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Cotrimoxazole *versus* sulfadoxine-pyrimethamine for intermittent preventive treatment of malaria in HIV-infected pregnant women in Bangui, Central African Republic: a Pragmatic Randomized Controlled Trial

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Abstract

Introduction

Co-infection with malaria and HIV constitutes a dual health burden on the African continent, particularly among pregnant women. Management of these two infections is a challenge. The national programme in the Central African Republic (CAR) recommends for prevention of malaria in HIV-positive pregnant women with CD4 count > 350 cells/mm3 the administration of 3 doses of intermittent-preventive-treatment with sulfadoxine-pyrimethamine (SP-IPTp). Because of the emergence of SP-resistant plasmodium falciparum in CAR, cotrimoxazole (CTX) could be an alternative for preventing malaria in this population.

Objective

The main objective of the MACOMBA (Maternity and Control of Malaria-HIV co-infection in Bangui) trial was to show that CTX has a higher effectiveness than SP-IPTp to prevent placental infection (primary end-point) among HIV-positive pregnant women with a CD4+ count ≥ 350 cells/mm3 in Bangui, CAR.

Methods

Macomba, is a multicenter, open-label randomized trial conducted in four maternity hospitals in Bangui aimed to show that CTX is more efficacious than IPTp-SP to preventing placental infection in pregnant HIV+ women. Between 2013 and 2017, 193 women were randomized and 112 (59 and 53 in CTX and IPTp-SP arms, respectively) were documented for the primary endpoint (placental infection defined by microscopic parasitemia or PCR).

Results

Thirteen women had a placental infection: 5 in the CTX arm (1 microscopic placental parasitemia and 4 PCR) and 8 PCR in the SP-IPTp (8.5% vs 15.1%, p = 0.28). The percentage of newborns with low birthweight (< 2500 g) was not statistically different between the two arms. Self-reported compliance to CTX prophylaxis was good. In the two arms, there was a low rate of adverse events.

Conclusion

Although our results do not allow us to conclude that CTX is more effective, drug safety and good compliance among women with this treatment favor its widespread use among HIV-infected pregnant women, as the WHO currently recommends.

58 **Introduction**

59 Malaria and HIV infection are two endemic diseases that constitute a dual health problem on the
60 African continent [1]. The interaction between the two infections is particularly deleterious in
61 pregnancy leading to increased risk and severity of both malaria infection and disease, as well as to
62 increased HIV viral load, which may raise the frequency of mother to child transmission of HIV [2].
63 Pregnant women living with HIV more often have malaria episodes that evolve into complicated
64 forms with increased morbidity, in the form of maternal anemia, intrauterine growth retardation,
65 low birth weight and mortality in infancy [3-4].
66 In 2012, Manirakiza *et al* reported a 23% prevalence of malaria among women at their first antenatal
67 care (ANC) visit in Bangui, Central African Republic (CAR) [5]. In CAR, prevalence rate of HIV infection
68 in the general population was 15% in 2006-2008 in Bangui [6].
69 At the time of the present study, the national malaria programme in CAR recommended for the
70 prevention of malaria administering two doses of intermittent preventive treatment (IPTp) with
71 sulfadoxine-pyrimethamine (SP) for pregnant women who were not living with HIV, and three doses
72 for those living with HIV. To prevent opportunistic infections among women with HIV, cotrimoxazole
73 was recommended to those at WHO clinical stages 2, 3 and 4 and those at stage 1 with a CD4+ count
74 < 350 cells/mm^3 from the second trimester onwards and throughout pregnancy (Ministère santé
75 publique, CAR) [7]. According to national recommendations, pregnant women with a CD4+ count <
76 350 cells/mm^3 receiving CTX to prevent opportunistic infections should not be given SP-IPTp for
77 malaria prevention to avoid adverse drug reactions [8].
78 These national recommendations were not entirely consistent with those of the WHO, which had
79 been advising the monthly administration of SP-IPTp since 2012 [9].
80 Nevertheless, the emergence of *Plasmodium falciparum* resistance to SP reported in many sub-
81 Saharan countries, including CAR, raised questions about the usefulness of this treatment to prevent
82 malaria among pregnant women [10-13]. Studies carried out in Bangui in 2004-2005 reported a
83 treatment failure rate of 24% after 14 days of follow-up among children treated with SP for
84 uncomplicated malaria, *in vitro* resistance of *P. falciparum* to pyrimethamine of 38%, a frequency of
85 triple mutations in alleles Ile-51, arg-59 and Asn-108 of 50% and a strong correlation between these
86 mutations and *in vitro* resistance to *P. falciparum* [14-16].
87 On the other hand, there was growing evidence of the efficacy of cotrimoxazole (CTX) in preventing
88 *P. falciparum* malaria in adults and children [17-18]. In addition, CTX had been reported as safe for
89 long-term use during pregnancy [19]. Nevertheless, its efficacy in preventing malaria among
90 pregnant women and women's compliance in adhering to daily treatment throughout pregnancy had
91 not been evaluated under real-world conditions. For this reason, we conducted the MACOMBA
92 (Maternity and Control of Malaria-HIV co-infection in Bangui) clinical trial with the main hypothesis

that CTX given daily would be more efficacious than SP-IPTp to prevent placental parasitaemia due to a higher plasma concentration of CTX achieved with daily doses. If demonstrated, CTX could be recommended as prophylaxis for HIV-infected women, regardless of CD4 count, in countries where this dosage was not available routinely.

Objectives

The main objective of the MACOMBA (Maternity and Control of Malaria-HIV co-infection in Bangui) trial was to show that CTX has a higher effectiveness than SP-IPTp to prevent placental infection (primary end-point) among HIV-positive pregnant women with a CD4+ count ≥ 350 cells/mm3 in Bangui, CAR. This study also assessed women's compliance with daily doses of CTX and the safety of both prevention strategies.

Ethics

The study protocol and informed consent forms were reviewed and approved by the National Ethics Committee of the Central African Republic and the Clinical Research Committee of the Institut Pasteur in Paris. The trial was registered prior to the enrolment of the first participant under the ClinicalTrials.gov Identifier, NCT01746199.

All pregnant women provided written, informed consent before participating in the study.

An independent Data Safety Monitoring Board (DSMB), set up prior to the beginning of the trial, regularly reviewed and monitored the safety data collected.

This trial was funded by the Fondation de France and conducted by the Institut Pasteur de Bangui and the Institut Pasteur de Paris.

All treatment received during pregnancy in relation to the pregnancy and malaria were undertaken by the study (including caesarian sections). Women received a preventive antiretroviral treatment to reduce HIV Mother-To-Child-Transmission: i) AZT from week 16 of amenorrhoea, ii) AZT, 3TC and NVP during labor and delivery and iii) AZT and 3TC for 7 days after delivery. Antiretroviral treatments for HIV were secured for all the women and insecticide-treated mosquito nets were offered by the Total Foundation.

Material and method

Study design

MACOMBA is a multicenter, randomized, controlled open-label superiority trial comparing SP-IPTp with CTX under real-life conditions. The protocol was previously described in Trials [20].

Physicians and Participants

128 MACOMBA was conducted in Bangui's four main maternity clinics. All pregnant women attending
129 one of these maternity clinics and fulfilling the inclusion/non-inclusion criteria were asked to
130 participate in the study.
131
132 **Inclusion/non-inclusion criteria**
133 To be included in this study, pregnant women had to i) be at least 18 years old, i) be HIV positive, iii)
134 be between 16 and 28 weeks of gestation, iv) have a CD4+ count >= 350 cells/mm3 and no sign of
135 WHO stage 2, 3 or 4, v) agree to attend all ANC visits and have signed informed consent. The main
136 non-inclusion criteria were psychological instability, known hypersensitivity to sulfonamides or
137 dermatological diseases, severe anemia (Hb < 7g/dl) and severe diseases requiring hospitalization.
138 Women with a symptomatic malaria infection at pre-inclusion visit were treated with quinine or Co-
139 Artem® in case of known allergy to quinine. They had the option to be included later when no longer
140 parasitaemic [20].
141
142 **Recruitment and Randomization**
143 HIV-seropositive pregnant women were identified by midwives at ANC visits in the four maternity
144 clinics. When eligible, they were invited for additional counselling by trained midwifes to be fully
145 informed of the study before signing the consent form.
146 Randomization of women was centralized and stratified on maternity clinic and gravidity
147 (primigravidae versus multigravidae). Randomization lists were generated using 1:1 ratio.
148
149 **Interventions**
150 The drugs used in this study were supplied by the International Dispensary Association in the
151 Netherlands. CTX (one daily tablet containing 160 mg of trimethoprim and 800 mg of
152 sulfamethoxazole) was administered from 16 weeks until the end of pregnancy. Three doses of SP-
153 IPTp (1500 mg of sulfadoxine and 75 mg of pyrimethamine per dose) were given under direct
154 observed administration at one month of interval from 16 weeks' gestation.
155 All pregnant women received daily iron (200 mg) and folic acid (0.4 mg) supplementation throughout
156 the pregnancy, and an insecticide-treated net.
157 During follow up, in case of suspicion of malaria episode, defined by fever within 24 hours and a
158 positive Rapid Diagnostic test (RDT) or thick blood smear (TBS), treatment with quinine at a dose of
159 24 mg/kg body weight was given at three doses per day 8 hourly apart for 7 days. In case of severe
160 clinical symptoms, a quinine perfusion in 10% serum glucose was administered parenterally at a dose

161 of 24 mg/kg body weight per day until oral quinine could be taken. In case of adverse events due to
162 quinine, Co-Artem® was given.
163
164 **Data collected:**
165 The following data were collected from pregnant women at inclusion: socio-demographic
166 characteristics, clinical data, obstetric history, and gestational age estimated either by the date of the
167 last menstrual period (LMP) or by uterine fundal height if LMP was unknown. CD4 and blood cell
168 counts were determined. Malaria diagnosis using RDT, TBS and Polymerase Chain Reaction (PCR) was
169 performed. During follow-up, clinical examination was performed every month. The total number of
170 doses of SP-IPTp delivered during pregnancy was documented. Adverse effects were recorded
171 according to their severity stage (low, moderate or severe) and relation to SP-IPTp or CTX. CD4 count
172 was determined and any suspected malaria episode was investigated by laboratory testing (RDT,
173 thick blood smear and PCR). At delivery, CD4 count and blood cell count were determined. Malaria
174 diagnosis was performed using RDT, TBS and PCR on maternal peripheral blood. In addition, PCR and
175 TBS were performed on placental blood.
176 Compliance with CTX was quantitatively estimated, at each ANC visit, by the number of doses of CTX
177 taken since the last visit reported by the woman.
178 For new-borns, vital status at birth was collected and birthweight measured within 24 hours after
179 birth using SECA 745 Mechanical baby-scales. HIV status was determined by using Heel Dried Blood
180 Spot (Determine and Unigold™). Malaria diagnosis was performed from umbilical blood using both
181 RDT and TBS.
182
183 **Laboratory analysis**
184 Details on blood drawing and laboratory analyses were previously described in Trials [19].
185 Briefly, venous blood was collected at inclusion; at each ANC visit in case of symptoms suggestive of
186 malaria for CD4 cell counts and malaria diagnosis; and at delivery. CD4+ cells were counted by
187 cytometry (FACSCalibur, Becton Dickinson, USA).
188 For malaria diagnosis, the antigen Pf/Pan-SD Bioline TM rapid rapid diagnostic test was used. Thick blood
189 smears were air-dried, stained with 4% Giemsa and analyzed under a light microscope to detect
190 asexual forms of *P. falciparum,* with negative result defined when examination of 100 high power
191 fields did not reveal asexual parasites. Anested species-specific PCR was performed to screen for
192 malaria in maternal peripheral and placental blood [21]. Maternal-to-child transmission of HIV was
193 determined on Dried Blood Spot by Generic HIV DNA Cell kits (Biocentric, Bandol, France). HIV status

194 was determined based on two consecutive positive Heel Dried blood spot, according to national
195 procedures (Determine and Unigold™).
196 Immediately after delivery, a block of tissue was excised from the basal side of the placenta to collect
197 blood at the excision site. The placental tissues were pressed to prepare thin and thick blood smears.
198
199 **Primary and secondary endpoints**
200 The primary endpoint was placental infection, defined by a positive result for microscopic placental
201 infection or PRC placental infection.
202 Secondary outcomes were: Compliance to CTX, assessed by the number of doses taken between
203 each ANC visit, Number of doses of SP-IPTp and percentage of women who received at least 3 doses
204 until delivery, Adverse events related to the two treatments, Incidence of clinical malaria episodes
205 during follow-up, Maternal anemia (Hb < 10 g/dL) at delivery, Miscarriage (died foetus < 28 weeks of
206 gestation), Stillbirth (died foetus ≥ 28 weeks of gestation), Low birth weight (< 2500 g), Umbilical
207 blood parasitemia and Mother-to-child HIV transmission.
208
209 **Statistical considerations**
210 **Sample size**
211 According to the following hypotheses, we estimated positive placental parasitemia rates of 6.2% in
212 the CTX arm and 16.8% in the SP-IPTp arm from previous studies (i.e., an absolute reduction of 10.6%
213 on CTX), a power of 80%, a type 1 error of 0.05, a two side-test, 300 pregnant women were necessary
214 (150 per arm) [19,22-23].
215
216 **Statistical analysis**
217 The primary analysis of placental infection (parasitemia and PCR infection) was conducted for all
218 randomized women treated with at least one dose of CTX or SP-IPTp and documented for the
219 primary endpoint (modified ITT analysis). Secondary endpoints were analysed for documented data.
220 Safety data were analyzed for all randomized women treated with at least one dose of treatment,
221 whether the primary endpoint was documented or not.
222 Medians and interquartile ranges (IQR) and proportions were used to describe the distributions of
223 continuous and categorical variables, respectively. Distributions of variables were compared between
224 the two arms using the Student test or Mann-Whitney U test for continuous variables, Chi-Squared
225 or Fisher exact test for categorical variables.
226 Data were recorded in an Access database and analyzed using Stata 15 software (StataCorp LP,
227 College Station, TX, USA). Statistical significance was achieved for p values < 5%.
228

229 **RESULTS:**

230

231 **Recruitment** (Flow chart summarized in Figure 1).

232 Between November 2013 and April 2017, 334 women were screened in the study: 60, 107, 83 and 84
233 in the Hôpital Communautaire, the Hôpital de l'Amitié, the Centre de Santé des Castors, and the
234 Maternité du camp militaire Henry Izamo, respectively. Among these 334 women, 193 were
235 randomized: 94 and 99 in the CTX and SP-IPTp arms, respectively. The reasons for non-inclusion were
236 as follows: 107 women with CD4+ count < 350 cells/mm3 at pre-inclusion visit, 1 negative for HIV, 1
237 with a known allergy to sulphonamides, 3 with a gestational age ≥ 28 weeks, and 29 lost to follow-up
238 between screening and randomization. In addition, five randomized women were wrongly included
239 (4 and 1 in the CTX and SP-IPTp, respectively) and did not start treatment.

240 Among the 193 randomized women, 188 received at least one dose of treatment: 90 and 98, in the
241 CTX and SP-IPTp arms, respectively. The primary outcome was documented only in 112 women, 59 in
242 the CTX arm and 53 in the SP-IPTp arm, mainly because some gave birth at home during an imposed
243 curfew, so the study had no means of obtaining the placenta.

244

245 **Baseline characteristics of pregnant women**

246 Table 1 shows at inclusion well-balanced characteristics of the 188 randomized women in the 2 arms.
247 The median age of women was 28 (24-33) years. In the CTX arm, women were included at 21 (18-24)
248 weeks of gestation and 8% (7/90) were primigravidae. In the SP-IPTp arm, women were included at
249 21 (18-26) weeks of gestation and 9% (9/98) were primigravidae. Most women had confirmation of
250 their HIV-positive status just prior to inclusion in the trial. The median CD4+ count was 516 (432-644)
251 cells/mm3 in the CTX arm and 543 (445-665) cells/mm3 in the SP-IPTp arm. Forty-one percent
252 (37/90) of women suffered from anemia at inclusion, and 12% (11/90) had an associated pathology
253 during pregnancy (sickle cell disease, known diabetes, high blood pressure, obesity) in the CTX arm,
254 while 41% (40/98) and 31% (30/98) of women presented with anemia and reported at least one
255 pathology in the SP-IPTp arm. Fifty-eight percent (52/90) of women in the CTX arm and 53% (51/98)
256 in the SP-IPTp arm reported at least one malaria episode before randomization.

257

258 **Primary and secondary endpoints Primary endpoint**

259 Placental infection at delivery was documented in 112 women, 59 in the CTX arm and 53 in the SP-
260 IPTp arm. Among them, 13 women had a placental infection: 5 in the CTX arm (1 positive microscopic
261 placental parasitemia and 4 positive PCR) and 8 positive PCR in the SP-IPTp (8.5% vs 15.1%, p = 0.28).
262 The 13 women with positive placental infection were well balanced across the four maternity clinics,
263 although at the "Maternité des Castors", all included women had a negative placental infection.

264 **Secondary endpoints (Table 2)**

265 **Mothers' characteristics at delivery**

266 Two cases (one in each arm) of clinical malaria episode were reported during follow-up.

267 Among the 112 women randomized and documented for the primary endpoint, 111 (99%) women
268 gave birth at the maternity and one at home. Four (7%) and 3 (6%) women had a caesarean section
269 in CTX and SP-IPTp arms, respectively. The median gestational age at delivery was 39 (38-40) weeks
270 in both arms, respectively (p = 0.86). No maternal deaths were reported. Only one woman in the CTX
271 arm had a malaria attack during pregnancy follow-up.

272 At delivery, the median CD4+ count was 645 (423; 832) cells/mm3 and 549 (437; 810) cells/mm3 in
273 the CTX and the SP-IPTp arms, respectively, with no significant difference between medians (p =
274 0.48).

275 The difference of CD4+ count between inclusion and delivery did not differ significantly between
276 arms (p = 0.15) with a median difference of 171 [-71; 283] and 35 [-153; 135] in the CTX arm and in
277 the SP-IPTp arm, respectively.

278 Twenty women (18%) suffered from anemia: 11 (19%) and 9 (17%) in CTX and SP-IPTp arms,
279 respectively; p = 0.82. Women randomized in the SP-IPTp arm received an average of 3.9 (SD ± 1.2)
280 doses of SP-IPTp, 87% (46/53) of them received at least 3 doses, and 15 (28%), 14 (26%) and 4 (8%)
281 received 4, 5 and 6 doses, respectively.

282

283 **CTX treatment compliance*:***

284 CTX treatment was given for an average of 4 months (SD ± 1.3). Between each monthly visit, the
285 median number of tablets that women declared they had taken was 30 (28; 30), indicating a very
286 good compliance.

287

288 **New-borns:**

289 Out of the 112 women with a documented outcome at delivery, one woman gave birth to twins and
290 2 women had stillbirths, so that data for 111 live-born children are presented in Table 3. Among the
291 111 children, one child died one day after birth. Seven percent (8/111) of new-borns had a birth
292 weight less than 2500 gr, with no statistically significant difference between arms (p = 0.93). All
293 screened children were negative for HIV and malaria at birth. The two stillbirths and the neonatal
294 death documented for placental parasitemia had negative results.

295

296 Adverse events:

297 Twenty-six adverse events were reported in the 188 randomized women having received at least one
298 dose of treatment, 12% (11/90) and 15 % (15/98) in the CTX and SP-IPTp arms, respectively (p =

299 0.68). Most events were of low or moderate severity (asthenia, lumbo-pelvic pains, shivers and
300 headaches), with no impact on study continuation or on the treatment. Two moderate events (1
301 vomiting in the SP-IPTp arm and 1 pruritus in the CTX arm) were considered to be related to the
302 study treatment, resulting in its early discontinuation.
303 Six serious adverse pregnancy outcomes, all unrelated to the study medication, were reported: 3 in
304 the SP-IPTp arm (2 miscarriages and 1 stillbirth) and 3 in the CTX arm (1 miscarriage, 1 stillbirth, and 1
305 neonatal death), resulting in an early termination of the study. All 6 women were discharged safely
306 from the maternity.
307
308 **Discussion**
309 This study assessed the effectiveness of CTX for preventing malaria and its safety in pregnant women
310 infected with HIV. It was conducted at a time and location where both CTX and SP-IPTp were
311 recommended for preventing malaria among pregnant HIV-positive women. Since then,
312 recommendations have changed. However, very few randomized trials seeking to determine the
313 protective efficacy of daily CTX on malaria among pregnant women have been performed. In a
314 randomized non-inferiority trial conducted in Togo among HIV type 1-infected pregnant women with
315 CD4 count ≥ 200 /mm^3, Klement *et al*. concluded that daily CTX was not non-inferior to SP-IPTp for
316 preventing maternal malaria, but it was safe, and no differences between arms regarding placental
317 malaria and birth outcomes were in evidence [24]. These conclusions should be interpreted with
318 caution, because the sample size was low and could not demonstrate the non-inferiority at a margin
319 as high as 12%. In addition, secondary endpoints, including incidence of clinical malaria during
320 pregnancy and safety, did not lend support for favor using CTX for this population [25]. In Benin,
321 between 2009 and 2011, Denoeud-Ndam *et al*. conducted two randomized controlled trials among
322 HIV-infected pregnant women [26]. The first, carried out in women with CD4 < 350 cells/mm^3,
323 demonstrated the non-inferiority of CTX alone versus CTX plus IPTp with mefloquine (MQ) on
324 microscopic placental malaria, but placental malaria detected by PCR was significantly reduced in the
325 CTX+MQ-IPTp arm. In the second trial, conducted among 140 pregnant women with CD4 count > 350
326 cells/mm3, the authors could not conclude to the non-inferiority of CTX alone versus MQ-IPTp alone
327 because of the study's small sample size. Finally, in Malawi, Kapito-Tembo *et al*. showed that daily
328 CTX was associated with reduced maternal malaria parasitemia and anemia compared with SP-IPTp
329 [27]. Causal inferences, however, could not be made from these findings because of the study's
330 cross-sectional design.

331 Overall, there is little evidence of the efficacy of CTX alone in preventing malaria during pregnancy
332 among HIV-positive women. In the present study, we showed that the proportion of women with

333 placental *Plasmodium falciparum* infection was lower with CTX than with SP-IPTp, but the difference
334 was not statistically significant. Moreover, we did not find that the median birthweight or the
335 percentage of low birthweight (< 2500 g) new-borns were statistically different between the two
336 arms. Almost 90% of women in the SP-IPTp arm received at least three doses during pregnancy. Self-
337 reported compliance to CTX prophylaxis was very good, since women declared a median of 30 tablets
338 taken each month. This figure does not differ substantially from results reported in a Tanzanian
339 study, in which only 16.7% of pregnant women reported poor adherence to CTX or in a Beninese
340 clinical trial, where under 10% of pregnant women were non-adherent to CTX [25,27]. Despite the
341 difficult context and social disturbances in which our study took place, compliance of women to a
342 daily CTX prophylaxis was high. Use of a telephone reminder system for maternity appointments may
343 have contributed to the good compliance of women with treatment. In addition, compliance was
344 evaluated accurately at each monthly follow-up visit based on the remaining tablets.

345 There was a low overall rate of adverse events. These events were similar in the two arms, and most
346 were mild, with no impact on the treatment continuation. There were few severe adverse events.
347 This finding corroborates those of other studies on the safety of CTX during the second and third
348 trimesters of pregnancy in HIV-infected women [26,28]. In a phase 3b randomized controlled trial,
349 Manyando et *al*. found that exposure to daily CTX in pregnancy may not be associated with particular
350 safety risks in terms of birth outcomes [29].

351 Unexpectedly, the median CD4+ count at delivery was higher in the CTX arm (645 cells/mm3) than in
352 the SP-IPTp arm (549 cells/mm3), although the difference was not statistically significant. This
353 difference cannot be explained by a difference at baseline, or by a difference in ARV compliance, self-
354 reported as very good in both arms. Good compliance was also confirmed by the fact that no child
355 was found to be HIV-infected at birth. Unfortunately, HIV viral load, initially planned for this study,
356 could not be performed because of technical issues.

357 The initially planned number of pregnant women for this study, i.e. 300 women total, could not be
358 achieved during the expected period. This limitation occurred primarily because of a worsening
359 socio-political crisis in the Central African Republic. Since December 2012, the country has undergone
360 a severe military and political crisis, causing general insecurity throughout the country and severe,
361 chronic disruptions of the public health system, including the antenatal and maternity health care
362 services. Hence, a substantial number of pregnant women in the study delivered at home or were
363 lost to follow up. For this reason, the trial was prematurely terminated without being able to reach
364 the targeted number of pregnant women. We are therefore unable to provide a definitive answer to
365 the primary endpoint or to the secondary ones about prophylaxis with CTX. Another limitation is the
366 absence of placental histopathology, a more sensitive method to measure placental malaria.

Conclusion

Our results do not support the conclusion that CTX is more effective than three doses of SP-IPTp in preventing malaria during pregnancy among HIV-infected women with CD4+ counts $\geq$ 350 cells/mm3. Our sample size was smaller than expected, which may have resulted in a loss of power. Current WHO recommendations are based on the universal use of CTX prophylaxis for all HIV-infected pregnant women, regardless of CD4 count. Ongoing trials will conclude on the effectiveness of CTX, alone or in combination with an IPTp, in protecting pregnant women from malaria [30-31]. Our reassuring results regarding the drug safety and good compliance of women to CTX, however, are arguments supporting its widespread use among HIV-infected pregnant women, as the WHO currently recommends.

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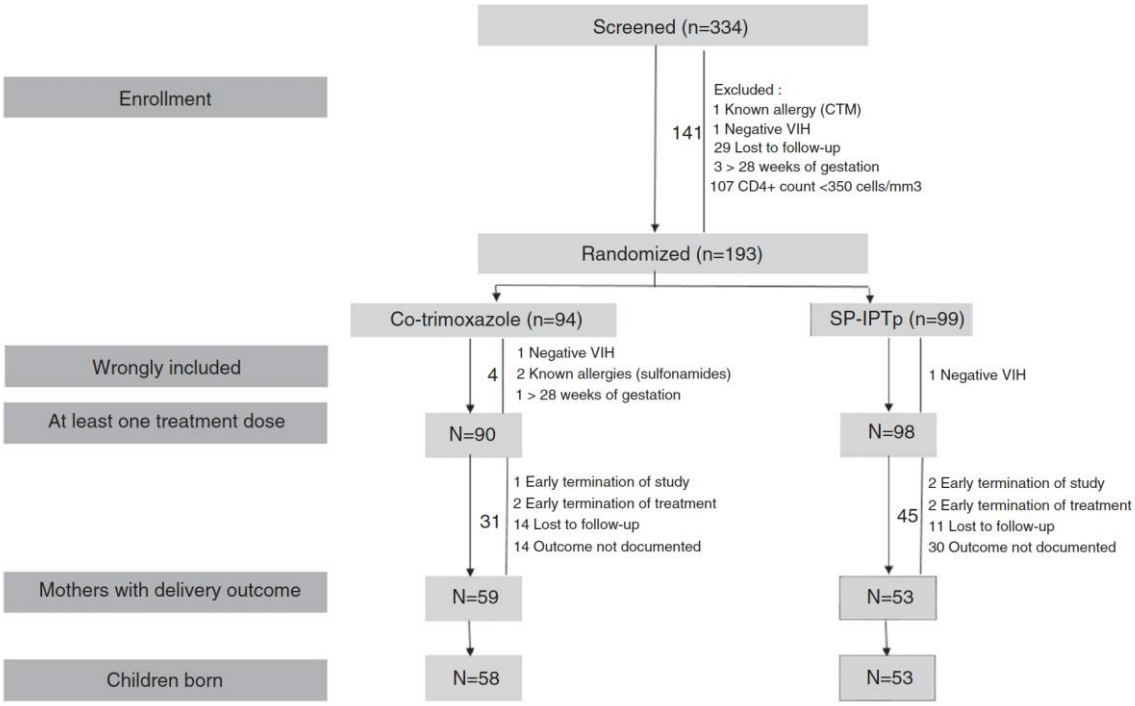

FIGURE 1 Study flow chart

TABLE 1 Baseline characteristics of the 188 randomised women

	Total (*N* = 188)	CTX group (*N* = 90)	SP-IPTp group (*N* = 98)
	N (%)	*N* (%)	*N* (%)
Age (years)[a]	28 (24–33)	26.5 (23–32)	30 (26–33)
Maternity hospitals			
Hopital communautaire	32 (17)	13 (15)	19 (19)
Hopital de l'Amitié	61 (33)	28 (31)	33 (34)
Centre de santé des Castors	57 (30)	29 (32)	28 (29)
Maternité du camp Henry Izamo	38 (20)	20 (22)	18 (18)
Obstetrical history			
Primigravidae	16 (9)	7 (8)	9 (9)
Previous alive born children[a]	2 (1–3)	1 (1–3)	2 (1–3)
At least one previous stillbirth (Missing = 1)		9 (10)	10 (10)
At least one previous miscarriage (Missing = 1)	88 (47)	47 (52)	41 (42)
Clinical characteristics			
Gestational age at inclusion[a] (Missing = 2)	21 (18–25)	21 (18–24)	21 (18–26)
Length of duration since HIV diagnosis (days)[a] (Missing = 7)	15 (8–38)	15.5 (8–40)	13 (8–36)
CD4+ count (cells/mm^3)[a] (Missing = 4)	526 (440–661)	516 (432–644)	543 (445–665)
Haemoglobin (g/dl)[b]	11.1 ± 8.1	11.2 ± 8.1	11.1 ± 8.1
Anaemia (Hb < 10 g/dl)	77 (41)	37 (41)	40 (41)
Pathology during pregnancy[c]	19 (10)	8 (9)	11 (11)
Medical history[d]	41 (22)	11 (12)	30 (31)
≥1 malarial episode(s) reported during current pregnancy before randomisation	103 (55)	52 (58)	51 (53)
If yes: number of malaria episodes[a]	2 (1–3)	2 (1–2.5)	2 (1–3)

[a]Median (IQR).
[b]Mean ± SD.
[c]Declared by women: oedema of the lower limbs, high blood pressure, gestational diabetes, albumin in urine and glycosuria.
[d]Sickle cell disease, known diabetes, high blood pressure and obesity.

TABLE 2 Baseline and delivery characteristics in the 112 women with a documented primary outcome

	Total of mothers with outcome $n = 112$	CTX arm $n = 59$	SP-IPTp arm $n = 53$	
Baseline characteristics	*N* (%)	*N* (%)	*N* (%)	*p*-value
Age (years)[a]	29 (24–34)	27 (24–33)	30 (26–34)	0.08
Maternity hospitals				
Hôpital communautaire	21 (18.7)	8 (13.6)	13 (24.5)	0.44
Hôpital de l'Amitié	40 (35.7)	21 (35.6)	19 (35.8)	
Centre de santé des Castors	33 (29.5)	20 (33.9)	13 (24.5)	
Maternité du camp Henry Izamo	18 (16.1)	10 (16.9)	8 (15.1)	
Primigravidae	10 (8.9)	4 (6.8)	6 (11.3)	0.51
CD4+ count at inclusion (cells/mm^3)[a] (Missing = 4)	520 (447–675)	510 (433–666)	540 (453–683)	0.48
≥1 malarial episode(s) reported during current pregnancy before randomisation	64 (58)	36 (61)	28 (55)	0.52
If yes: number of malaria episodes[a]	2 (1–3)	2 (1–2.5)	2 (1–3)	0.91
Delivery characteristics				
Gestational age at delivery[a] (weeks)	39 (38–40)	39 (38–40)	39 (38–40)	0.86
Place of delivery				
Maternity clinic	111 (99)	58 (98)	53 (100)	0.99
At home	1 (1)	1 (2)	0 (0)	
Pregnancy outcome				
Stillbirth	2 (2)	1 (2)	1 (2)	
Live birth[b]	111 (98)	58 (98)	53 (98)	
Mode of delivery				
Caesarean section	7 (6)	4 (7)	3 (6)	0.99
CD4+ count at delivery (cells/mm^3)[a] (Missing = 2)	595 (430–830)	645 (423–832)	549 (437–810)	0.48
Anaemia (Hb < 10 g/dl)	20 (18)	11 (19)	9 (17)	0.82

[a]Median (IQR).
[b]Including two twins.

TABLE 3 Characteristics of the 111 newborns

	Total $n = 111$	CTX arm $n = 58$	SP-IPTp arm $n = 53$	
	N (%)	*N* (%)	*N* (%)	*p*-value
Status of newborn at discharge				
Alive	110 (99)	57 (98)	53 (100)	0.52
Neonatal death[a]	1 (1)	1 (2)	0 (0)	
Sex (Female)	48 (43)	26 (45)	22 (42)	0.72
Number of newborns				
Single	109 (98)	58 (100)	51 (96)	0.13
Twins	2 (2)	0 (0)	2 (4)	
Premature birth (<37 weeks of amenorrhea)	13 (12)	5 (9)	8 (15)	0.38
Birthweight (g)[b]	3000 (2800–3300)	3000 (2750–3300)	3000 (2850–3300)	0.52
Birthweight (g)[c]	3000 (2750–3300)	3000 (2700–3300)	3000 (2750–3400)	0.77
Low birthweight (<2500 g)	8 (7)	4 (7)	4 (7)	0.89
HIV status at birth by PCR (Negative)[d]	94 (100)	50 (100)	44 (100)	-
Malaria in cord blood by RDT (Negative)[e]	100 (100)	53 (100)	47 (100)	-

[a]1 day after birth.
[b]Median (IQR).
[c]Including 26 additional children to undocumented mothers for the primary end point.
[d]Missing data $n = 17$.
[e]Missing data $n = 11$.