Lessons learnt from IPTp with Mefloquine clinical trials in Benin, Gabon, Kenya, Mozambique and Tanzania

Raquel González, MD, MPH, PhD

Barcelona Institute for Global Health (ISGlobal)

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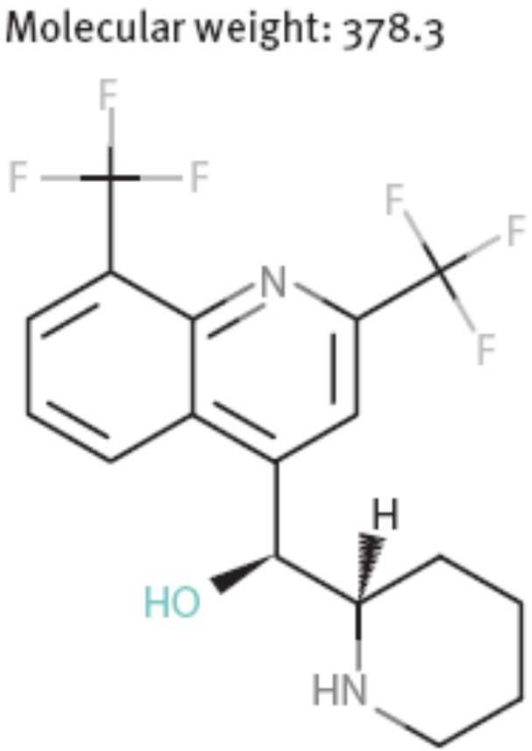
Background

- Increased SP resistance → evaluation of other antimalarials for IPTp needed
- **Mefloquine (MQ)** was considered a good alternative to be evaluated as IPTp
- Developed in the 1970's by the US army
- MQ belongs to the arylaminoalcohol antimalarials



Background

- Comparative advantages of MQ for IPTp:
  - Long half life (12-17 days at prophylactic doses)
  - Can be given as single dose
  - Acceptable reprotoxicity profile in animal studies
  - Reclassified as pregnancy category B by the US-FDA
  - Recommended for chemoprophylaxis for pregnant women of all GA by the WHO and CDC
  - Well characterized in terms of PK in pregnancy
  - Resistance to MQ is rare in Africa
- Tolerability could be improved by splitting drug administration over 2 days (ter Kuile et al. 1995)

Background

- HIV-infected pregnant women are an special vulnerable group for malaria
- SP is not recommended in women receiving daily cotrimoxazole (CTX) prophylaxis
- CTX has some antimalarial effect
- Evaluation of drugs to be used as IPTp in HIV-infected women receiving CTX is needed

→**MiPPAD** (Malaria in Pregnancy Preventive Alternative Drugs) study that included two randomized controlled trials (RCT)

MiPPAD Trial 1:

Safety and Efficacy of Mefloquine as Intermittent Preventive Treatment for malaria in Pregnancy: a randomized multicenter trial in HIV-negative women

IPTp- Mefloquine (MQ) RCT

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Intermittent Preventive Treatment of Malaria in Pregnancy with Mefloquine in HIV-Negative Women: A Multicentre Randomized Controlled Trial

Raquel González[1,2☯], Ghyslain Mombo-Ngoma[3,4☯], Smaïla Ouédraogo[5,6☯], Mwaka A. Kakolwa[7☯], Salim Abdulla[7], Manfred Accrombessi[5,6], John J. Aponte[1,2], Daisy Akerey-Diop[3,4], Arti Basra[3,4], Valérie Briand[6,8], Meskure Capan[3,4], Michel Cot[6,8], Abdunoor M. Kabanywanyi[7], Christian Kleine[3,4], Peter G. Kremsner[3,4], Eusebio Macete[2], Jean-Rodolphe Mackanga[3,4], Achille Massougbodgi[5], Alfredo Mayor[1,2], Arsenio Nhacolo[2], Golbahar Pahlavan[1], Michael Ramharter[3,4,9], María Rupérez[1,2], Esperança Sevene[2], Anifa Vala[2], Rella Zoleko-Manego[4,10], Clara Menéndez[1,2¶*]

2014

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Morocco
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(Western Sahara)
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Chad
Sudan
Eritrea
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Senegal
Gambia
Guinea Bissau
Guinea
Burkina Faso
Sierra Leone
Ivory Coast
Ghana
Togo
Benin
Nigeria
Cameroon
Central African Republic
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Ethiopia
Somalia
Liberia
Equatorial Guinea
Gabon
Congo
Democratic Republic of Congo
Uganda
Kenya
Rwanda
Burundi
Tanzania
Angola
Zambia
Malawi
Mozambique
Zimbabwe
Namibia
Botswana
Madagascar
Swaziland
South Africa
Lesotho
Benin
Gabon
Tanzania
Mozambique

Objectives

Primary:

- To compare the safety, tolerability and efficacy of MQ to SP as IPTp for the prevention of malaria in pregnancy for the mother and her infant

Secondary:

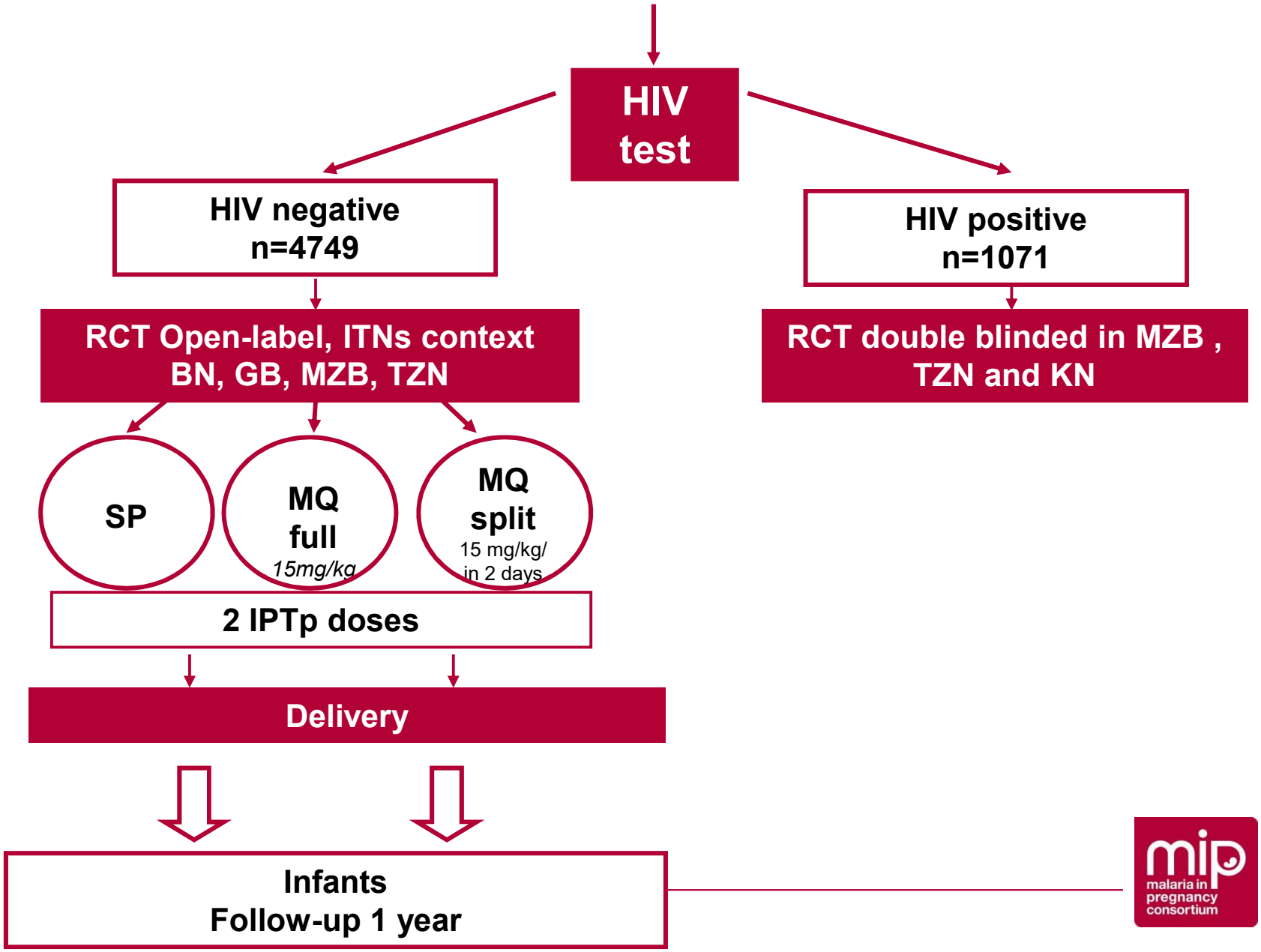
- To compare MQ tolerability given as full dose with a split dose administered over 2 days

Study design

Randomized open-label 3 arms trial to compare 2-dose MQ versus **2-dose** SP for IPTp in the prevention of the adverse effects of malaria during pregnancy and to compare MQ tolerability of 2 different MQ administration regimens. Study arms:

- IPTp with SP
- IPTp with MQ given as full dose
- IPTp with MQ given as an split dose

Pregnant women attending ANC



Efficacy results

Endpoint	SP n/N	SP %	MQ n/N	MQ %	RR	95% CI	p-value
Prevalence of LBW	**177/1398**	**12.7**	**360/2778**	**13.0**	1.02	(0.86 , 1.22)	0.801
Benin	47/349	13.5	110/703	15.6	1.16	(0.82 , 1.64)	0.391
Gabon	54/331	16.3	112/652	17.2	1.05	(0.77 , 1.44)	0.749
Mozambique	37/360	10.3	66/712	9.3	0.90	(0.60 , 1.36)	0.621
Tanzania	39/358	10.9	72 /711	10.1	0.93	(0.63 , 1.36)	0.709
Mean birth weight, m (SD)	3001.5 (517.8)		2997.4 (535.5)		-4.1[1]	(-39.2 , 31.1)	0.821
Maternal parasitemia at delivery (O.M.)	63/1372	**4.6**	88/2737	**3.2**	0.70	(0.51 , 0.96)	0.026
Maternal anemia at delivery (Hb<11 g/dl)	609/1380	**44.1**	1110/2743	**40.5**	0.92	(0.85 , 0.99)	0.026
Maternal Hb at delivery mean (SD)[n]	**11.0** (1.6) [1380]		**11.1** (1.5) [2743]		0.15[2]	(0.05 , 0.25)	0.003

ITT cohort

[1]Proportional difference

Efficacy results

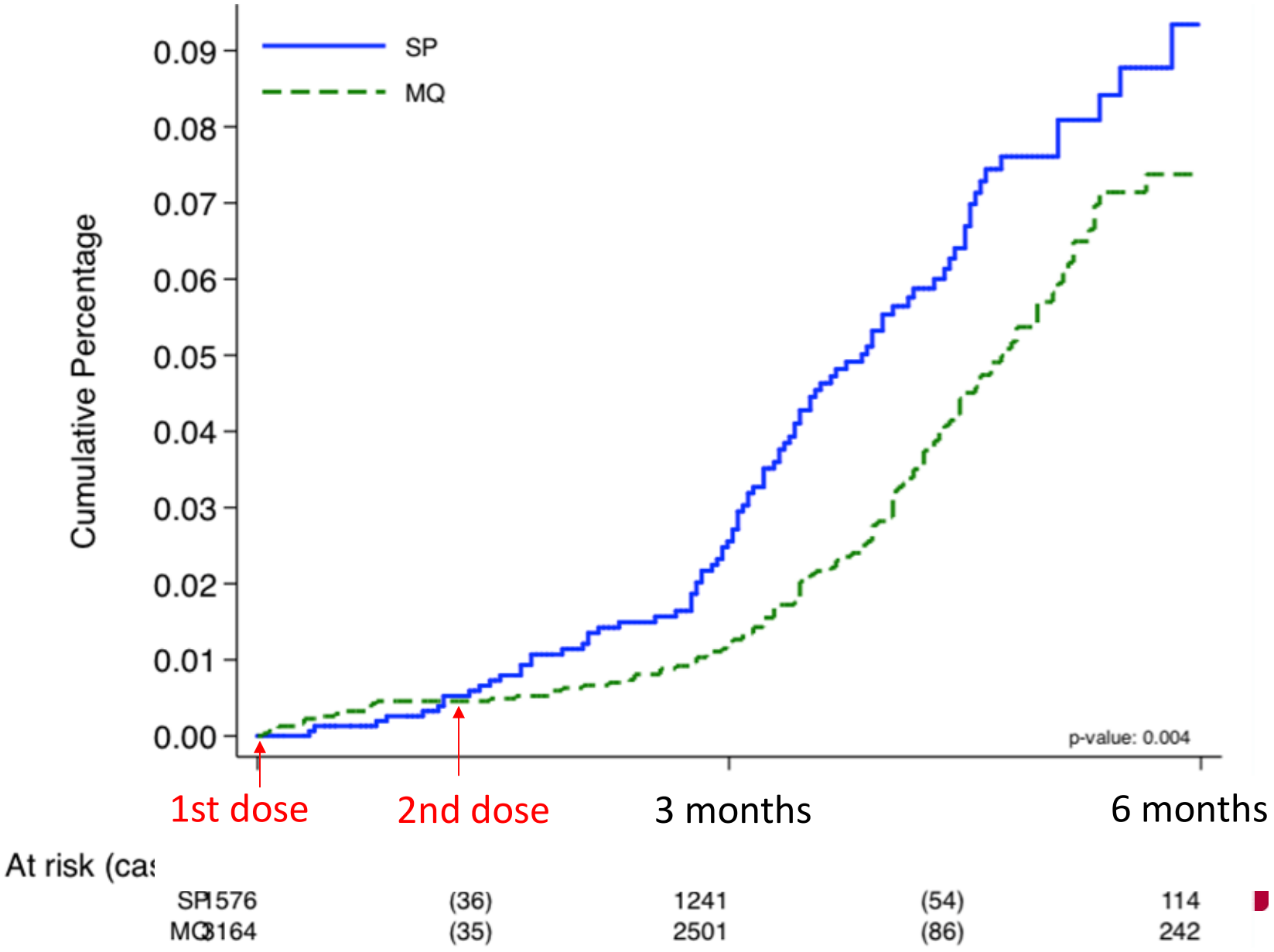
Endpoint	SP	MQ	RR	95% CI	p-value
Incidence of **clinical malaria**	96/552.8 **0.17**[1]	130/1106.1 **0.12**[1]	0.67	(0.52 , 0.88)	**0.004**
Incidence of **outpatients visits**	850/558.8 **1.52**[1]	1475/1113 **1.33**[1]	0.86	(0.78 , 0.95)	**0.002**
Hospital Admissions	106/558.8 0.19[1]	186/1113.0 0.17[1]	0.88	(0.68 , 1.14)	0.346

ITT cohort [1] Episodes person/year

Definition of clinical malaria episode: *P falciparum* parasitemia of any density plus any signs and/or symptoms suggestive of malaria: fever in the last 24 hours and/or axillary temperature (Tª ≥ 37.5 ºC), and/or pallor and/or arthromyalgias and/or headache and/or history of convulsions.

ITT cohort

Time to first malaria episode



Adverse events related to medication

After 1st IPTp	SP (N=1559)			MQ full (N=1550)			MQ split (N=1562)		
	n	%	95%CI	n	%	95%CI	n	%	95% CI
Vomiting	100	6.41	(5.25; 7.75)	491	**31.68**	(29.37; 34.06)	471	**30.15**	(27.88; 32.50)
Dizziness	115	7.38	(6.13; 8.79)	526	**33.94**	(31.58; 36.35)	554	**35.47**	(32.90; 37.90)
Headache	115	7.38	(6.13; 8.79)	123	7.94	(6.64; 9.39)	131	8.39	(7.06; 9.87)
Nausea	55	3.53	(2.67; 4.57)	136	8.77	(7.41; 10.29)	152	9.73	(8.31; 11.31)
Asthenia	14	0.90	(0.49; 1.50)	107	6.90	(5.69; 8.28)	104	6.66	(5.47; 8.01)

No differences between groups on frequency of:

- Adverse pregnancy outcomes (miscarriages, stillbirths, congenital malformations, prematurity)
- SAEs
- Maternal and neonatal deaths

Safety cohort

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Summary of main findings

- No differences in LBW prevalence between groups
- **MQ** group presented **lower rates** of
  - Maternal **parasitemia** at delivery
  - Maternal **anemia** at delivery
  - Incidence of **clinical malaria** during pregnancy
  - Incidence of **outpatient** clinic visits
- No differences in the frequency of adverse pregnancy outcomes (miscarriage, stillbirths, congenital malformations, maternal deaths)
- **MQ** group presented **higher** rates of **drug related- Adverse Effects**
  - Poorer immediate tolerability than the SP group
  - Higher frequency of **vomiting** and **dizziness**
- **No differences** in efficacy, frequency of adverse effects and drug tolerability between **MQ** full and MQ split **groups**

Conclusions

- **MQ** has a **better prophylactic** antimalarial effect than **SP**
- MQ is a **safe** drug in terms of adverse pregnancy outcomes
- MQ (15 mg/kg) has **worse tolerability** than SP as IPTp
- Splitting the MQ dose does not seem to confer benefits in terms of drug tolerability
- **MQ** at the **dose** used in this study is **not** an alternative to SP for IPTp

MiPPAD Trial 2:

Mefloquine as Intermittent Preventive Treatment for malaria in Pregnancy in HIV-infected women receiving cotrimoxazole prophylaxis: a randomized double-blind multicenter placebo-controlled trial

IPTp- Mefloquine RCT

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Intermittent Preventive Treatment of Malaria in Pregnancy with Mefloquine in HIV-Infected Women Receiving Cotrimoxazole Prophylaxis: A Multicenter Randomized Placebo-Controlled Trial

Raquel González[1,2¶], Meghna Desai[3,4¶], Eusebio Macete[2¶], Peter Ouma[3,5¶], Mwaka A. Kakolwa[6¶], Salim Abdulla[6], John J. Aponte[1,2], Helder Bulo[2], Abdunoor M. Kabanywanyi[6], Abraham Katana[3,5], Sonia Maculuve[2], Alfredo Mayor[1,2], Arsenio Nhacolo[2], Kephas Otieno[3,5], Golbahar Pahlavan[1], María Rupérez[1,2], Esperança Sevene[2], Laurence Slutsker[4], Anifa Vala[2], John Williamsom[3,4], Clara Menéndez[1,2*¶]

2014

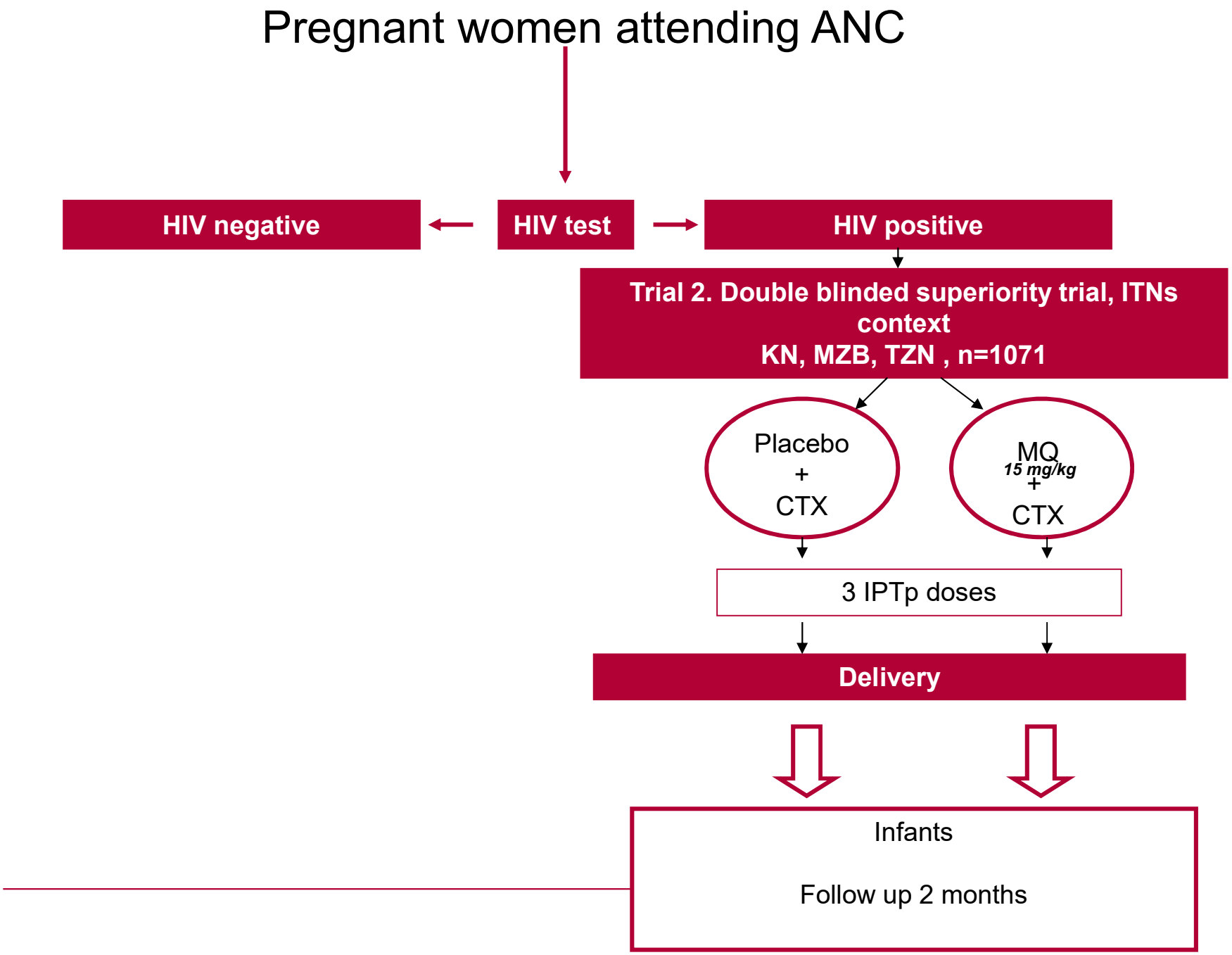

Morocco
Tunisia
Algeria
Libya
Egypt
(Western Sahara)
Mauritania
Mali
Niger
Chad
Sudan
Eritrea
Djibouti
Senegal
Gambia
Guinea Bissau
Guinea
Burkina Faso
Sierra Leone
Liberia
Ivory Coast
Ghana
Togo
Benin
Nigeria
Cameroon
Central African Republic
Republic of South Sudan
Ethiopia
Somalia
Equatorial Guinea
Gabon
Congo
Democratic Republic of Congo
Uganda
Kenya
Rwanda
Burundi
Tanzania
Angola
Zambia
Malawi
Mozambique
Zimbabwe
Namibia
Botswana
Madagascar
Swaziland
South Africa
Lesotho
Kenya
Tanzania
Mozambique

Objective

To evaluate the safety and efficacy of mefloquine (MQ) as intermittent preventive treatment for malaria in pregnancy (IPTp) in HIV-infected women taking daily CTXp and in the context of long lasting insecticide treated nets (LLITNs) .

Study design

Randomized double-blind clinical trial to compare the efficacy of MQ as IPTp with placebo-IPTp in HIV-infected pregnant women receiving CTX prophylaxis.


Pregnant women attending ANC
HIV negative
HIV test
HIV positive
Trial 2. Double blinded superiority trial, ITNs context
KN, MZB, TZN , n=1071
Placebo
+
CTX
MQ
15 mg/kg
+
CTX
3 IPTp doses
Delivery
Infants
Follow up 2 months

Efficacy

Endpoint	Control n/N	Control %	MQ n/N	MQ %	RR	95% CI	p-value
Maternal **parasitemia** at delivery (smear or PCR)	37/490	**7.6**	17/483	**3.5**	**0.47**	(0.27; 0.82)	0.008
Placental infection (Histology, smear or PCR)	34/462	**7.4**	17/449	**3.8**	**0.52**	(0.29; 0.90)	0.021

ITT cohort

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Efficacy

	Control n/PYAR [1] Incidence		Mefloquine n/PYAR [1] Incidence		Relative Rate	95% CI	p-value
Clinical malaria	16/189.1	0.09	8/182.2	0.04	0.52	(0.22; 1.21)	0.128
Outpatient visits	401/190.2	2.11	332/182.8	1.82	0.86	(0.72; 1.03)	0.098
All-cause hospital admissions	68/190.2	0.36	41/182.8	0.22	**0.65**	(0.41; 1.03)	0.065
Non-obstetric admissions	67/190.2	0.35	37/182.8	0.20	**0.59**	(0.37; 0.95)	0.031

[1] Episodes person/year. ITT analysis adjusted by country.

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Safety

After 1st IPTp	Placebo (N=531)			MQ (N=520)		
	n	%	95%CI	n	%	95%CI
Dizziness	40	**7.5**	(5.43; 10.10)	155	**29.6**	(25.75; 33.75)
Vomiting	16	**3.0**	(1.73; 4.84)	125	**23.9**	(20.31; 27.79)
Headache	40	7.5	(5.43; 10.10)	38	7.3	(5.19; 9.84)
Nausea	21	**4.0**	(2.46; 5.97)	54	**10.3**	(7.85; 13.26)

No differences between groups on frequency of:

- Adverse pregnancy outcomes (miscarriages, stillbirths, congenital malformations, prematurity)
- SAEs
- Maternal and neonatal deaths

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Mother to child transmission of HIV by treatment group (exploratory analysis)

Infant HIV PCR results[1]	Control n	Control %	Mefloquine n	Mefloquine %	Risk Ratio (95%CI)	p-value
ITT [N=855]						
Positive	19	**4.4**	36	8.6	**1.95** (1.12; 3.39)	**0.018**
Negative	416	95.6	384	91.4		
ATP [N=754]						
Positive	15	**3.8**	29	8.0	**2.04** (1.08; 3.85)	**0.028**
Negative	378	96.2	332	92.0		

[1]Median age 5.9 weeks (Interquartile Range 1.7). ITT analysis adjusted by country. ATP analysis adjusted by baseline variables: country, literacy, gestational age, gravidity, anemia, MUAC, CD4 counts and viral load. Interaction MQ x Country = p-value 0.642 for ITT cohort, and 0.860 for ATP cohort.

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Risk factors for MTCT of HIV

	ITT			ATP		
	Risk Ratio	CI 95%	p-value	Risk Ratio	CI 95%	p-value
Treatment **Mefloquine** vs Control	2.05	1.16; 3.63	0.014	**2.17**	1.12 ; 4.19	**0.021**
Viral load at delivery (copies/mL)						
400-999 vs <400	4.80	1.38;16.65	0.013	3.32	0.88; 12.50	0.075
1000- 9999 vs < 400	3.59	1.39; 9.29	0.008	3.75	1.43; 9.87	0.007
>9999 vs < 400	5.82	2.01; 16.84	0.001	3.62	1.14; 11.51	0.029
No data vs < 400	2.78	0.80; 9.74	0.109	1.22	0.16; 9.20	0.847
Clinical malaria episodes in pregnancy[2]	3.05	1.35; 6.92	0.008	**4.76**	2.01; 11.24	**<0.001**
Maternal compliance to PMTCT or ART guidelines						
Incomplete[3] vs Complete[4]	1.94	1.06; 3.57	0.031	1.96	0.98; 3.92	0.056
Nothing[5] vs Complete	2.86	1.43; 5.74	0.003	3.01	1.22; 7.37	0.016

[1]Median age of infants was 5.9 weeks (IQR 1.7) at the time of the HIV PCR test. Analysis adjusted by baseline variables: country, literacy, gestational age, gravidity, anemia, MUAC, CD4 counts and viral load. PMTCT: Prevention of Mother to Child Transmission. ART: Antiretroviral therapy. [2] At least one episode of clinical malaria during study follow-up in pregnancy. [3] Incomplete: received partially PMTCT (either antenatal, intrapartum or postpartum) or ART. [4] Complete: received PMTCT (antenatal, intrapartum, and postpartum) or ART according to national guidelines. [5] The mother did not receive either PMTCT or ART.

Summary of main findings

- In IPTp-MQ group, **reduced** rate of :
  - Maternal **parasitemia** at delivery
  - **Placental** infection
  - Hospital **admissions**
- **No differences** on frequency of adverse pregnancy outcome
- No maternal SAEs related to medication
- In IPTp-MQ group, **higher:**
  - Frequency of **vomiting and dizziness**
  - HIV **viral loads** at delivery
  - Rates of **MTCT of HIV**

Conclusions

- The **addition** of an **effective antimalarial** drug to daily **CTX** prophylaxis in **HIV-infected women** can have a benefitial effect by:
  - Halving the risk of maternal **parasitemia** at delivery
  - Reducing the incidence of hospital **admissions**

- Poor tolerability of MQ (15mg/kg) → search for alternative antimalarials

- The increased MTCT of HIV calls for the need of **specifically designed studies** to fully understand the effects of antimalarials and ARVs co-administration

- There is an **urgent** need to address the **prevention** of **malaria** in **HIV-infected pregnant women** who are one of the most **vulnerable** group to the infection in malaria endemic areas in **Africa**

MiPPAD investigators

ISGlobal, Barcelona, Spain
- John J. Aponte
- Raquel González
- Alfredo Mayor
- **Clara Menéndez**

CDC, Atlanta, USA
- Meghna Desai
- Laurence Slutsker
- John Williamson

FSS, Cotonou, Benin
- Manfred Accrombessi
- Achille Massougbodji
- Smaïla Ouédragou

IHI, Dodoma, Tanzania
- Salim Abdulla
- Mwaka A. Kakolwa
- Abdunoor M. Kabanywanyi

IRD, Paris, France
- Valérie Briand
- Michel Cot

KEMRI, Kisumu, Kenya
- Peter Ouma
- Kephas Otieno
- Abraham Katana

UoTübingen, Tübingen, Germany
- Peter G. Kremsner
- Michael Ramharter

CISM, Manhiça, Mozambique
- Eusébio V. Macete
- Arsénio Nhacolo
- María Rupérez
- Esperança Sevene
- Anifa Valá

MRU, Lambaréné, Gabon
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- Rella M Zoleko

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