse outcomes of malaria in pregnancy,^{4, 5} but the emergence of widespread
101 resistance to SP is posing a potential threat to the gains made in reducing the burden of malaria
102 in pregnancy.⁶⁻⁸ SP is well tolerated, safe in the 2nd and 3rd trimester, affordable, widely available
103 and has the important advantage that it can be given as a single-dose, enabling directly-observed-
104 therapy in the antenatal clinics.^{4, 9} The recent search for safe, effective and well-tolerated
105 alternative drugs to replace SP for IPTp has proven elusive.¹⁰⁻¹³ Dihydroartemisinin-piperaquine
106 (DP) is a fixed-dose artemisinin-based combination therapy (ACT) that has several properties
107 that make it a potentially suitable replacement for SP, but has not yet been evaluated as IPTp. It
108 is well tolerated, highly effective at clearing infections and importantly, the piperaquine
109 component provides at least 4 weeks of post-treatment prophylaxis, the longest of all 4 fixed-
110 dose ACTs currently available.¹⁴⁻¹⁶

111 An alternative strategy, called intermittent screening and treatment in pregnancy (ISTp), involves
112 screening of asymptomatic women for malaria parasites with rapid diagnostic tests (RDTs)
113 during every scheduled antenatal clinic visit and treating only those who test RDT-positive. In
114 west Africa, where SP resistance is low, studies of the efficacy of IST with SP, amodiaquine-
115 artesunate (AQ+AS)¹⁷, and artemether-lumefantrine (AL)¹⁸ as an alternative strategy to IPTp-SP
116 for the control of malaria in pregnancy have shown that IST with these drugs was non-inferior to
117 IPTp-SP.

118 Here we present the results of the first randomized controlled trial to determine if ISTp with DP
119 (ISTp-DP) or IPTp with DP (IPTp-DP) is superior to the existing strategy of IPTp-SP for the
120 control of malaria during pregnancy in an area with intense year-round malaria transmission and
121 high SP resistance in western Kenya.

Methods

Study design and participants

We conducted an open-label parallel three-arm randomized controlled superiority trial at four rural health facilities in Siaya County, western Kenya. In this area, 96% of parasites harbour high-level SP resistance due to a series of five (quintuple) mutations in the parasite genes that encode the targets of pyrimethamine (*dhfr*) and sulfadoxine (*dhps*), and 5.8% carry the additional *Pf dhps*-A581G mutation (sextuple mutant)⁶. In this study area, SP either failed to clear parasites or new infections occurred by day-42 in 45% of asymptomatic parasitaemic pregnant women who had received SP for IPTp.⁶

HIV-negative pregnant women between 16-32 weeks gestation who had a viable pregnancy, no history of receiving IPTp-SP during the pregnancy, were resident of the study area, and willing to deliver in the study hospital were eligible. Women with high risk pregnancies, severe anaemia or who were unable to give consent were excluded.

The study protocol received ethical approval from the Kenya Medical Research Institute and the US Centers for Disease Control and Prevention (CDC).

Randomization and masking

Permuted block randomization lists were computer generated for each site by the trial statistician in CDC, Atlanta, GA, USA. The randomization assignments were put in sequentially numbered and sealed opaque envelopes which were distributed to the study facilities and opened sequentially upon enrolment of a study participant by the study nurse. Study participants, study clinic nurses, and the study coordinator were aware of the treatment allocation. The study investigators, delivery unit nurses and the laboratory staff remained masked to the treatment assignment.

Procedures

Pregnant women presenting to the antenatal care clinics at each of the study facilities who met the eligibility criteria and provided written informed consent were enrolled. Standardized questionnaires were administered to all participants and comprised demographic and socioeconomic information, insecticide treated net and indoor residual spraying use, medical and obstetric history, medication use, and clinical assessment. The gestational age was ascertained by history of last menstrual period and physical examination. A 5ml venous blood sample was collected for routine and study specific testing including haemoglobin levels, syphilis and malaria (microscopy and filter paper for polymerase chain reaction (PCR)), as well as urine to test for leukocytes and proteinuria. All participants received a LLIN on enrolment.

Women were randomly allocated to receive one of the following interventions at enrolment and at each scheduled focused antenatal care (FANC) visit during the second and third trimesters of pregnancy. The IPTp-SP arm received three tablets of quality-assured SP (supplied by Durbin

PLC, Middlesex, U.K., 500/25 mg/tablet). The IPTp-DP arm received a standard 3-day course with DP (Eurartesim®, Sigma Tau, Pomezia, Italy, 40mg/320 mg/tablet) and the ISTp-DP arm was screened for malaria using a histidine-rich protein-2 (HRP-2)/plasmodium lactate dehydrogenase (pLDH) combination RDTs (First Response® Malaria pLDH/HRP2 Combo Test, Premier Medical Corporation Ltd, India). RDT-positive women received a standard 3-day course of DP. DP dosing was based on enrolment bodyweight: 2, 3, or 4 tablets/day for 24-35.9, 36-74.9, and >75kg, respectively. SP and the first dose of DP were given as directly observed therapy (DOT). If vomiting occurred within the first 30 minutes the full dose was repeated. Those who vomited a repeat dose were treated with parenteral quinine or AL, but not withdrawn from study follow-up. Those receiving DP were given the remaining 2 doses to take at home. All women were visited at home two days after enrolment to assess for drug safety, adherence and LLIN use, however, a systematic sample of every fifth participant was visited at home in subsequent visits.

Women with symptoms of malaria were not excluded. If they were enrolled in the IPTp-SP group, they were screened and if found to be RDT-positive, treated with AL as per national guidelines. The first course of SP was then given at the next scheduled visit.

All participants were required to make 3 or 4 additional scheduled visits, depending on the gestational age at enrolment, at intervals of four to eight weeks approximately mirroring the FANC schedule in Kenya. At each of these visits, the participants received the study intervention as per the group allocation. Information on bed net use, symptomatology and concomitant drug use was obtained and a physical exam conducted. In addition, blood samples for assessment of anaemia, malaria PCR and microscopy were taken. All women were retested for HIV in the third trimester as per Kenyan guidelines.

Participants who presented to the study clinic for unscheduled visits were examined by study staff and blood was taken for haemoglobin and malaria testing with RDT for point of care (if needed) and malaria microscopy. Participants were assessed for adverse and serious adverse events during scheduled and unscheduled visits. Clinical malaria was treated with AL in the SP arm and DP in the other arms, or with AL if this was within 4 weeks of the last dose of DP.

At delivery, maternal peripheral blood was collected for malaria testing (by RDT, microscopy and PCR) and haemoglobin levels. Blood was collected from the maternal side of the placenta for malaria RDT, microscopy and PCR. An umbilical cord blood sample was collected for malaria RDT and assessment of haemoglobin concentrations. A placental biopsy and placental impression smears were also collected. Newborns were weighed on a digital scale which was calibrated on a daily basis and measured weight to the nearest 10 grams. Study nurses examined newborns for congenital malformation within 24 hours of birth. The Ballard score was used to determine the gestational age at delivery.¹⁹

Participants and their babies were seen between 6-8 weeks post-delivery. Babies were re-assessed for congenital anomalies. Clinical and treatment findings for mother and babies were recorded. A blood sample was taken from the infant for malaria testing using RDT and microscopy.

Outcomes

The primary outcome was malaria infection at delivery defined as the composite of peripheral or placental parasitaemia detected by placental histology, microscopy or RDT (eMethods). The main secondary outcomes were: the incidence of malaria infection and clinical malaria during pregnancy (defined as fever or recent history of fever in the presence of malaria parasites), the prevalence of adverse newborn morbidity at birth defined as the composite of either preterm-delivery (PT, <37 weeks gestation), low birth-weight (LBW, <2500 grams) or small-for-gestational age (SGA, <10th percentile relative to an external growth reference²⁰); anaemia (haemoglobin level <11 g/dL) during pregnancy or at delivery.

Statistical analysis

The modified intention to treat (ITT) analytical population was used for the primary analysis and defined as all eligible women who were randomized, received at least one study intervention, and contributed to the outcome. The adherence to protocol (ATP) analytical population included women who received on at least three separate occasions at least four weeks apart either the scheduled study intervention; an approved alternative treatment for symptomatic malaria according to protocol that replaced the need for the scheduled intervention; or delivered before completion of the three-visit schedule but received the intervention at least once. The ATP population also required that women took all the daily study doses on each occasion, and contributed to the endpoint.

Treatment groups were compared for binary responses with unadjusted log-binomial models and for continuous responses with unadjusted linear regression models. Multivariable log-binomial models were fit for the composite primary outcome and newborn morbidity at birth. The model did not converge for the latter variable and a Poisson regression model was used instead. Count variables were expressed as incidence rate, and compared using Poisson regression with follow-up time calculated from enrolment to delivery or time to loss to follow-up.

Role of the funding source

The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Access and submission of data

VW, JW, JG and MD had complete access to the data. MD and FtK had the responsibility for the decision to submit the manuscript.

Results

Baseline characteristics of study participants at enrolment

Between 21st August 2012 and 19 June 2014, 3314 pregnant women were screened and 1546 randomized (ISTp-DP=515, IPTp-DP=516, IPTp-SP=515, Figure 1). The baseline characteristics were well-balanced across study arms (Table 1). At enrolment, between 58-63% of women were anaemic. The mean (standard deviation [SD]) gestational age was 22.9 (4.8) weeks. About a third of women were infected with malaria parasites. The median (interquartile range [IQR]) number of intervention visits by study arm was 3 [3-4] and similar across study arms ($p=0.29$). The median time between intervention visits was 33 (IQR 29-42) days. In the ISTp-DP arm, 67.6%, 27.2%, 5.2%, and 0% received 0, 1, 2, 3 courses of DP respectively (Table S1). Those who did not contribute to the primary outcome at delivery ($n=178$) did not differ by treatment arm (Figure 1). The prevalence of malaria (by microscopy) at baseline was not different in those lost to follow-up prior to delivery (32/157, 20.4%) compared to those followed successfully (213/1313, 16.2%).

Primary endpoint

Compared to women who received IPTp-SP, the prevalence of malaria infection at the time of delivery was lower in the IPTp-DP arm: 10.2% vs 3.3%; relative risk (RR)=0.32 (95% CI 0.18-0.56); $p<0.0001$, but not in the ISTp-DP arm: 12.6%; RR=1.23 (0.86-1.77); $p=0.26$, Figure 2a. Their effect was not modified by gravidity (p -value for interaction=0.74), and similar results were obtained when adjusted for baseline covariates (Figure 2a), in ATP analyses (Table S2), or when adding PCR to the composite outcome (Table 2).

Secondary endpoints

There was no significant difference between treatment arms in the prevalence of LBW/SGA/PT (ISTp-DP=13.5%, IPTp-DP=11.2%, IPTp-SP=10.0%), overall and within each gravidity strata both with ITT (Figure 2b) and ATP analyses (Table S3). However, the mean birth-weight was lower in the IPTp-DP than IPTp-SP arm (mean difference 87g, 95% CI 24-150, $p=0.006$, Table 2, Table S4).

Women in the IPTp-DP arm, relative to IPTp-SP, had fewer malaria infections (incidence rate (IR) of 54.4 versus 192.0 events per 100 person years), clinical malaria (IR of 6.1 versus 37.9), and all-cause sick clinic visits during pregnancy (IR of 224.8 versus 265.0) (incidence rate ratio [IRR] 0.28 [0.22-0.36], $p<0.0001$, IRR=0.16 [0.08-0.33], $p<0.0001$, and IRR=0.85 [0.73-0.98], $p=0.03$, respectively, Figure 3). Anaemia at time of delivery (27.0% vs 34.4%, RR=0.78 [0.64, 0.96], $p=0.02$), stillbirths (0.9% vs 3.5%, RR=0.25 [0.08-0.74], $p=0.01$) and infant mortality within 6-8 weeks were also lower (0.9% vs 2.9%, RR=0.31 [0.10-0.94], $p=0.04$) (Table 2).

Women in the ISTp-DP arm had more malaria infection during pregnancy than in the IPTp-SP arm (Figure 3). The prevalence of any malaria at delivery (by RDT, microscopy, histology

[including past infections] or PCR in peripheral or placental blood) was higher in the ISTp-DP arm (RR=1.22 [1.04-1.43], p=0.02) (Table 2).

Performance of RDTs in ISTp-arm

Post-hoc analysis of the sensitivity of RDTs in the ISTp arm to detect PCR positive infections in the peripheral blood was 52.5% (95% CI 47.8-57.2%) overall and 64.9% (58.6-71.3%) and 40.4% (33.9-46.8%) in pauci-, and multigravidae, which could be explained by higher geometric mean parasite densities observed in paucigravidae (geometric mean [IQR] 157.9 [24.0-609.0] compared to 32.7 [8.0-97.0] in multigravidae).

Safety and Tolerability

The first dose of DP was well tolerated by the majority of women: nine women had a single episode of vomiting, and only one vomited the repeat dose (Table S5). There were 65 adverse events potentially associated with drug tolerability, with the highest incidence reported in the IPTp-SP arm (Table S5). There were 251 maternal and infant SAEs, and these were least frequent in the IPTp-DP arm (Tables S6a and S6b). There were three maternal deaths (ISTp-DP=1, IPTp-SP=2), all unrelated to the intervention or malaria. The frequency of congenital malformations was 1.2%, 1.4%, and 2.2% in the ISTp-DP, IPTp-DP, and IPTp-SP arms, respectively (p=0.42).

Discussion

This is the first trial assessing the impact of IPTp with DP in pregnancy. Conducted in the context of high SP resistance and high malaria transmission, this trial showed that IPTp-DP was associated with a 68% reduction in the risk of malaria infection at delivery relative to the current IPTp-SP strategy, an 84% reduction in the incidence of clinical malaria during pregnancy and a 22% lower risk of anaemia at delivery. The risk of stillbirths and early infant mortality were also 69 to 75% lower in the IPTp-DP arm, both in pauci-, and multigravid women. IPTp-DP was not associated with improvements in birth-weight relative to IPTp-SP. ISTp-DP, consisting of screening with RDTs and provision of DP to RDT-positive women at scheduled visits, was not superior to the existing IPTp-SP strategy, and was associated with a higher incidence of malaria infection and clinical malaria during pregnancy than IPTp-SP.

The study was conducted in an area with high SP resistance, with near saturation of the quintuple mutant parasites but where the sextuple mutant is prevalent at <6%, currently characteristic of much of east and southern Africa. It is possible that the observed beneficial effect of IPTp-DP may be even greater in areas where the prevalence of the sextuple *dhfr/dhps* mutation is more frequent.²¹ Furthermore, our study provided IPTp as part of the focussed antenatal care package as per current WHO policy and the median number of courses was 3. It is possible that greater effectiveness can be achieved by monthly dosing regimens, as documented in recent trials among

adults from Thailand showing that monthly dosing with DP provided almost complete chemoprophylaxis compared to dosing spaced every two months.²²

Despite the large reductions in the risk of malaria conferred by IPTp-DP, the birth-weight was higher in the IPTp-SP arm. The mean z-score for birth-weight for gestational age was also lower, yet the gestational age at birth was similar suggesting that the higher birth-weight mainly reflected differences in intra-uterine growth. There are several potential explanations for this difference. Firstly, the sample size was not based on birth-weight and it is possible this could reflect a chance finding. It is unlikely that repeated courses of DP impacted negatively on fetal growth despite the lower risk of malaria as there was no dose response relationship between the number of DP courses received and birth-weight for gestational age z-scores ($p=0.92$). However, it is also possible that IPTp-DP may have saved pregnancies with borderline viability that may otherwise have resulted in foetal loss had they been randomized to one of the other two less efficacious arms. Their survival could have resulted in more live births with lower birth-weights in the IPTp-DP arm. It could also be that SP still maintains some beneficial impact on birthweight. Even though the efficacy of SP to clear existing malaria infections or prevent new ones is clearly compromised in this area,⁶ only 5.8% of parasites carry the sextuple *dhfr/dhps* mutation, conferred by the *Pfdhps*-A581G mutation, reflecting the highest level of resistance. SP is thus likely to have provided partial protection against malaria especially now that IPTp-SP is given at least 3 times in the 2nd and 3rd trimester instead of twice with the original regimen^{23, 24}, possibly by suppressing parasite densities in the placenta and thereby reducing placental inflammation. Furthermore, SP is known to have broad antimicrobial activity, which, in addition to antimalarial activity, may have conferred some protection against undetected bacterial infections, particularly gram-positive bacteria,²⁵ and this deserves further study. Because of the even broader anti-bacterial spectrum of activity of azithromycin²⁵ the evaluation of the combined effect of azithromycin and DP to improve birth outcomes may also be warranted in this part of the world with a high dual burden of malaria and sexually transmitted infections and reproductive tract infections in pregnancy.^{26 27}

The lack of superiority of ISTp-DP in this trial is consistent with a recent multi-centre non-inferiority trial among paucigravidae in four countries with very low SP resistance in West Africa, which concluded that ISTp with AL was non-inferior in terms of reductions in low birth-weight to IPTp-SP.¹⁸ Also similar was the observation that paucigravidae in the ISTp arm had a higher incidence of clinical malaria compared to the IPTp-SP arm in West Africa: IRR=1.66, $p<0.001$ compared to IRR=1.50, $p=0.04$ in the current study, and lower mean birth-weights (-28 grams, $p=0.04$ compared to -62grams, $p=0.15$ in the current study). The inferior effect of ISTp on birth-weight was also observed in the first trial of ISTp in Ghana comparing ISTp-AQ+AS against IPTp-SP ($p=0.06$).¹⁷

The lack of superiority of ISTp-DP is likely explained by the high number of infections missed by RDTs, combined with the absence of a prophylactic benefit among women who tested RDT

negative allowing low density infections to persist and new infections to occur before the next scheduled visit. It also suggests that SP still provides some degree of benefit on clearing or suppressing malaria infection and reducing the incidence of clinical malaria, despite the known limited efficacy of SP to clear existing infections and the shortened duration of post-treatment prophylaxis observed in our previous in-vivo follow-up studies in this high resistance area.⁶ The combination RDT used in this trial was the best performing RDT for the diagnosis of *P. falciparum* at low densities evaluated in the WHO product testing of malaria RDTs²⁸ and, combined with these results, suggests that the performance of the current generation of RDTs is not sufficient for the screening of asymptomatic women who typically have low densities infection.

There are some limitations that should be considered. This was an open label study and the participants and field staff were aware of the study allocation. Our observed loss-to-follow-up was 20% and identical to what was taken into account in our sample size calculations. Although there was no differential follow-up between the three treatment arms, and the baseline prevalence of malaria among those who were lost did not differ from those who completed follow-up, we cannot completely rule out some level of bias. Only the first dose of DP was provided under DOT and the remaining two doses were taken at home. Nevertheless, very high (>95%) compliance to the 2nd and 3rd dose was reported among the subsample of women visited by field staff at home on the last day of the course. We did not determine the effect of repeat dosing of DP on cardiac repolarisation, but previous trials in young children did not show evidence that piperaquine associated QT prolongation increases with monthly dosing.²⁹ Pregnancy does not affect the degree of piperaquine-associated QTc prolongation,³⁰ and piperaquine use by the mother is unlikely to result in QTc prolongation in the newborn as amounts of piperaquine ingested by breastfed infants are within established safety limits.³¹

Our data suggest that in an area with high malaria transmission, high SP resistance, and in the context of high LLIN use, ISTp-DP with the current generation of RDTs is not a suitable alternative to an IPTp strategy. By contrast, IPTp-DP resulted in marked reductions in clinical malaria and malaria infection, anaemia, stillbirths and early infant mortality. The long half-life, good tolerability, safety, and once daily dosing are all desirable properties of DP which make IPTp-DP a potential suitable replacement to IPTp-SP in areas where the efficacy of IPTp with SP is threatened. Additional multi-centre studies are now justified to further determine the impact of IPTp-DP on birth outcome, the feasibility and cost-effectiveness of using a 3-day IPTp regimen.

Research in context panel

Evidence before this study

We conducted two separate searches on Pubmed and the Malaria in Pregnancy Library³² for studies that investigated ISTp and IPTp with alternative drugs in HIV-negative women in Africa. We first identified studies reporting on the efficacy of ISTp measured at delivery using the

following search terms: ‘(Malaria AND pregnan* AND intermittent) AND (screen* OR treat* OR clearance) AND (delivery OR malaria OR birth OR LBW or preterm OR premature). Subsequently, we used the following search terms to identify studies reporting on the efficacy of IPTp with alternative drugs: ‘(Malaria AND pregnan* AND intermittent) AND (prevent* OR prophyla* OR presumpt* OR chemoprevent* OR chemoprophyla* OR IPT*) AND (delivery OR malaria OR birth OR LBW or preterm OR premature). For both searches, results were unrestricted by language or publication date.

Through these searches, and by scanning reference lists of articles and trial registers, we identified a total of 2 and 6 publications in peer reviewed journals, respectively. The only two previous ISTp studies were conducted in West Africa in areas of low SP resistance, both showing non-inferiority of ISTp compared with the existing 2-course strategy of IPT with SP at the time.^{17, 18} For previous trials designed to identify alternative drugs for IPTp, 2 trials evaluated mefloquine and both indicated high efficacy but low tolerability.^{12, 33} One trial in Ghana evaluated AQ with and without SP, showing no additional benefit to IPTp-SP and low tolerability of the AQ based regimens.¹⁰ Three studies in west Africa evaluated chloroquine (CQ) for IPTp (one in combination with pyrimethamine) and all observed superiority of the IPTp-SP strategy over IPTp with CQ.³⁴⁻³⁶ One further unpublished multi-centre trial comparing IPTp-SP with IPTp with a fixed dose combination of chloroquine and azithromycin was stopped early because CQ-AZ was not superior to IPTp-SP and associated with more SAEs and treatment emergent adverse events that resulted in treatment discontinuation or were considered treatment-related.^{13, 37} Thus none of the previous IPTp trials have been able to identify an alternative to SP that was effective, safe and well tolerated by asymptomatic pregnant women.

Added value of this study

We present the first trial assessing the impact of IPT with an ACT, namely DP, in pregnancy and the third trial assessing ISTp as alternative to IPTp-SP.

Implications of all the available evidence

We show that IPTp-DP holds promise as an alternative to IPTp-SP where SP resistance is high. We also show that, while IST as a strategy has been shown to be non-inferior in areas of lower SP resistance, it is not a suitable alternative for areas of high malaria transmission and high SP resistance given the limitations of sensitivity of current RDTs.

Supporting information

Electronic Supplement
Study protocol
Consort checklist
Statistical Analysis Plan

Contributors

MD, JG and FtK conceived the concept of the study and wrote the protocol. MD and FtK acquired the funding. MD and AK were the co-principal investigators, supported by JG and AL. AL conducted the fieldwork under supervision of PO, AK, KL and MD. EJ acted as government liaison with the Ministry of Health in Kenya. JG and AL maintained the safety database and supported safety reporting to the respective oversight committees, ethical boards, and the centralized safety registry of the Malaria in Pregnancy Consortium. KO and SK were responsible for the PCR and placental histology conducted at KEMRI-CDC laboratories in Kisumu, Kenya. VW, JG, AL and MD supported the data management. JW was the study statistician, conducted the primary data analysis and together with MD, JG and FtK, interpreted the data. JG, JW, MD and FtK co-wrote the statistical analysis plan. MD and FtK wrote the first draft of this manuscript. All authors reviewed, revised and approved the final version of the manuscript.

Declaration of interests

There are no conflicts of interest to declare. The study drug dihydroartemisinin-piperaquine (Eurartesim) was provided free of charge by the manufacturer Sigma Tau, Rome, Italy.

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Figure 1: Trial Profile (ITT)

*Women reporting to ANC prior to 16wks gestation were “booked” into the trial, but randomization and intervention was withheld until their next visit ≥ 16 wks gestation.

Table 1: Baseline Characteristics

Characteristic	ISTp-DP	IPTp-DP	IPTp-SP
Number of participants (N)*	515	514	514
Site (N)			
Bondo	153 (29.7)	153 (29.8)	154 (30.0)
Lwak	126 (24.5)	125 (24.3)	125 (24.3)
Madiany	160 (31.1)	159 (30.9)	159 (30.9)
Siaya	76 (14.8)	77 (15.0)	76 (14.8)
Age in years; mean (SD)	23.4 (5.9)	23.4 (5.5)	23.5 (6.0)
Gravidity; n (%)			
Primigravid/Secundigravid (G1/G2)	267 (51.8)	263 (51.2)	292 (56.8)
Multigravid (G3+)	248 (48.2)	251 (48.8)	222 (43.2)
Gestational age in weeks [#] ; mean (SD)	22.9 (4.7)	23.0 (4.0)	22.8 (4.4)
Weight in kg; mean (SD)	61.1 (8.3)	61.8 (9.3)	61.5 (9.1)
Height in cm (mean, SD)	164.1 (6.8)	164.3 (6.7)	164.3 (6.9)
Educational status rank; n (%)			
Low	121 (23.5)	119 (23.4)	118 (23.1)
Medium	231 (44.9)	222 (43.6)	224 (43.8)
High	162 (31.5)	168 (33.0)	169 (33.1)
SES Index; n (%)			
Low	181 (35.2)	162 (31.7)	173 (33.9)
Medium	174 (33.9)	170 (33.3)	167 (32.7)
High	159 (30.9)	179 (35.0)	171 (33.5)
Slept under LLIN previous night	292 (56.7)	292 (56.8)	294 (57.2)
Haemoglobin in g/dl; mean (SD)	10.5 (1.6)	10.6 (1.5)	10.5 (1.5)
Anaemia (Hb<11g/dl); n, %	325 (63.1)	302 (58.8)	307 (59.7)
Malaria infection (by PCR); n/N; %	178/513 (34.7)	157/509 (30.8)	168/510 (32.9)
Symptomatic malaria infection (by microscopy); n (%)	14 (3.0)	8 (1.7)	4 (0.8)
Syphilis infection; n (%)	7/515 (1.4%)	3/514 (0.6%)	7/514 (1.4%)

ITT cohort; [#] GA determined by history of last menstrual period and physical examination * 3 women excluded due to withdrawal of consent before baseline intervention was given (n=1), loss of study data file (n=1), and enrolment violation (n=1)

Figure 2a: Malaria at time of delivery (composite excluding PCR)

Figure 2b: Newborn morbidity outcome (composite LBW/SGA/PTB) by treatment group

ITT population; malaria infection at delivery defined as the composite of peripheral or placental parasitaemia detected by placental histology, microscopy or RDT; Adjusted for site, gravidity (in all gravidities model), malaria at enrolment by PCR, rain/seasonality six months prior to delivery, maternal height (malaria infection model only), LLIN use during pregnancy, Hb at enrolment, gestational age at enrolment, and educational status of mother.

Figure 3: Incidence of malaria infection, clinical malaria, and all-cause sick clinic visits during pregnancy by treatment group

*Malaria infection defined by microscopy or PCR; SCV Sick clinic visits.

ITT population. Incidence data represent the number of women with an event, the number of events/ the person time follow-up (the incidence rate per 100 person years).