SDC1. Conditional power and error analyses

Rationale and methods

Because of a small rate of events, the DSMB advised the use of exact instead of asymptotic non-inferiority tests for estimating the primary endpoint. According to such tests, 180 patients per treatment group should have been enrolled (StatXact9®, Cytel Studio 9). To address the discrepancy in sample size that was underestimated by asymptotic calculations in the first place (the trial was initially designed to enrol 123 patients per group), conditional power and error analyses were carried out. The conditional power and error are the probabilities of rejecting the null hypothesis if the trial was prolonged up to enrolment of 180 patients per group given current results, under the alternative and null hypotheses, respectively. A small conditional power is in favour of stopping the trial for futility, whereas a large conditional error may be regarded as sufficient for early rejection of the null hypothesis [1]. Conditional power and error were computed for an unconditional non-inferiority test based on an exact likelihood ratio test statistics [2], with R® software (R foundation for statistical computing).

Results and discussion

In the "cotrimoxazole mandatory" sub trial, the primary endpoint was collected in 116 and 117 women in each group. Conditional error and power were 61.7% and 99.4%, respectively. The large conditional error showed it would have been useless to continue the trial up to 180 patients per arm (indeed, results were already significant).

In the "cotrimoxazole not mandatory" sub trial of less immunocompromised women, the sample size achieved was only 55 and 53 women with placental blood smear collected, and results were not significant. The conditional error and power were 13.4% and 94.5%, respectively. The large conditional power indicated that the probability to conclude would have been high in case of trial continuation. However, this was unrealistic regarding the amount of time needed: the enrolment period should have been tripled to achieve a sample size of 180 women per group.

References

1. Halperin M, Lan KK, Ware JH, Johnson NJ, DeMets DL. An aid to data monitoring in long-term clinical trials. Control Clin Trials **1982**; 3:311-323.

2. Skipka G, Munk A, Freitag G. Unconditional exact tests for the difference of binomial probabilities – contrasted and compared. Comput Stat Data Anal **2004**; 47:757-773.

Table SDC2. Baseline characteristics of randomized population (N=432)

	CTX not mandatory trial		CTX mandatory trial	
	CTX N=72	MQ N=68	CTX N=146	CTX + MQ N=146
	n/N (%) or *mean (SD)* [a]	n/N (%) or *mean (SD)* [a]	n/N (%) or *mean (SD)* [a]	n/N (%) or *mean (SD)* [a]
Sociodemographic characteristics				
Study site				
Centre National Hospitalier Universitaire	18 (25.0)	18 (26.5)	50 (34.2)	50 (34.2)
Hôpital d'Instruction des Armées	13 (18.1)	14 (20.6)	25 (17.1)	24 (16.4)
Clinique Louis Pasteur, Porto-Novo	5 (6.9)	3 (4.4)	11 (7.5)	10 (6.9)
Hôpital de zone de Suru Lere	28 (38.9)	26 (38.2)	46 (31.5)	46 (31.5)
Hôpital de la mère et de l'enfant Lagune	8 (11.1)	7 (10.3)	14 (9.6)	16 (11.0)
Age (years) (N=431)	28.7 (5.3)	28.2 (4.9)	29.5 (4.4)	29.7 (4.5)
Urban or suburban residence	67 (95.0)	60 (88.2)	130 (89.0)	129 (88.4)
Household possessions				
Latrines	42 (58.3)	38 (55.9)	90 (61.6)	79 (54.1)
Electricity	55 (76.4)	55 (80.9)	117 (80.1)	118 (80.8)
Monogamous	41 (56.9)	43 (63.2)	96 (65.8)	91 (62.3)
Attended secondary school	29 (40.3)	28 (41.2)	53 (36.3)	52 (35.6)
General and obstetric characteristics				
Weight (Kg)	*66.8 (14.5)*	*63.3 (11.9)*	*62.3 (11.8)*	*60.9 (11.8)*
Body mass index (Kg/m^2)	*26.1 (5.3)*	*24.9 (4.2)*	*24.6 (4.4)*	*24.0 (4.2)*
Primigravid. n (%)	11 (15.3)	8 (11.8)	17 (11.6)	14 (9.6)
Gestational age (weeks of pregnancy)	*22.1 (4.2)*	*21.0 (4.0)*	*21.8 (3.8)*	*21.7 (3.5)*
Number of ANC visits before enrolment (N=423)	*2.0 (1.1)*	*1.9 (1.1)*	*1.9 (1.2)*	*1.9 (1.1)*
Bed net possession and use the previous night (N=428)	44 (61.1)	45 (66.1)	92 (64.3)	90 (62.1)
Previous SP IPTp[†](N=430)	15 (21.2)	5 (7.4)	23 (15.8)	16 (11.0)

Biologic characteristics				
Microscopic malaria at enrolment	6 (8.3)	4 (5.9)	5 (3.4)	8 (5.5)
PCR malaria at enrolment (N=407)	24 (35.8)	23 (35.4)	49 (36.3)	58 (41.4)
Hemoglobin level (g/dl)(N=404)	*10.4 (1.1)*	*10.5 (1.2)*	*10.0 (1.6)*	*9.9 (1.5)*
Anemia (<9.5 g /dl)	14 (19.4)	12 (19.1)	44 (32.6)	45 (33.6)
HIV-related characteristics				
Time since diagnosis[*] (months) (N=424)	*24 (1-48)*	*12 (2-45)*	*14 (1-37)*	*15 (1-43)*
HIV diagnosed during pregnancy	27 (37.5)	32 (47.1)	64 (43.8)	57 (39.0)
WHO clinical stage 1 [c]	62 (86.1)	59 (86.8)	91 (62.3)	91 (62.3)
CD4 cell-count (/mm^3)	*570 (166)*	*560 (125)*	*257 (120)*	*299 (154)*
Undetectable HIV viral load (N=257 [§])	15 (34.9)	11 (29.7)	27 (31.0)	29 (31.9)
CTX before pregnancy[‡]	14 (19.4)	19 (27.9)	85 (58.2)	86 (58.9)
ART before pregnancy	22 (30.6)	22 (32.4)	59 (40.4)	62 (42.5)
Duration of ART if before pregnancy[*] (months) (N=163)	*48 (31-71)*	*45 (30-57)*	*33 (16-54)*	*25 (15-50)*
Gestational age at ART initiation, if during pregnancy (weeks) (N=251)	*22.8 (5.7)*	*21.9 (5.6)*	*21.7 (6.5)*	*21.7 (6.7)*
ART regimen				
AZT-3TC-EFV	36 (50.0)	30 (44.1)	42 (28.8)	41 (28.1)
AZT-3TC-NVP	13 (18.1)	9 (13.2)	36 (24.6)	37 (25.3)
D4T-3TC-NVP	8 (11.1)	9 (13.2)	28 (19.2)	30 (20.6)
D4T-3TC-EFV	8 (11.1)	12 (17.7)	24 (16.4)	25 (17.1)
Other or unknown[‖]	6 (8.3)	6 (8.8)	15 (10.3)	13 (8.9)
None	1 (1.4)	2 (3.0)	1 (0.7)	0

[*] For time since HIV diagnosis and duration of ART, median and interquartile range are presented.

[†] IPTp was received more than 1 month before enrolment. P=0.03 for the comparison between treatment groups in the CNM trial (Fisher exact test).

[‡] Women in WHO clinical stage >1 and women treated with CTX before pregnancy could be allocated to the CNM trial if they met criteria to discontinue CTX prophylaxis at the time of enrolment.

[§] Due to logistic difficulties in the PNLS laboratory, only 257 results were available.

[‖] Overall 6 women received protease inhibitors.

CNM, cotrimoxazole not mandatory; CM, cotrimoxazole mandatory; CTX, cotrimoxazole; MQ, mefloquine ; AZT, zidovudine.

Table SDC 3: Sensitivity analysis on the primary endpoint accounting for women who received other antimalarials than the study drugs, CM trial.

	Primary endpoint=missing		**Primary endpoint=failure**	
	CTX	CTX + MQ	CTX	CTX + MQ
Modified intent to treat analysis				
Percentage failure* (range)	0.9% (0.02-4.9)	0% (0-3.2)	4.3% (1.4-9.8)	4.3% (1.4-9.7)
n/N	1/112	0/112	5/116	5/117
Difference (ULCI)	**+0.9% (+4.9%)**		**+0.04% (+6.0%)**	
Per protocol analysis				
Percentage failure* (range)	0.9% (0.02-4.9)	0% (0-3.5)	4.3% (1.4-9.8)	3.7% (1.0-9.1)
n/N	1/112	0/105	5/116	4/109
Difference (ULCI)	**+0,9% (+4.9%)**		**+0.6% (+6.5%)**	

CNM, cotrimoxazole not mandatory; CM, cotrimoxazole mandatory; CTX, cotrimoxazole; MQ, mefloquine; ULCI, upper limit of the exact 95% confidence interval.

In the CM trial, 9 women received other antimalarials during follow-up in the mTT population, 8 in the PP population. Those woman are successively considered in sensitivity analyses as primary endpoint=missing, then primary outcome=failure. In the main analysis shown in table 1, women who received other antimalarials were included and counted as success (no placental infection).In the CNM trial, no woman received other antimalarials during follow-up, thus sensitivity analysis does not apply.

Figure SDC 4. Adverse drug reactions to mefloquine reported on each visit.

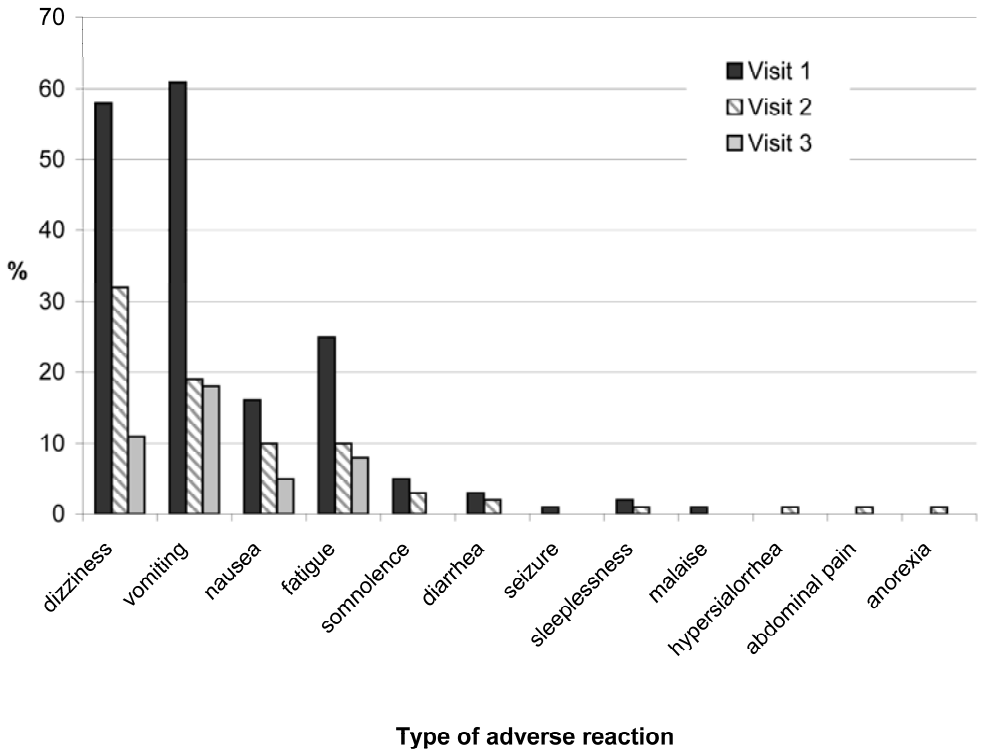

Table SDC 5. Serious adverse events in the offspring

	CNM trial			CM trial		
	CTX n (%)	MQ n (%)	P	CTX n (%)	CTX + MQ n (%)	P
Among exposed pregnancies, N=431	N=72	N=67		N=146	N=146	
Spontaneous abortion (<28 weeks), n (%)	1(1.4)	1(1.5)	1	1(0.7)	6 (4.1)	0.12
Stillbirth (≥28 weeks), n (%)	1(1.4)	4 (6.0)	0.20	5 (3.4)	6 (4.1)	1
Congenital abnormality, n (%)	2 (2.8)	1 (1.5)	1	3 (2.1)	1 (0.7)	0.62
Encephalocele and ventral hernia[*]	1					
Polydactyly (surplus finger)[†]						
Clubfoot	1			2		
Umbilical hernia				1	1	
Hydrocephaly[‡]		1				
Among live births, N=388	N=66	N=63		N=130	N=129	
Early neonatal death (<7 days)[§], n (%)	1 (1.5)	1 (1.6)	1	2 (1.5)	3 (2.3)	0.68
Infant death after 7 days[‖], n (%)	1 (1.5)	2 (3.0)	0.61	5 (3.4)	3 (2.3)	0.72

NOTE. CNM, cotrimoxazole not mandatory; CM, cotrimoxazole mandatory; CTX, cotrimoxazole; MQ, mefloquine. The probabilities were obtained from the Fisher exact test.

[*] associated with intra uterine fetal death at 35 weeks of pregnancy.

[†] Associated bilateral syndactylia in one infant

[‡] The infant had surgery at 6 weeks and improved. He was lost to follow-up and died at 10 months, of unknown cause.

[§] 4 neonatal infections, 1 neonatal respiratory distress syndrome in a premature twin, 1 neonatal haemorrhagic syndrome, 1 enterocolitis.

[‖] 4 diarrhea, 3 respiratory infections, 1 severe sepsis, 1 HIV-related death, 2 unknown causes.