



Efficacy and Safety of Quinine vs. Artemether/Lumefantrine in uncomplicated malaria during pregnancy, Mbarara, Uganda 2006-2009

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Malaria in Pregnancy

■ Associated with

- ❑ Low birth weight
- ❑ Increased maternal anaemia
- ❑ Severe malaria (mortality of 50%)

■ Treatment

- ❑ Before 2006: quinine is given at all trimesters
 - ❑ WHO (2006) recommend ACTs in the 2nd or 3rd trimesters
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Rationale

- Coartem[®]: - Data scarce on efficacy and safety in pregnancy in Africa
 - 3-day regimen
 - Quinine: - Poorly tolerated
 - Low adherence with the 7-day regimen
 - Optimum strategy for malaria treatment during pregnancy needs to be defined (PK)
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Study Objectives

■ Primary

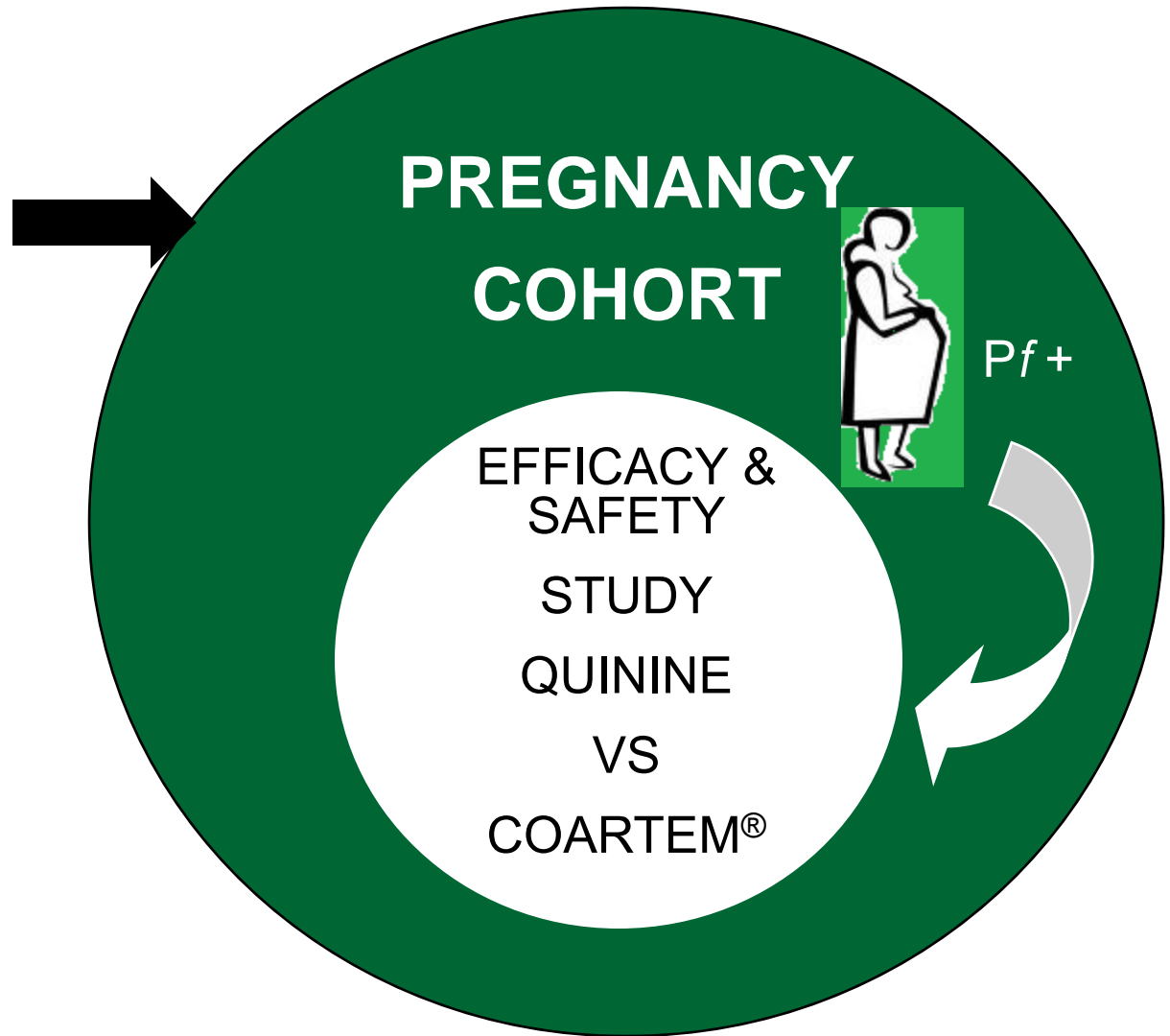
- ❑ To establish efficacy of Coartem[®] is not inferior to oral quinine for the treatment of uncomplicated *Pf* malaria in 2nd and 3rd trimester pregnancy

■ Secondary

- ❑ To describe and compare the safety of Coartem[®] and quinine
 - ❑ To define the PK of Coartem[®] and quinine in pregnancy
 - ❑ To collect data on pregnancy and infant outcomes
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Design

ANC
(Mbarara,
Uganda)



Methods - Cohort

- Prospective
 - Weekly follow up (Paracheck) till 3 months after delivery
 - Newborns followed until 1 year

 - **Inclusion Criteria**
 - Weeks of pregnancy between 13 and 35 weeks
 - Resident in Mbarara Municipality
 - Signed informed consent form
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Methods - Efficacy & Safety

- Phase IV, open label, randomized, non-inferiority trial
 - Primary endpoint: cured = PCR recrudescence-free at D42
 - Secondary endpoint: cured at D42 or delivery whichever is last
 - Non inferiority margin: 5%, $\alpha=5\%$, power=80%
 - Sample size: 304 women (152 per arm)
 - Weekly follow up (BS) until D42 or delivery (whichever is last)

 - Analysis in Intention-To-Treat and Per Protocol

 - Frequency of adverse events
-

Methods - Efficacy Study

■ Inclusion Criteria

- Malaria infection, detected by microscopy, with *P. falciparum* (mixed or mono-infection)
- Signed informed consent form

■ Exclusion Criteria

- *P. falciparum* > 250,000 parasites/ μ l
 - Severe anaemia (Hb < 7g/dL)
 - Signs or symptoms of severe/complicated malaria requiring parenteral treatment (WHO 2000)
-

Results - Study Progress

- Study start – October 2006
- In December 2008:
 - 304 in efficacy study
 - 152 in quinine arm
 - 152 in Coartem arm
 - 1229 inclusions in cohort



- Last Efficacy Trial Delivery on June 7th 2009

Results - Baseline Characteristics

		Inclusions 304	
		quinine 152	Coartem 152
Mean <i>P falciparum</i> density	Pf/ μ L	10 739	10 029
Median <i>P falciparum</i> density	Pf/ μ L	1 686	1 528
Gametocyte carriage	%	9.2%	6.6%
Mean Gestational Age	weeks	24.2	24.8
Mean Blood Hemoglobin	g/dL	10.9	10.9
Fever (>37.5 C)	%	20%	23%

Results - Efficacy Cure Rates

Day 42 analysis

Per Protocol		Intention To Treat	
quinine	Coartem	quinine	Coartem
97.6% (122/125)	99.3 % (137/138)	85.7% (120/140)	93.8 % (136/145)
d=+1.7 (LLCI: -0.9%)		d=+8.1 (LLCI:+2.2%)	

DELIVERY or D42 analysis (preliminary)

Per Protocol		Intention To Treat	
quinine	Coartem	quinine	Coartem
96.1% (98/102)	98.2% (108/110)	72.4% (97/134)	78.1 % (107/137)
d=+2.1 (LLCI:-1.7%)		d=+5.7 (LLCI:-2.9%)	

Unfinished treatment or Consent Withdrawal before end of treatment: 7 in quinine (1 in Coartem)

Results - Clearances

	Quinine 152	Coartem 152
Apyrexia at D0	80% (121/151)	77% (117/152)
Apyrexia at D2	99% (127/128)	100% (130/130)
Apyrexia at D3	100% (146/146)	100% (149/149)
Gametocyte free at D2	93% (133/143)	99% (147/149)
Gametocyte free at D7	94% (135/143)	99% (142/143)
Parasite free at D2	86% (123/143)	100% (149/149)
Parasite free at D3	98% (141/144)	99% (136/137)

Results - Safety

SAEs Mothers

- **Serious Adverse Events (SAEs)**
 - Occurring during the follow up period
 - Whether or not related to the drug

 - **Maternal deaths: 1 death in quinine arm**
 - Sepsis after Caesarean Section at 40 weeks
 - Included at 20 weeks in the trial
 - Considered not related
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Results - Safety:

SAEs Fetuses and Newborns

- Malformations at birth

- 2 polydactyly in each treatment group
- 1 acyanotic Heart Disease treated at 19 weeks of pregnancy (unrelated to drug)

- Spontaneous abortions and Neonatal deaths

Deliveries / Births	Quinine	Coartem	No Malaria
	137	144	806
Spontaneous Abortions	2 (1.5%)	2 (1.4%)	20 (2.5%)
Intra Uterine Fetal Deaths	2 (1.5%)	1 (0.7%)	11 (1.4%)
Stillbirths	3 (2.2%)	2 (1.4%)	6 (0.7%)
Early neonatal Deaths	6 (4.4%)	3 (2.1%)	20(2.5%)

Results - Safety (2): Common clinical Adverse Events

	Quinine (N=152)			Coartem (N=152)		
	Baseline Symptom	Adverse Event	Mean Delay (days)	Baseline Symptom	Adverse Event	Mean Delay (days)
<u>Tinnitus</u>	0	111 (73%)	2.4	0	0	0
Abdominal Pain	35 (23%)	46 (30%)	8.0	24 (16%)	43 (28%)	11.3
Flu	5 (3%)	18 (12%)	20.3	10 (7%)	25 (16%)	20.6
Weakness	13 (9%)	23 (15%)	6.4	12 (8%)	13 (9%)	9.2
Headache	71 (47%)	9 (6%)	19.2	57 (38%)	26 (17%)	10.6
<u>Nausea</u>	5 (3%)	26 (17%)	3.1	5 (3%)	8 (5%)	2.6
<u>Vomiting</u>	5 (3%)	28 (18%)	4.2	3 (2%)	6 (4%)	21.0
Dizziness	14 (9%)	13 (9%)	7.2	15 (10%)	14 (9%)	5.6
<u>Anorexia</u>	2 (1%)	16 (11%)	3.8	2 (1%)	6 (4%)	10.2

Results - Safety (3): Hematology

- Hb gain of 0.8g/dL in both arms 42 days after treatment, after a temporary decrease at D14 (0.1 g/dL in Q, 0.3g/dL in AL):
 - 24/138 (17%) became anemic* in Q arm after treatment
 - 36/139 (26%) became anemic in AL arm after treatment (2 cases severely anemic, 1 during delivery)
- 14 days after treatment:
 - No Neutropenia on either arms after treatment
 - 4/134 (3%) Lymphopenia in AL arm (out of which 1 reaching 0.75)
 - Platelets : +50% (1AE in AL at 483 G/L)
 - Not clinically significant
- 42 days after treatment: Eosinophils doubled in both arms by D42 (11 AE in Q, 5 in AL). p=0.11

* Anemia during pregnancy is defined as Hb<11g/dL (WHO)

Results - Safety (3): Biochemistry

- Creatinine (Normal range [0.5,1.1]): 2 AE in quinine (max 1.18)
 - ALAT (Normal range [0,40]):
 - 6 AE in quinine (max=56)
 - 10 AE in Coartem (max=131)
 - Bilirubine ((Normal range [0,1]):
 - 5 AE in quinine (max = 1.51)
 - 11 AE in Coartem (max = 2.26)
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Discussion

- Coartem is non inferior to quinine
 - Efficacy is high in both arms
 - Quinine seems poorly tolerated with lower adherence to treatment
 - Defining optimum strategy for treatment of malaria in pregnancy is a priority: PK Evidence needed.
 - We still need to address the treatment of malaria during the first trimester
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Acknowledgements

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 - ❑ University of Cape Town, South Africa
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 - ❑ IRD Sénégal



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 - MSF France
 - MSF International
 - EU

EXTRA SLIDES

Deviation or Efficacy Endpoint	ITT	PP
Included without malaria	C	C
Included with severe anemia	-	-
No or discontinued treatment	F	C
ETF	F	F
LTF (PCR adjusted)	F	F
Non Plasmodium Falciparum	F	-
Missed D42 Outcome (Accepted = D40 to D48 inclusive)	F	C
Missed Delivery Outcomes [-7 days,+7 days]	F	C
More than 3 missed visits before D42 (D42 analysis)	F	C
More than 25% missed visits before Delivery (Del analysis)	F	C
Antimalarial for no malaria before D42 (D42 & Del analysis)	C	C
Antimalarial for no malaria after D42 (Del analysis only)	F	C
Cotrimoxazole for AIDS prophylaxis	-	-
Antimalarial for non PF malaria (not a deviation)	C	C
Withdrawals of Consent	F	C
LFU1 (attributed to IP or malaria)	F	C
LFU2 (not attributed to IP or malaria)	C	C
LFU3 (Unknown)	F	C
PCR Indeterminate	F	C
PCR Re-Infection (falciparum)	F	C
PCR Recrudescence	F	F

Definitions of treatment failures

- **Early treatment failure (ETF):**

- development of danger signs or severe malaria on Day 0, 1, 2 or 3 in the presence of parasitaemia
- parasitaemia on Day 2 > Day 0 count irrespective of axillary temperature;
- presence of parasitaemia on Day 3 with fever (axillary temperature $\geq 37.5^{\circ}\text{C}$);
- parasitaemia on Day 3 $\geq 25\%$ of count on Day 0.

- **Late clinical failure (LCF):**

- development of danger signs or severe malaria after Day 3 in the presence of parasitaemia without previously meeting the criteria of ETF
- presence of parasitaemia and axillary temperature $\geq 37.5^{\circ}\text{C}$ on any day from Day 4 to Day 42/day of delivery (whichever is the last), without previously meeting the criteria of ETF;

- **Late parasitological failure (LPF):**

- presence of parasitaemia on any day from day 7 to Day 42/day of delivery (whichever is the last) and axillary temperature $< 37.5^{\circ}\text{C}$ (and no history of fever in the last 48 h) without previously meeting any of the criteria of ETF or LCF.

- **Adequate Clinical and Parasitological Response (ACPR):**

- absence of parasitaemia on Day 42/day of delivery (whichever is the last) without previously meeting any of the criteria of ETF, LCF or LPF.
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Drug administration

- Group 1 (Active Control): Quinine hydrochloride (10 mg/Kg/8h for 7 days) administered orally.
 - Group 2 (Test): Coartem®, fixed Artemether-Lumefantrine (20/120 mg) GMP manufactured by Novartis Pharma AG (Basel, Switzerland), 4 tablets twice a day for 3 days with 200 ml of milk tea at each dose .
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Results:

Placental Crush Smear & Blood Smear

- Out of 214 placentas examined at delivery 10 had parasites out of which:
 - 6 were from patients under treatment
 - 2 had re-infections
 - 2 potentially had prolonged sub microscopic parasitaemia.

 - There was no congenital malaria in screened infants.
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Results:

Maternal Hemoglobin at Delivery

Documented	Quinine N=107	Coartem N=122	No Malaria N=507
Mean Hb at delivery (g/dL)	12.1	11.9	12.4
95% Confidence Interval	(7.4-16.8)	(8.0-15.7)	(8.6-16.2)
Severe anemia n (%)	3 (2.8%)	1 (0.8%)	3 (0.6%)

Results: Infant Weight at Birth

Documented	Quinine N=119	Coartem N=118	No Malaria N=577
Mean weight (grams)	3012	3047	3109
95% Confidence Interval	(2074-3950)	(2169-3925)	(2141-4077)
Low Birth Weight <2500g n(%)	16 (13.4%)	12 (10.0%)	52 (8.6%)

Results:

Gestational Age at End of Pregnancy

Documented	Quinine N=131	Coartem N=141	No Malaria N=728
Mean gestational at delivery	39.0	39.1	38.7
Prematurity < 37 weeks n (%)	29 (21.2%)	24 (16.8%)	144 (16.8%)
Severe Prem < 28 weeks n (%)	5 (3.6%)	2 (1.4%)	31 (4.0%)

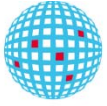


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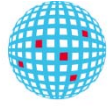


Introduction to WWARN

[Patrice PIOLA, Clinical Scientific Coordinator]
[13 October 2009]



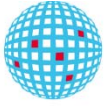
- Global collaboration working to ensure that anyone affected by malaria receives *effective* and safe drug treatment
- Provide comprehensive, timely and quality-assured information to track the emergence of malarial drug resistance
- Success will depend on active participation



WWARN

WWARN database

- Data input into four modules
 - Clinical efficacy
 - Clinical pharmacology
 - in vitro susceptibility
 - Molecular markers
- WWARN Uniquely collates data from clinical efficacy, pharmacology, molecular markers and in vitro
- Informatics team drives data input, analysis and outputs



WWARN

Clinical efficacy

- The WWARN data system will analyze individual patient data, including demographic information, treatment history, and outcome
- Reporting of resistance will be produced over time and space, using a wide variety of statistical methods and software applications (mapping, graphs, etc...).