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Supplementary appendix

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Supplement to: Desai M, Gutman J, L'lanziva A, et al. Intermittent screening and treatment or intermittent preventive treatment with dihydroartemisinin–piperaquine versus intermittent preventive treatment with sulfadoxine–pyrimethamine for the control of malaria during pregnancy in western Kenya: an open-label, three-group, randomised controlled superiority trial. *Lancet* 2015; published online Sept 29. http://dx.doi.org/10.1016/S0140-6736(15)00310-4.

Supplemental Content

Desai M, Gutman J, L'lanziva A, et al: 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

Contents

eMethods

Interim analysis

One interim analysis was planned and conducted to examine the efficacy of ISTp-DP versus IPTp-SP, with the plan to stop the ISTp-DP arm only (not the whole trial) if ISTp-DP is significantly less efficacious than IPTp-SP. This was conducted after 777 completed deliveries (half of the proposed total sample size). As per protocol, the main outcome was the presence or absence of malaria infection at the time of delivery (the composite of peripheral and placental parasitemia), detected by placental histology, positive peripheral blood smear at the time of delivery, or positive RDT at the time of delivery. A two-sided Pearson's chi-square exact test at alpha = 0.000824 (O'Brien-Fleming spending function) was used to compare the ISTp-DP arm versus the IPTp-SP arm. The interim analysis resulted in a p-value of 0.77 that is not close to the O'Brien-Fleming spending function of alpha = 0.000824. Thus, the ISTp-DP arm was not stopped. The final analyses were tested at a significance level of 0.025 - 0.000824 = 0.024176 to decide whether or not we rejected the respective null hypotheses for the comparison between ISTp-DP and IPTp-SP using a 2-sided p-value.

Endpoint definitions

Malaria infection endpoints

While the primary malaria infection endpoint excluded PCR and past infections by histology, secondary malaria infection endpoints included consideration of PCR and past infections, the latter defined as malaria pigment in the absence of parasites on histology.

Morbidity endpoints

Birthweight data

The aim of the study was to measure birthweight within 24 hours after birth. Birth weights taken 24-48h hours (n= 39, 2.6%), and 48-168 hours after delivery (n= 5, 0.3%) were corrected for the physiological fall in birth weight in breastfed infants occurring in the first days following delivery[1, 2] by a factor +2% and +4%, respectively to obtain the estimated weight at birth.[3, 4] All analyses used corrected birthweight unless indicated otherwise. Low birth weight was defined as <2,500 grams.

Gestational age and preterm

If more than one gestational age measurement was available we used estimates in the following order of preference: neonatal clinical exam within 96 hours of delivery (Ballard score), last menstrual period (if known), and fundal height at enrolment. Preterm was defined as a gestational age of less than 37 completed weeks.

Small for gestational age (SGA)

SGA was defined as birthweight below the tenth percentile for a given gestational age and sex, using a reference population from Tanzania population was used, as ultrasound-based fetal growth charts were not available for Kenyan populations. This also allowed the calculation of Z-scores.[5]

Laboratory methods

HIV serology was performed by the study health facilities as part of routine ANC profiling. Syphilis serology was assessed according to Kenya Ministry of Health guidelines. Hemoglobin levels were determined using portable HemoCue Hb 201+ (HemoCue AB, Ängelholm Sweden) machines following manufacture instructions. Malaria rapid diagnostic test (RDT) was performed as per the manufacturer's instruction. *Plasmodium falciparum* parasites identification and quantification by microscopy on Giemsa-stained thick and thin peripheral blood smears were performed according to standard, quality-controlled procedures. In brief, the blood smears were stained with 10% Giemsa for 15 minutes and examined under oil immersion for malaria parasites.[6, 7] A thick smear was considered negative if 100 microscopic high powered fields showed no parasites. If thick smear was positive, malaria parasites and white blood cells (WBC) were counted in the same fields until a corresponding 500 WBCs were counted. Parasite densities per microliter of blood in the thick blood smears were estimated using an assumed count of 8,000 WBC per microliter of blood.[6, 7] If the blood smear was positive for thin/impression smear, parasitized red blood cell (pRBC) and red blood cells (RBCs) were counted in the same field until a corresponding 2000 RBCs were counted and expressed as parasites per microlitre of blood using an assumed count of 4,500,000 RBCs per microliter of blood.[6-8] All the blood films were read by microscopists deemed competent through an external quality assurance programme provided by the national institute of communicable diseases (NICD), South Africa.[9]
Real-time quantitative polymerase chain reaction (RT-qPCR) using *P. falciparum*-specific primers and probes targeting *P. falciparum* 18S rRNA gene was performed on maternal peripheral and placental samples, with the inclusion in all reactions of a positive standard and a negative control with no template DNA. All the PCR assays were done from dried blood spot (DBS) on a filter paper following standard operating procedures[10, 11]. The lower detection limit of PCR was 5 parasites/uL of blood. Tissue samples collected from the maternal side of the placenta and fixed with 10% neutral buffered formalin were processed, stained, and examined following standard procedures.[12] Giemsa-stained placental impression smears were read following a standardized protocol.[13] Women were screened for syphilis as part of routine ANC care, using either RPR, VDRL or a Determine rapid diagnostic test kit (on site). Those determined to be positive for syphilis were treated per national guidelines with Benzathine Penicillin.

Analysis

Pre-specified endpoints

The pre-specified endpoints included the primary endpoint of malaria infection at delivery (composite or peripheral and placental parasitaemia), and several secondary endpoints: low birthweight, small for gestational age, preterm births, maternal haemoglobin and anaemia,

106 congenital malaria, incidence of malaria infection and all-cause sick visits by the mother and
107 infant, and serious adverse events in both the mothers and infants.
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eResults

Table S1: Follow-up visits schedule (ITT)

Characteristic	ISTp-DP	IPTp-DP	IPTp-SP
Achieved number of scheduled intervention visits (including enrolment, excluding delivery); n (%)			
1	39	32	31
2	61	82	62
3	172	175	172
4	158	149	160
5	76	63	71
6	8	12	18
7	1	1	0
Total visits	1738	1705	1774
Number of DP or SP courses received; n (%)			
0	348 (67.6)	0 (0)	1 (0.2)
1	140 (27.2)	37 (7.2)	46 (9.0)
2	27 (5.2)	230 (44.8)	210 (40.9)
3	0	134 (26.1)	127 (24.7)
4	0	76 (14.8)	95 (18.5)
5	0	34 (6.6)	30 (5.8)
6	0	3 (0.6)	5 (1.0)

Total courses received (multigravidae) Median (range) Mean (SD)	73 0 (0, 2) 0.29 (0.54)	685 2 (1, 6) 2.73 (1.03)	603 2 (0, 6) 2.72 (1.15)
Number of women requiring AL for symptomatic malaria within 4 weeks of study dosing	10	5	20
Person weeks contributed till delivery or till lost to follow-up, median (IQR)	16.3 (12.7, 19.6)	16.0 (12.4, 19.4)	16.7 (12.7, 20.1)

Table S2: Malaria at time of delivery (composite excluding PCR) by treatment group (adherence to protocol population)

ISTp-DP **n/N (%)**	IPTp-DP **n/N (%)**	IPTp-SP **n/N (%)**		**PR/Difference (95%CI), p-value** ISTp-DP vs IPTp-SP	**PR/Difference (95%CI), p-value** IPTp-DP vs IPTp-SP	**PR/Difference (95%CI), p-value** IPTp-DP vs ISTp-DP
All Gravidae						
50/411 (12.2)	11/409 (2.7)	47/418 (11.2)	Unadjusted	1.08 (0.74, 1.57) p=0.68	0.24 (0.13, 0.46) **p<0.0001**	0.22 (0.12, 0.42) **p<0.0001**
			Adjusted [a]	1.05 (0.70, 1.58) p=0.80	0.24 (0.12, 0.48) **p<0.0001**	0.23 (0.11, 0.45) **p<0.0001**
Paucigravidae (G1+2)						
32/206 (15.5)	8/211 (3.8)	34/235 (14.5)	Unadjusted	1.07 (0.69, 1.68) p=0.75	0.26 (0.12, 0.55) **p=0.0004**	0.24 (0.12, 0.52) **p=0.0002**
			Adjusted [a]	1.04 (0.64, 1.71) p=0.86	0.27 (0.12, 0.62) **p=0.0019**	0.26 (0.12, 0.60) **p=0.0015**
Multigravidae (G3+)						
18/205 (8.8)	3/198 (1.5)	13/183 (7.1)	Unadjusted	1.24 (0.62, 2.45) p=0.54	0.21 (0.06, 0.74) **p=0.0145**	0.17 (0.05, 0.58) **p=0.0043**
			Adjusted [a]	1.14 (0.55, 2.37) p=0.72	0.21 (0.06, 0.72) **p=0.0138**	0.18 (0.05, 0.62) **p=0.0063**

ATP cohort; [a] adjusted for site, gravidity (in pooled model), malaria at enrolment by PCR, rain/seasonality six months prior to delivery, ITN use, hb at enrolment, gestational age at enrolment, and educational status

Table S3: Newborn outcome (composite LBW/SGA/PTB) by treatment group (adherence to protocol population)

ISTp-DP **n/N (%)**	IPTp-DP **n/N (%)**	IPTp-SP **n/N (%)**		**PR/Difference (95%CI), p-value** ISTp-DP vs IPTp-SP	**PR/Difference (95%CI), p-value** IPTp-DP vs IPTp-SP	**PR/Difference (95%CI), p-value** IPTp-DP vs ISTp-DP
All Gravidae						
52/412 (12.6)	42/402 (10.5)	40/413 (9.7)	Unadjusted	1.30 (0.88, 1.92) p=0.18	1.08 (0.72, 1.63) p=0.72	0.83 (0.56, 1.21) p=0.33
			Adjusted [a]	1.33 (0.86, 2.04) p=0.20	0.88 (0.55, 1.42) p=0.60	0.66 (0.42, 1.05) p=0.08
Paucigravidae (G1+2)						
31/207 (15.0)	30/210 (14.3)	25/232 (10.8)	Unadjusted	1.39 (0.85, 2.27) p=0.19	1.33 (0.81, 2.18) p=0.27	0.95 (0.60, 1.52) p=0.84
			Adjusted [a]	1.40 (0.81, 2.43) p=0.24	1.02 (0.57, 1.82) p=0.96	0.73 (0.41, 1.28) p=0.27
Multigravidae (G3+)						
21/205 (10.2)	12/192 (6.3)	15/181 (8.3)	Unadjusted	1.24 (0.66, 2.32) p=0.51	0.75 (0.36, 1.57) p=0.45	0.61 (0.31, 1.21) p=0.16
			Adjusted [a]	1.11 (0.55, 2.24) p=0.76	0.60 (0.26, 1.38) p=0.23	0.54 (0.24, 1.19) p=0.13

ATP cohort; [a] adjusted for site, gravidity, malaria at enrolment by PCR, rain/seasonality six months prior to delivery, ITN use, hb at enrolment, gestational age at enrolment, and educational status

Table S4a: Malaria related perinatal outcomes by treatment group (Paucigravidae)

	ISTp-DP n/N (%)or N, mean (SD)	**IPTp-DP** n/N (%)or N, mean (SD)	**IPTp-SP** n/N (%)or N, mean (SD)	Crude PR/Difference (95%CI), p-value **ISTp-DP vs IPTp-SP**	Crude PR/Difference (95%CI), p-value **IPTp-DP vs IPTp-SP**	Crude PR/Difference (95%CI), p-value **IPTp-DP vs ISTp-DP**
Maternal Hb 3rd trimester	184, 10.9 (1.5)	181, 11.2 (1.4)	213, 11.1 (1.6)	-0.16 (-0.46, 0.14) p=0.29	0.05 (-0.25, 0.35) p=0.74	0.21 (-0.10, 0.52) p=0.18
Maternal anemia (Hb<11g/dl) 3rd trimester	89/184 (48.4)	80/181 (44.2)	100/213 (47.0)	1.03 (0.84, 1.27) p=0.78	0.94 (0.76, 1.17) p=0.59	0.91 (0.73, 1.14) p=0.43
Maternal moderate anemia (Hb<9g/dl) 3rd trimester	16/184 (8.7)	7/181 (3.9)	22/213 (10.3)	0.84 (0.46, 1.55) p=0.58	0.37 (0.16, 0.86) **p=0.0199**	0.44 (0.19, 1.06) p=0.07
Maternal Hb, at delivery; mean (SD)	211, 11.6 (1.6)	212, 11.9 (1.5)	244, 11.7 (1.9)	-0.06 (-0.36, 0.25) p=0.72	0.21 (-0.10, 0.51) p=0.19	0.26 (-0.06, 0.58) p=0.11
Maternal anemia (Hb<11g/dl) at delivery	70/211 (33.2)	54/212 (25.5)	83/244 (34.0)	0.98 (0.75, 1.26) p=0.85	0.75 (0.56, 1.00) p=0.05	0.77 (0.57, 1.04) p=0.08
Maternal moderate anemia (Hb<9g/dl) at delivery	11/211 (5.2)	5/212 (2.4)	11/244 (4.5)	1.16 (0.51, 2.61) p=0.73	0.52 (0.18, 1.48) p=0.22	0.45 (0.16, 1.28) p=0.13
Malaria infection (3rd trimester)	32/236 (13.6)	20/240 (8.3)	60/268 (22.4)	0.61 (0.41, 0.90) **p=0.0121**	0.37 (0.23, 0.60) **p<0.0001**	0.61 (0.36, 1.04) p=0.07
Peripheral or placental malaria at delivery (any measure including PCR, excluding past infections)	40/225 (17.8)	16/224 (7.1)	51/258 (19.8)	0.90 (0.62, 1.31) p=0.58	0.36 (0.21, 0.62) **p=0.0002**	0.40 (0.23, 0.70) **p=0.0011**
Maternal peripheral malaria infection (at delivery, any measure)	34/225 (15.1)	10/224 (4.5)	37/258 (14.3)	1.05 (0.69, 1.62) p=0.81	0.31 (0.16, 0.61) **p=0.0007**	0.30 (0.15, 0.58) **p=0.0004**
Placental malaria (any measure including PCR and past infections on histology)	119/207 (57.5)	92/209 (44.0)	121/242 (50.0)	1.15 (0.97, 1.37) p=0.11	0.88 (0.72, 1.07) p=0.21	0.77 (0.63, 0.93) **p=0.0066**
Peripheral or placental malaria at delivery (any measure including PCR and past infections on histology)	124/225 (55.1)	93/224 (41.5)	123/258 (47.7)	1.16 (0.97, 1.38) p=0.10	0.87 (0.71, 1.07) p=0.18	0.75 (0.62, 0.92) **p=0.0044**
Fetal cord Hb (mean, SD)	200, 14.3 (2.4)	204, 14.5 (2.4)	231, 14.6 (2.9)	-0.37 (-0.86, 0.11) p=0.13	-0.18 (-0.67, 0.30) p=0.46	0.19 (-0.31, 0.69) p=0.45
Fetal anemia (Hb<12.5g/dl cord blood)	35/200 (17.5)	42/204 (20.6)	42/231 (18.1)	0.96 (0.64, 1.44) p=0.85	1.13 (0.77, 1.66) p=0.53	1.18 (0.79, 1.76) p=0.43
Birthweight (mean, SD)	3138.1 (444.7)	3110.7 (450.2)	3201.0 (456.1)	-62.9 (-147.4, 21.7) p=0.15	-90.2 (-174.7, -5.8) **p=0.0362**	-27.4 (-114.5, 59.8) p=0.54
Corrected birthweight (mean, SD)	3139.7 (444.7)	3115.1 (448.5)	3201.8 (455.0)	-62.2 (-146.0, 21.6)	-86.7 (-170.5, -2.9) **p=0.0425**	-24.5 (-110.5, 61.5) p=0.58

				p=0.15		
Gestational age at birth (weeks)	225 38.8 (1.8)	223, 38.8 (2.3)	255, 39.0 (1.9)	-0.21 (-0.57, 0.15) p=0.25	-0.18 (-0.54, 0.18) p=0.32	0.03 (-0.34, 0.40) p=0.88
Birthweight for gestational age (Z-score)	212, 0.27 (1.01)	211, 0.18 (0.95)	240, 0.37 (1.02)	-0.09 (-0.28, 0.09) p=0.31	-0.19 (-0.37, -0.002) **p=0.0478**	-0.09 (-0.28, 0.10) p=0.35
Small-for-gestational age (SGA)	21/212 (9.9)	17/211 (8.1)	18/240 (7.5)	1.32 (0.72, 2.41) p=0.36	1.07 (0.57, 2.03) p=0.83	0.81 (0.44, 1.50) p=0.51
Low Birthweight (LBW)	11/209 (5.3)	16/209 (7.7)	13/233 (5.6)	0.94 (0.43, 2.06) p=0.88	1.37 (0.68, 2.78) p=0.38	1.45 (0.69, 3.06) p=0.32
Preterm birth (PTB)	16/225 (7.1)	15/223 (6.7)	10/255 (3.9)	1.81 (0.84, 3.91) p=0.13	1.72 (0.79, 3.74) p=0.18	0.95 (0.48, 1.87) p=0.87
Still birth	3/225 (1.3)	1/224 (0.5)	10/255 (3.9)	0.34 (0.09, 1.22) p=0.10	0.11 (0.01, 0.88) **p=0.0375**	0.33 (0.04, 3.19) p=0.34
Fetal loss	4/225 (1.8)	3/224 (1.3)	11/255 (4.3)	0.41 (0.13, 1.28) p=0.12	0.31 (0.09, 1.10) p=0.07	0.75 (0.17, 3.33) p=0.71
Any adverse birth outcome	35/225 (15.6)	31/224 (13.8)	35/256 (13.7)	1.14 (0.74, 1.75) p=0.56	1.01 (0.65, 1.59) p=0.96	0.89 (0.57, 1.39) p=0.61
Congenital malaria infection	4/267 (1.50)	2/261 (0.77)	0/290 (0.0)	Not applicable	Not applicable	Not applicable
Infant clinical malaria by 6-8wks (cumulative)	1/174 (0.6)	4/176 (2.3)	4/198 (2.0)	0.29 (0.03, 2.60) p=0.27	1.12 (0.28, 4.47) p=0.88	3.85 (0.43, 34.5) p=0.23
Neonatal death	4/225 (1.8)	4/224 (1.8)	8/255 (3.1)	0.57 (0.17, 1.86) p=0.35	0.57 (0.17, 1.86) p=0.35	1.00 (0.25, 3.97) p=0.99
Perinatal death	7/225 (3.1)	5/224 (2.2)	17/255 (6.7)	0.47 (0.20, 1.10) p=0.08	0.33 (0.13, 0.89) **p=0.0288**	0.72 (0.23, 2.23) p=0.57
Infant deaths by 6-8wks (end of follow up)	4/225 (1.8)	4/224 (1.8)	8/255 (3.1)	0.57 (0.17, 1.86) p=0.35	0.57 (0.17, 1.86) p=0.35	1.00 (0.25, 3.97) p=0.99
ITT cohort; [a] spontaneous abortion or stillbirth; [b] SGA/LBW/PTB or fetal loss						

Table S4b: Malaria related perinatal outcomes by treatment group (Multigravidae G3+)

	ISTp-DP **n/N (%)or N, mean (SD)**	IPTp-DP **n/N (%)or N, mean (SD)**	IPTp-SP **n/N (%)or N, mean (SD)**	**Crude PR/Difference (95%CI), p-value** ISTp-DP vs IPTp-SP	**Crude PR/Difference (95%CI), p-value** IPTp-DP vs IPTp-SP	**Crude PR/Difference (95%CI), p-value** IPTp-DP vs ISTp-DP
Maternal Hb (mean, SD), 3rd trimester	200, 11.0 (1.3)	189, 10.8 (1.4)	162, 11.0 (1.4)	0.05 (-0.24, 0.33) p=0.75	-0.13 (-0.42, 0.15) p=0.36	-0.18 (-0.45, 0.09) p=0.19
Maternal anemia (Hb<11g/dl) 3rd trimester	87/200 (43.5)	106/189 (56.1)	76/162 (46.9)	0.93 (0.74, 1.16) p=0.52	1.20 (0.97, 1.47) p=0.09	1.29 (1.05, 1.58) **p=0.0138**
Maternal moderate anemia (Hb<9g/dl) 3rd trimester	14/200 (7.0)	14/189 (7.4)	9/162 (5.6)	1.26 (0.56, 2.84) p=0.58	1.33 (0.59, 3.00) p=0.49	1.06 (0.52, 2.16) p=0.88
Maternal Hb, at delivery; N, mean (SD)	210, 11.5 (1.5)	214, 11.5 (1.6)	183, 11.4 (1.4)	0.12 (-0.18, 0.42) p=0.44	0.11 (-0.19, 0.41) p=0.48	-0.01 (-0.30, 0.28) p=0.93
Maternal anemia (Hb<11g/dl) at delivery	72/210 (34.3)	61/214 (28.5)	64/183 (35.0)	0.98 (0.75, 1.29) p=0.89	0.82 (0.61, 1.09) p=0.17	0.83 (0.63, 1.10) p=0.20
Maternal moderate anemia (Hb<9g/dl) at delivery	9/210 (4.3)	14/214 (6.5)	9/183 (4.9)	0.87 (0.35, 2.15) p=0.77	1.33 (0.59, 3.00) p=0.49	1.53 (0.68, 3.45) p=0.31
Malaria infection (3rd trimester)	43/237 (18.1)	14/238 (5.9)	30/202 (14.9)	1.22 (0.80, 1.87) p=0.36	0.40 (0.22, 0.73) **p=0.0027**	0.32 (0.18, 0.58) **p=0.0001**
Peripheral or placental malaria at delivery (any measure including PCR, excluding past infections)	39/227 (17.2)	10/233 (4.3)	22/201 (11.0)	1.57 (0.96, 2.55) p=0.07	0.39 (0.19, 0.81) **p=0.0112**	0.25 (0.13, 0.49) **p<0.0001**
Maternal peripheral malaria infection (at delivery, any measure)	31/227 (13.7)	6/233 (2.6)	17/201 (8.5)	1.61 (0.92, 2.83) p=0.09	0.30 (0.12, 0.76) **p=0.0105**	0.19 (0.08, 0.44) **p=0.0001**
Placental malaria (any measure including PCR and past infections on histology)	71/207 (34.3)	47/212 (22.2)	38/184 (20.7)	1.66 (1.18, 2.33) **p=0.0035**	1.07 (0.73, 1.57) p=0.71	0.65 (0.47, 0.89) **p=0.0066**
Peripheral or placental malaria at delivery (any measure including PCR and past infections on histology)	75/227 (33.0)	47/233 (20.2)	43/201 (21.4)	1.54 (1.12, 2.13) **p=0.0084**	0.94 (0.65, 1.36) p=0.75	0.61 (0.45, 0.84) **p=0.0022**
Fetal cord Hb (mean, SD)	200, 14.0 (2.4)	197, 14.1 (2.2)	172, 14.1 (2.2)	-0.15 (-0.61, 0.31) p=0.53	-0.02 (-0.49, 0.44) p=0.92	0.13 (-0.32, 0.57) p=0.58
Fetal anemia (Hb<12.5g/dl cord blood)	45/200 (22.5)	39/197 (19.8)	34/172 (19.8)	1.14 (0.77, 1.69) p=0.52	1.0 (0.66, 1.51) p=0.99	0.88 (0.60, 1.29) p=0.51
Birthweight (mean, SD)	3320.5 (502.5)	3255.0 (395.0)	3365.0 (447.1)	-44.5 (-136.4, 47.4) p=0.34	-110.0 (-201.7, -18.3) **p=0.0188**	-65.5 (-153.5, 22.5) p=0.14
Corrected birthweight (mean, SD)	3330.6 (503.9)	3262.6 (404.4)	3372.9 (457.0)	-42.4 (-134.3, 49.5) p=0.37	-110.3 (-202.1, -18.5) **p=0.0185**	-67.9 (-156.2, 20.4) p=0.13

Gestational age at birth (weeks)	226, 39.3 (1.7)	225, 39.2 (2.0)	196, 39.3 (1.7)	0.003 (-0.34, 0.35) p=0.99	-0.09 (-0.43, 0.26) p=0.63	-0.09 (-0.42, 0.24) p=0.60
Birthweight for gestational age (Z-score)	204, 0.59 (1.14)	206, 0.40 (0.97)	182, 0.69 (1.11)	-0.10 (-0.31, 0.12) p=0.37	-0.29 (-0.50, -0.07) **p=0.0084**	-0.19 (-0.40, 0.02) p=0.07
Small-for-gestational age (SGA)	15/204 (7.4)	10/206 (4.9)	7/182 (3.9)	1.91 (0.80, 4.58) p=0.15	1.26 (0.49, 3.25) p=0.63	0.66 (0.30, 1.44) p=0.29
Low Birthweight (LBW)	8/204 (3.9)	5/176 (2.8)	6/205 (2.9)	1.38 (0.46, 4.14) p=0.56	1.03 (0.32, 3.32) p=0.96	0.75 (0.26, 2.11) p=0.58
Preterm birth (PTB)	13/226 (5.8)	8/225 (3.6)	11/196 (5.6)	1.02 (0.47, 2.24) p=0.95	0.63 (0.26, 1.54) p=0.32	0.62 (0.26, 1.46) p=0.27
Still birth	7/229 (3.1)	3/228 (1.3)	6/198 (3.0)	1.01 (0.34, 2.95) p=0.99	0.43 (0.11, 1.71) p=0.23	0.43 (0.11, 1.64) p=0.22
Fetal loss	7/229 (3.1)	4/228 (1.8)	6/198 (3.0)	1.01 (0.34, 2.95) p=0.99	0.58 (0.17, 2.02) p=0.39	0.57 (0.17, 1.93) p=0.37
Any adverse birth outcome	29/229 (12.7)	17/228 (7.5)	19/198 (9.6)	1.32 (0.76, 2.28) p=0.32	0.78 (0.42, 1.45) p=0.43	0.59 (0.33, 1.04) p=0.07
Congenital malaria infection	1/247 (0.4)	0/243 (0.0)	0/218 (0.0)	Not applicable	Not applicable	Not applicable
Infant clinical malaria by 6-8wks (cumulative)	8/194 (4.1)	7/190 (3.7)	1/162 (0.6)	6.53 (0.82, 52.2) p=0.08	5.74 (0.71, 46.7) p=0.10	0.88 (0.32, 2.42) p=0.80
Neonatal death	2/229 (0.9)	0/228 (0.0)	4/198 (2.0)	0.43 (0.08, 2.34) p=0.33	Not applicable	Not applicable
Perinatal death	9/229 (3.9)	3/228 (1.3)	10/198 (5.1)	0.78 (0.32, 1.88) p=0.58	0.26 (0.07, 0.93) **p=0.0388**	0.33 (0.09, 1.22) p=0.1
Infant deaths by 6-8wks (end of follow up)	2/229 (0.9)	0/228 (0.0)	5/198 (2.5)	0.35 (0.07, 1.76) p=0.20	Not applicable	Not applicable
ITT cohort; [a] spontaneous abortion or stillbirth; [b] SGA/LBW/PTB or fetal loss						

Table S5: Adverse events

	ISTp-DP		IPTp-DP		IPTp-SP	
Within 30 minutes following drug administration						
Vomiting initial dose (each course)	2/ 245 (0.8%)		4/ 1725 (0.2%)		3/ 1787 (0.2%)	
Vomiting repeat dose	0/ 2 (0%)		3/ 4 (75%)		0/ 3 (0%)	
Tolerability 1-7 days following drug administration[a]						
	Events[b]	IR (95% CI)[c]	Events[b]	IR (95% CI)[c]	Events[b]	IR (95% CI)[c]
Total number of women who received medication at least once (N)	187		487		487	
Any reported drug tolerability event	2	45.4 (11.4-181.4)	27	83.8 (57.4-122.1)	36	108.2 (78.1-150.0)
Fever	2	45.4 (11.35-181.4)	2	6.2 (1.6-24.8)	8	24.1 (12.0-48.1)
Weakness	0	0	3	9.3 (3.0-28.9)	10	30.1 (16.2-55.9)
Headache	2	22.7 (3.2-161.1)	8	18.6 (8.4-41.4)	14	24.1 (12.0-48.1)
Abdominal pain	1	22.7 (3.2-161.1)	18	55.8 (35.2-88.6)	17	51.1 (31.8-82.2)
Muscle pain	1	22.7 (3.2-161.1)	6	18.6 (8.4-41.4)	8	24.1 (12.0-48.1)
Nausea	0	0	4	12.4 (4.7-33.1)	3	9.0 (2.9-28.0)
Rash	0	0	0	0	1	3.0 (0.4-21.3)
Diarrhea	0	0	1	3.1 (0.4-22.0)	1	3.0 (0.4-21.3)
Vomiting	0	0	4	12.4 (4.7-33.1)	3	9.0 (2.9-28.0)

[a] includes symptoms which were asked to all women presenting for unscheduled visits

[b] no woman had more than one event within seven days of drug administration, thus number of women is the same as the number of events

[c] incidence rate per 100 person years

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 (95% CI) 158 (88-283) compared to 33 (13-80) in multigravidae.

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