

# Effectiveness of Co-trimoxazole to Prevent *Plasmodium falciparum* Malaria in HIV-Positive Pregnant Women in Sub-Saharan Africa: An Open-Label, Randomized Controlled Trial

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**Background.** Human immunodeficiency virus (HIV) and malaria during pregnancy cause substantial perinatal mortality. As co-trimoxazole (CMX) protects children and HIV-positive adults against malaria, we compared the effectiveness of daily CMX with sulfadoxine-pyrimethamine intermittent preventive treatment (IPT-SP) on malaria risk in HIV-positive pregnant women in a *Plasmodium falciparum*-endemic African area.

**Methods.** From January 2009 to April 2011, we included in a randomized noninferiority trial all HIV type 1-infected pregnant women ( $\leq 28$  weeks' gestation, CD4 count  $\geq 200$  cells/ $\mu$ L, hemoglobin level  $\geq 7$  g/L) in 19 health centers in Togo. Women were randomly assigned to daily 800 mg/160 mg CMX, or IPT-SP. The primary outcome was the proportion of malaria-free pregnancies. Other outcomes included malaria incidence, parasitemia, placental malaria, anemia, and infants' birth weight.

**Results.** Of 264 women randomly assigned to the CMX or IPT-SP group, 126 of 132 and 124 of 132, respectively, were included in the analysis. There were 33 confirmed cases of clinical malaria among 31 women in the CMX group, and 19 among 19 women in the IPT-SP group. Ninety-five of 126 (75.4%) women in the CMX group and 105 of 124 (84.7%) in the IPT-SP group remained malaria-free during their pregnancy (difference, 9.3%; 95% confidence interval [CI],  $-.53$  to  $19.1$ , not meeting the predefined noninferiority criterion). The incidence rate in intention-to-treat analysis was 108.8 malaria episodes per 100 person-years in CMX (95% CI,  $105.4$ – $112.2$ ) and 90.1 in IPT-SP (95% CI,  $86.8$ – $93.4$ ) (not significant). Prevalence of parasitemia was 16.7% in the CMX group vs 28% in the IPT-SP group ( $P = .02$ ). Histology revealed 20.3% placental malaria in the CMX group vs 24.6% in the IPT-SP group (not significant). Grade 3–4 anemia was more frequent in the CMX group (10% vs 4%;  $P = .008$ ). No pregnant women died. Median birth weight was similar.

**Conclusions.** Daily CMX was not noninferior to IPT-SP for preventing maternal malaria but safe and at least similar regarding parasitemia or placental malaria and birth outcomes.

**Clinical Trials Registration.** ISRCTN98835811.

**Keywords.** co-trimoxazole; *P. falciparum* malaria; HIV-positive pregnant women; sub-Saharan Africa; randomized controlled trial.

The 2 leading causes of death in sub-Saharan Africa are malaria and human immunodeficiency virus (HIV)

infection [1]. Each year in Africa, 1 million HIV-infected pregnant women develop malaria, with predictable health consequences for them and their children [2, 3].

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Prevention of *Plasmodium falciparum* malaria during pregnancy relies on intermittent preventive treatment with sulfadoxine-pyrimethamine (IPT-SP), which decreases the risks of placental parasitemia, anemia, and low birth weight [4, 5]. However, in Togo, IPT coverage with 2 doses of SP during pregnancy was estimated at 67.5% in 2011 [6]. In addition, pyrimethamine is contraindicated before 16 weeks of pregnancy, and IPT-SP efficacy may be impaired by the development of resistance [1].

In parallel, the World Health Organization (WHO) recommends co-trimoxazole (CMX) prophylaxis for the prevention of opportunistic infections in all HIV-infected patients with symptomatic disease or CD4 count  $\leq 350$  cells/ $\mu$ L [7]. The United Nations Joint Programme on HIV/AIDS also recommends daily prophylaxis with a double-strength tablet of CMX (ie, 800 mg sulfamethoxazole and 160 mg trimethoprim) in all HIV-infected pregnant women after the first trimester [8]. As a result, both CMX prophylaxis and IPT-SP are often prescribed in HIV-infected pregnant women in sub-Saharan African countries such as Togo, even if the coadministration is not safe for pregnant women and infants, the risk being even higher in the HIV context [9].

CMX prophylaxis also reduces the risk of malaria in adults and children in sub-Saharan Africa, even in areas of widespread antifolate resistance–mediating mutations [10, 11]. Overall, CMX's efficacy in malaria prevention varies from 35% to 99.5% depending on the area, whereas SP is believed to have 95% preventive efficacy [12]. In 2004, a WHO expert panel raised the hypothesis that CMX could prevent malaria during pregnancy in HIV-infected women [13]. In a cross-sectional study of HIV-infected pregnant women in Malawi, daily CMX was associated with reduced malaria parasitemia and decreased risk of anemia compared with IPT-SP, whereas CMX plus IPT-SP was associated with further reduction in malaria parasitemia but toxicity was not fully assessed [14]. Given the benefits of CMX in malaria prevention, the WHO experts hypothesized that IPT-SP provided no additional benefit in individuals receiving CMX prophylaxis. However, this hypothesis has not been validated.

We report the results of a randomized controlled study that compared the effectiveness of CMX with that of the standard WHO IPT-SP regimen on the prevention of malaria in HIV-infected pregnant women.

## METHODS

### Study Design

This study was an open-label, randomized, field-based noninferiority clinical trial to compare the effectiveness of CMX with that of IPT-SP during pregnancy in HIV-infected women in a *P. falciparum*–endemic sub-Saharan area. It was conducted in

19 health centers supported by the nongovernmental organization AlterSanté in 8 districts of the Plateaux Region of Togo.

The main outcome was the proportion of malaria-free pregnancy in each group. Secondary outcomes included the incidence of malaria during pregnancy (calculated as the number of malaria events per 100 person-years during time at risk, defined by the time from the day of randomization until the day of delivery, miscarriage, treatment discontinuation, or last visit if lost to follow-up), peripheral blood parasitemia in women, treatment tolerance, pregnancy outcome, birth weight, placental malarial infection, congenital malaria, and infants' survival.

Written informed consent was signed by women, or parents of females aged <18 years, before enrollment. Study ethical approval was obtained from the National Ethics Committee of Togo.

### Participants

All HIV-infected pregnant women attending antenatal services from January 2009 until April 2011 were screened. Volunteer women were eligible if only HIV type 1 (HIV-1) infection was confirmed by serology through the national HIV testing program, and if they were aged  $\geq 15$  years and had a gestation of 14–28 weeks, CD4 count  $\geq 200$  cells/ $\mu$ L, and hemoglobin (Hb) concentration  $\geq 7$  g/L. Exclusion criteria were ongoing CMX or SP treatment or allergy to CMX or SP.

### Randomization

Women were randomized (in a 1:1 ratio using centralized random allocation tables) to receive either daily 800 mg/160 mg CMX, or IPT with 1500 mg/75 mg SP (first dose at inclusion day, second dose at least 4 weeks later, third dose if possible at least 4 weeks later).

### Interventions

All pregnant women received an insecticide-treated bed net (ITN) and WHO's recommended dose of iron and folic acid supplements. Women with WHO HIV stage 1–2 with a CD4 count of  $>200$  cells/ $\mu$ L received 300 mg zidovudine (ZDV) twice daily from 28 weeks of gestation and single-dose nevirapine (NVP) at labor, and women with WHO stage 3–4 HIV received antiretroviral therapy (ART) mostly with stavudine, lamivudine, and NVP fixed-dose combination. Newborns received single-dose NVP within 48 hours after birth and ZDV for 7 days. However, the regimen was changed to WHO option A in December 2010: ART was given for all women with a CD4 count of  $<350$  cells/ $\mu$ L, other women started ZDV at 14 weeks of gestation, and infants received NVP daily until ab lactation. Feeding was maternal or artificial according to the mother's informed choice. Malaria events during pregnancy were treated

with quinine, or artemisinin-based combined treatment in case of relapse.

### Follow-up

Women underwent no-cost monthly physical examination and peripheral blood sample collection for malaria test, Hb, and leukocyte count when available. Women were assessed for adherence to treatment and ITN use and were asked to deliver in the study center. At delivery, a placenta sample was collected. Infants were evaluated for malaria within the first week of life and tested for HIV at 6 and 14 weeks.

### Definition and Laboratory

Malaria was defined as a positive biological test, a body temperature  $\geq 37.5^{\circ}\text{C}$ , and at least 1 clinical sign (asthenia, headache, myalgia, or abdominal pain). Malaria testing was performed using thick blood smears stained with 2% May-Grünwald Giemsa (parasite density was estimated by counting the number of asexual parasites per 200 leukocytes and calculating parasites per microliter assuming a leukocyte count of 8000 cells/ $\mu\text{L}$ ), or, on a few occasions when microscopy was not available, with malaria rapid diagnostic tests using histidine-rich protein 2 antigen.

Congenital malaria was defined as symptoms attributable only to malaria with evidence of ring forms of malaria parasite in the erythrocytes of the newborn within the first 7 days of life [15].

For placental histology, an approximately 3cm<sup>3</sup>-sample was removed from the maternal placenta surface in an off-center position and placed in 25 mL of 10% neutral buffered formalin. All biopsy samples were kept at room temperature until transportation to the SO Hospital in Lomé, where the histological studies were performed. The samples were then processed and embedded in paraffin wax, by standard techniques. Paraffin sections 4 mm thick were stained with hematoxylin-eosin and Giemsa. Infant HIV testing was performed using DNA polymerase Chain Reaction (BioLIMS).

### Statistical Analysis

The noninferiority criterion was defined by the upper limit of a 2-sided 95% confidence interval (CI) around the difference in malaria-free pregnancy between treatment groups  $<12\%$  according to a predefined margin for the acceptable difference [16]. Assuming a protection of 90% for both CMX and IPT-SP, the number of patients required was 132 in each study group to establish noninferiority with 90% power.

Statistical analysis was performed with Stata software, version 10. To investigate potential differences at baseline characteristics between groups, variables were summarized as frequencies and medians (range) and compared using Fisher exact test or Kruskal-Wallis test as appropriate. Data were censored

for patients who prematurely withdrew from the study (lost to follow-up before the first visit). Efficacy was evaluated by intention-to-treat (ITT) analysis, in which patients were considered to have failed treatment if they prematurely discontinued randomized treatment for any reason (miscarriage, withdrawn for intolerance, or lost to follow-up). Cumulative risks of malaria episodes after randomization were estimated with the Kaplan-Meier product limit formula, and survival curves were compared using the log-rank test. Hazard ratios for comparison of event rates, adjusted for age, marital status, occupation, gravidity, mother-to-child preventive treatment history, WHO clinical stage, and CD4 cell count, were assessed using Cox regression analysis.

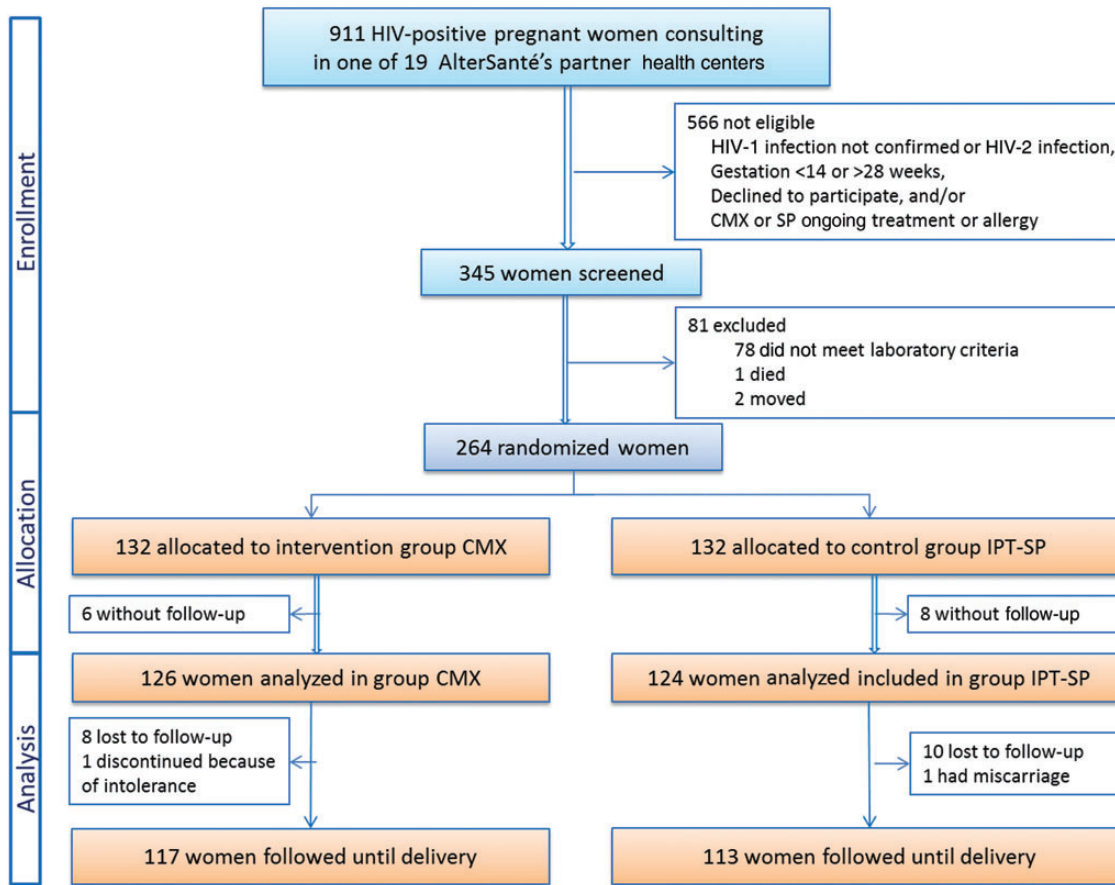
## RESULTS

Two hundred sixty-four of 345 women, screened between January 2009 and April 2011, were randomly allocated to receive daily CMX (n = 132) or IPT-SP (n = 132). Among the 264 participants randomized, 14 were excluded because they moved or were lost to follow-up. Two hundred fifty remaining women were analyzed, 126 included in the CMX group and 124 in the IPT-SP group (Figure 1). Overall, 20 women withdrew from the study before delivery, including 18 lost to follow-up (8 in the CMX group and 10 in the IPT-SP group), 1 because of intolerance in the CMX group, and 1 because of miscarriage in IPT-SP group.

No statistical difference between variables was found in the 2 groups at inclusion except in immunological and ART treatment status with lower median CD4 counts (391 cells/ $\mu\text{L}$  [range, 200–1150 cells/ $\mu\text{L}$ ] vs 467 cells/ $\mu\text{L}$  [range, 200–1988 cells/ $\mu\text{L}$ ];  $P = .02$ ) and an accordingly higher proportion of women under ART in the CMX group (25.4% vs 8.9%;  $P = .001$ ) (Table 1). After discussion with the investigators, no explanation was found for this difference. Respectively, 13 430 and 11 760 days of follow-up were cumulated in the CMX and IPT-SP groups (median duration, 110 vs 92 days;  $P = .004$ ), and the proportion of patients lost to follow-up was 6.5% and 8.1% ( $P = .8$ ). ITN use and treatment adherence were  $>95\%$  in both groups.

Overall, 52 documented episodes of *P. falciparum* malaria occurred during the study period: 33 in 31 women in the CMX group and 19 in 19 women in the IPT-SP group. Ninety-five of 126 (75.4%) women in the CMX group and 105 of 124 (84.7%) in the IPT-SP group remained malaria-free during their pregnancy. The difference, 9.3% (95% confidence interval [CI],  $-.53$  to 19.1), did not meet the prespecified criterion for noninferiority because the upper limit of the CI exceeds 12%.

Regarding the secondary outcomes, 89.7 (95% CI, 88.5–89.8) malaria cases per 100 person-years occurred in the CMX group vs 59 (95% CI, 57.6–59.5) in the IPT-SP group in the per-protocol analysis (Table 2). The incidence ITT was 108.8 (95%



**Figure 1.** Flow diagram of the progress through a parallel randomized trial of 2 groups: co-trimoxazole prophylaxis and intermittent preventive treatment with sulfadoxine-pyrimethamine. In the intention-to-treat analysis, patients were considered to have failed treatment if they prematurely discontinued randomized treatment for any reason (miscarriage, withdrawn for intolerance, or lost to follow-up). Abbreviations: CMX, co-trimoxazole; HIV, human immunodeficiency virus; IPT-SP, intermittent preventive treatment with sulfadoxine-pyrimethamine.

CI, 105.4–112.2) and 90.1 (95% CI, 86.8–93.4), respectively, per 100 person-years ( $P = .2$ ). Figure 2 shows malaria-free survival curves of the 2 study groups. Asymptomatic parasitemia during pregnancy was observed 33 times in 21 women (1–4 times per woman) in the CMX group and 44 times in 35 women (1–2 times/woman) in the IPT-SP group, giving a prevalence of parasitemia of 16.7% and 28%, respectively ( $P = .02$ ). However, 66 of all the 273 malaria tests performed (24.2%) were positive in the CMX group and 63 of 253 (24.9%) in the IPT-SP group ( $P = .6$ ). Median parasite density and proportion of parasite density  $>1250$  parasites/ $\mu\text{L}$  did not differ between the 2 groups. Histology of placenta revealed placental malaria in 15 of 74 (20.3%) in the CMX group vs 14 of 57 (24.6%) in the IPT-SP group ( $P = .3$ ).

Three and 1 skin reactions were reported in the CMX and IPT-SP groups, respectively, and only 1 woman was withdrawn from the study for intolerance (grade 3 skin allergy in the CMX

group). There were significantly more women with anemia declared by the physicians in the CMX group (27 vs 14,  $P = .03$ ). Hb concentration was measured 289 times in the CMX group and 248 times in IPT-SP, and the median Hb level was similar in both arms (10.1 g/dL [range, 5.5–18.5 g/dL] vs 10.0 g/dL [range, 6.7–17.2 g/dL];  $P = .46$ ), but the risk of grade 3 and 4 anemia (Hb  $<8$  g/dL) was higher in the CMX group (10.0% vs 4.0%;  $P = .008$ ). Leukocyte counts were performed 237 times in the CMX group and 189 times in the IPT-SP group; the median leukocyte count was lower in the CMX group (6000 cells/ $\mu\text{L}$  vs 6600 cells/ $\mu\text{L}$ ;  $P = .01$ ), but grade 3 and 4 leukopenia ( $t < 2000$  cells/ $\mu\text{L}$ ) occurred only once in the IPT-SP group. Unexpectedly, the number of visits with reported opportunistic infections during follow-up was higher in the CMX group (in 18 and 6 antenatal consultations, respectively;  $P = .04$ ), and consisted mostly of cutaneous infections (candidiasis, zoster) or diarrhea. No pneumocystosis or toxoplasmosis infections

**Table 1. Baseline Characteristics of HIV-Infected Pregnant Women According to Co-trimoxazole Prophylaxis or Intermittent Preventive Treatment With Sulfadoxine-Pyrimethamine**

Characteristic	CMX (n = 126)	IPT-SP (n = 124)	P Value
<b>District of residence</b>			
Agou	3 (2.4)	5 (4.0)	.6
Amou	12 (9.5)	8 (6.5)	
Avé	6 (4.8)	5 (4.0)	
Dayes	4 (3.2)	5 (4.0)	
Est-Mono	1 (0.8)	0 (0.0)	
Haho	6 (4.8)	12 (9.7)	
Kloto	42 (33.3)	46 (37.1)	
Ogou	52 (41.3)	43 (34.7)	
Married	115 (93.5)	110 (89.4)	.2
<b>Occupation</b>			
Salaried worker	38 (31.4)	34 (27.9)	.9
Self-employed craft or sales worker	45 (37.2)	48 (39.3)	
Farmer	7 (5.8)	8 (6.7)	
Unemployed/housewife/student	31 (25.6)	32 (26.2)	
Age, y, median (range)	28 (17–43)	28 (15–40)	.8
Gravidity, median (range)	3 (1–8)	2 (1–8)	.4
Primigravidae women	28 (22.2)	37 (29.8)	.2
Weeks of pregnancy, median (range)	22.0 (14–28)	24.0 (14–28)	.08
MTCPT history	13 (10.3)	8 (6.4)	.4
<b>WHO HIV clinical stage</b>			
Stage 1	115 (91.3)	115 (92.7)	.9
Stage 2	6 (4.8)	5 (4.0)	
Stage 3	5 (4.0)	4 (3.2)	
Stage 4	0 (0.0)	0 (0.0)	
Weight, kg <sup>a</sup> , median (range)	60.5 (47–98)	62.0 (47–91)	.5
<b>CD4 count, cells/μL</b>			
200–349	53 (42.1)	29 (23.4)	.006
350–499	29 (23.0)	42 (33.9)	
≥500	44 (34.9)	53 (42.7)	
Hb level, g/dL, median (range)	9.8 (7–18.5)	9.9 (7–14)	.9
Insecticide-treated bednet use	95.8	94.2	.3
<b>Antiretroviral drug use</b>			
MTCPT	94 (74.6)	113 (91.1)	.001
ART	32 (25.4)	11 (8.9)	

Data are presented as No. (%) unless otherwise specified.

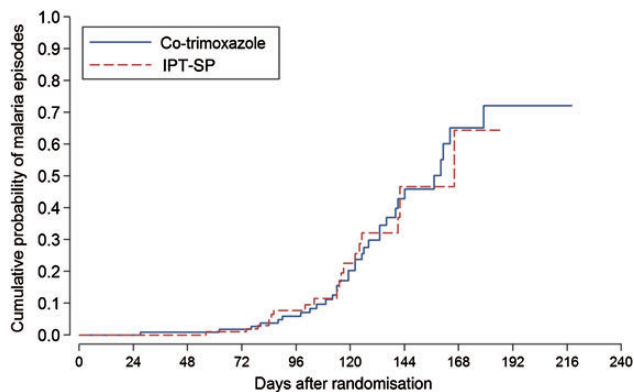
Abbreviations: ART, combined antiretroviral therapy; CMX, co-trimoxazole; Hb, hemoglobin concentration; HIV, human immunodeficiency virus; IPT-SP, intermittent preventive treatment with sulfadoxine-pyrimethamine; MTCPT, mother-to-child preventive treatment; WHO, World Health Organization.

<sup>a</sup> Values are missing for 6 patients in the CMX group and 5 patients in the IPT-SP group.

were diagnosed, and no women died during pregnancy or at delivery. One woman died 12 days after delivery with cachexia, fever, and hemoptysis in the CMX arm.

As shown in Table 3, the outcome of the pregnancies was good with 230 deliveries and 231 live infants (117 in the CMX group and 114 in the IPT-SP group), including 8 pairs of twins (4 in each group). There was no difference regarding miscarriage (0 in the CMX group vs 1 in the IPT-SP group), stillbirths

(4 vs 3), proportion of cesarean deliveries (21.4% vs 16.8%), preterm births ( $\leq 34$  weeks of gestation: 18 in CMX vs 16 in IPT-SP), and malformations (1 polydactylia in each group). Birth weight was similar; in 115 live newborns with known body weights, the median birth weight was 2900 g (range, 1950–3900 g) in the CMX group, vs 2800 g (range, 1530–4200 g) in 112 live newborns in the IPT-SP group ( $P = .7$ ). The proportion of low birth weight (LBW; defined as weight  $< 2500$  g) was



**Figure 2.** Time to first malaria episode among 250 human immunodeficiency virus–infected pregnant women randomized to co-trimoxazole or intermittent preventive therapy with sulfadoxine-pyrimethamine. Abbreviation: IPT-SP, intermittent preventive treatment with sulfadoxine-pyrimethamine.

19.8% in the CMX group and 17.0% in the IPT-SP group ( $P = .6$ ). Twelve congenital malaria cases were reported in the CMX group and 13 in the IPT-SP group ( $P = .5$ ). Infant survival was similar in both groups: at 1 month, 112 of 117 infants were alive, 2 had died (1 with LBW and 1 HIV infected), and 3 were lost to follow-up in the CMX group (98.2%; ITT = 95.7%), whereas in the IPT-SP group, 113 of 114 were alive and 1 was lost to follow-up (100%; ITT = 99.1%). At 3 months, 80 babies were alive, 2 had died, and 35 were lost to follow-up in the CMX group (96.5%; ITT = 68.4%), whereas 75 babies were alive, 1 (HIV infected) had died, and 38 were lost to follow-up in the IPT-SP group (99.1%; ITT = 66.4%).

In the CMX group, 9.5% of the infants were artificially fed; this was 15.2% in IPT-SP group ( $P = .2$ ). The HIV transmission rate at 6 weeks was similar in both groups (5.6% vs 5.5%;  $P = .97$ ). The HIV prevalence decreased over time; of 12 HIV-infected infants, 8 were born in 2009, 3 in 2010, and 1 in 2011.

## DISCUSSION

Noninferiority of CMX prophylaxis to the gold standard, IPT-SP, on clinical malaria prevention in HIV-infected pregnant women was not demonstrated with a predefined 12% margin, possibly because of a too-small sample size. The discrepancies in CD4 count or ART coverage at baseline (despite randomization) could also lead to differential susceptibilities to *P. falciparum*. Nevertheless, the malaria incidence rate during pregnancy did not significantly differ in per-protocol and ITT analysis, even after adjusting for confounders, and there was no significant difference in the malaria-free survival curves between the 2 study groups. Also, there was a tendency toward more

asymptomatic parasitemia in the IPT-SP group and no difference in placental malaria.

WHO recommends the administration of at least 2 IPTs in pregnant women and 4 antenatal consultations during pregnancy to allow the administration of 3 IPTs in areas of high HIV prevalence [4]. Unfortunately, only 68% of women in sub-Saharan Africa actually receive an antenatal consultation; 95% of these attend at least 2 consultations and only 60% attend 4. Moreover, all pregnant women with a CD4 count <200 cells/ $\mu$ L should receive daily CMX.

Togo is a high malaria transmission area with >750 cases per 1000 population (100% *P. falciparum*) [17]. At the community level, 62% of the children <5 years showed parasitemia, and 21% anemia (Hb level <8.0 g/dL), with a peak prevalence in children aged 6–17 months, and a strong correlation with parasitemia [18]. SP treatment failure after 28 days of follow-up was estimated in 2003 at 30% in the area where our study took place [19]. Cross-resistance between CMX and SP has been demonstrated in vitro. However, it has not yet been demonstrated that CMX prophylaxis reduces the efficacy of SP [20]. In Kenya, SP use in pregnancy only played a minor role in the increased drug-resistant parasites in pregnant women over time [21].

Histology revealed a placental malaria rate of 20.3% in the CMX group and 24.6% in the IPT group (not significant). Placental histology is more sensitive than peripheral blood examination in detecting malarial infection during pregnancy, and could be more appropriate to evaluate malaria prevention strategies as it is directly linked to the fetus and highly correlated with late peripheral infections, which are the most dangerous for infants [22]. In previous studies, placental malaria rates vary from 14.1% to 40% [23]. SP has blood and some tissue schizonticidal activity against *P. falciparum* and has a plasma half-life of approximately 96 hours, but an Ugandan study also found no difference in prevalence of placental malaria in HIV-infected pregnant women receiving CMX or HIV-negative pregnant women receiving IPT-SP [24]. In Zambia, a mesoendemicity area, monthly IPT-SP was not more efficacious than the standard 2-dose regimen for the prevention of placental malaria or adverse birth outcomes [25].

In our study, CMX prophylaxis was safe. However, if median Hb did not decrease from baseline during follow-up, 10% maternal anemia was reported with CMX vs 4% with IPT-SP, suggesting a greater hematotoxicity. Maternal anemia in HIV/malaria coinfection is multifactorial but strongly associated with higher morbidity and mortality during pregnancy and in infants [1]. There was also a lower median leukocyte count but no severe leukopenia in the CMX group. Significantly more (mostly minor) opportunistic infections occurred in the CMX group. Again, these findings could have been biased by differences in immunological and ART status at baseline. No women died.

**Table 2. Effectiveness and Safety of Co-trimoxazole Prophylaxis or Intermittent Preventive Treatment With Sulfadoxine-Pyrimethamine in HIV-Positive Pregnant Women**

Results	CMX (n = 126)	IPT-SP (n = 124)	P Value
Duration of follow up, d, median (range)	110 (2–218)	92 (28–188)	.004
Number of ANC visits, median (range)	3 (1–6)	2 (0–5)	.3
Lost to follow-up	8 (6.4)	11 (8.9)	.4
<b>Efficacy</b>			
Women with at least 1 clinical malaria episode (per protocol)	31 (24.6)	19 (15.3)	.07
Women with at least 1 clinical malaria episode (ITT)	40 (31.7)	29 (23.4)	.1
Clinical malaria episodes per 100 person-years, No. (95% CI) (per protocol)	89.7 (88.5–89.8)	59.0 (57.6–59.5)	.07
Clinical malaria episodes per 100 person-years, No. (95% CI) (ITT)	108.8 (105.4–112.2)	90.1 (86.8–93.4)	.22
Adjusted clinical malaria rate per 100 person-years, No. (95% CI) (ITT)	108.8 (105.4–112.2)	90.1 (86.8–93.4)	.2
Women with at least 1 asymptomatic parasitemia episode	21 (16.7)	35 (28.2)	.02
Positive malaria test	66 (24.2)	63 (24.9)	.4
Parasite density/μL, median (range)	320 (30–97 850)	390 (40–96 000)	.4
Parasite density >1250 parasites/μL	13 (15.8)	11 (13.8)	.7
Placental malaria infection, no./No. analyzed	15/74 (20.3)	14/57 (24.6)	.3
<b>Safety</b>			
Cutaneous reaction	3 (2.4)	1 (0.8)	.6
Grade 3 and 4 cutaneous reaction	1	0	. . .
Anemia declaration by physicians	27 (21.4)	14 (11.4)	.03
Hb, g/dL, median (range)	10.1 (5.5–18.5)	10.0 (6.7–17.2)	.5
Grade 3 and 4 anemia (Hb <8 g/dL)	29 (10.0)	10 (4.0)	.008
Leukocyte count, cells/μL, median (range)	6000 (2800–20 200)	6600 (1050–34 000)	.01
Grade 3 and 4 leukopenia (leukocyte count <2000 cells/μL)	0	1	.4 <sup>a</sup>
Opportunistic infections declared in ANC visits, no./No. of ANC visits	18/399 (4.8)	6/368 (1.7)	.04

Data are presented as No. (%) unless otherwise specified.

Abbreviations: ANC, antenatal consultation; ART, combined antiretroviral therapy; CI, confidence interval; CMX, co-trimoxazole; Hb, hemoglobin concentration; IPT-SP, intermittent preventive treatment with sulfadoxine-pyrimethamine; ITT, intention-to-treat; MTCPT, mother-to-child preventive treatment.

<sup>a</sup> Fisher exact test.

Prematurity, stillbirths, and LBW were similar between the CMX and IPT-SP groups. Mean birth weights were comparable to those of the general population in the area. LBW is a main indicator of the consequence of gestational malaria, but both HIV and malaria are associated with increased risk of LBW as well as anemia. In Malawi, HIV was associated with a 3.1-fold increased risk of LBW, and having  $\geq 3$  episodes of peripheral parasitemia with a 2.7-time increased risk of LBW [26]. In a retrospective study of CMX prophylaxis in pregnant HIV-infected women with CD4 counts <200 cells/μL in Zambia, the percentage of preterm births was lower (odds ratio, 0.49) after CMX prophylaxis was introduced than before; there was a significant decrease in neonatal mortality (9% to 0%) and a trend toward increased birth weight [27].

In our findings, the HIV transmission rate (5.5%) was similar in both groups with no difference according to primigravidae, parasitemia, or placental malaria. Concomitant malaria could be responsible for increased mother-to-child transmission of HIV (MTCT) [28]. The weighted summary

relative risk for MTCT in 3 studies that provided numerator and denominator was estimated at 0.79, whereas in a randomized placebo-controlled trial in women receiving single-dose NVP in Mozambique, 2-dose IPT-SP did not have a significant impact on MTCT (11.8% vs 13.2%) or on maternal HIV RNA level [29, 30]. However, in Rwanda, placental malaria was associated with a 6.3 times increased risk of MTCT, especially among primigravidae women [31].

Lack of sustainable funding for the research and the African rural context were the major difficulties. Study duration was extended because fewer women than expected met the inclusion criteria (many consulting too late during their pregnancy), and inclusions were sometimes delayed by laboratory reagents' shortages. Limitations of our study also include missing data for biological and placental analysis and infants' survival, and the fact that for ethical reasons we had to limit the study to women with CD4 counts of  $\geq 200$  cells/μL.

In conclusion, daily CMX prophylaxis could be an alternative to the gold standard, IPT-SP, for preventing malaria

**Table 3. Birth Outcome and Infants' Survival According to Co-trimoxazole Prophylaxis or Intermittent Preventive Treatment With Sulfadoxine-Pyrimethamine During Pregnancy in HIV-Positive Women**

Birth Outcome/Survival	CMX	IPT-SP	P Value
Delivery	117	113	
Time of birth, wk, median (range)	39 (32–42)	39 (31–44)	.3
Cesarean delivery	25 (21.4)	19 (16.8)	.4
Premature birth	18 (15.4)	16 (14.2)	.8
Twins	4	4	NS
Stillbirth	4 (3.3)	3 (2.6)	.7
Infants born alive	117	114	
Birth weight, g, median (range) <sup>a</sup>	2900 (1950–3900)	2800 (1530–4200)	.7
Birth weight <2500 g <sup>a</sup>	23 (19.3)	19 (17.0)	.6
Congenital malaria reported	12 (10.3)	13 (11.4)	.5
Infant survival at 1 month in ITT	112 (95.7)	113 (99.1)	.4
Infant survival at 3 months in ITT	80 (68.4)	75 (66.4)	.6
Artificial feeding <sup>b</sup>	11 (9.5)	17 (15.2)	.2
HIV infection at 6 weeks, no./No. PCR performed	6/107 (5.6)	6/109 (5.5)	.9

Data are presented as No. (%) unless otherwise specified.

Abbreviations: CMX, co-trimoxazole; IPT-SP, intermittent preventive treatment with sulfadoxine-pyrimethamine; ITT, intention-to-treat; NS, not significant; PCR, polymerase chain reaction.

<sup>a</sup> Two missing data in each group.

<sup>b</sup> One missing data in the CMX group and 2 missing data in the IPT-SP group.

maternal–infant complications in HIV-infected pregnant women. These findings need to be confirmed by further research to better inform national and international guidelines and apply to 1 million HIV-infected pregnant women each year in Africa.

## Notes

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## References

- Klement E. Paludisme et infection par le VIH en Afrique subsaharienne. Mise au point. *La Lettre de l'Infectiologue* **2008**; 23:42–9.
- Ter Kuile FO, Parise ME, Verhoeff FH, et al. The burden of co-infection with human immunodeficiency virus type 1 and malaria in pregnant women in sub-saharan Africa. *Am J Trop Med Hyg* **2004**; 71(2 suppl):41–54.
- Brentlinger PE, Behrens CB, Micek MA. Challenges in the concurrent management of malaria and HIV in pregnancy in sub-Saharan Africa. *Lancet Infect Dis* **2006**; 6:100–11.
- World Health Organization. Integrated management of pregnancy and childbirth. Pregnancy, childbirth and postpartum care. A guide for essential practice. Geneva, Switzerland: WHO, **2006**. Available at: [http://whqlibdoc.who.int/publications/2006/924159084X\\_eng.pdf](http://whqlibdoc.who.int/publications/2006/924159084X_eng.pdf). Accessed 4 February 2013.
- van Eijk AM, Nahlen BL, ter Kuile FO, et al. Effectiveness of intermittent preventive treatment with sulphadoxine-pyrimethamine for control of malaria in pregnancy in western Kenya: a hospital-based based study. *Trop Med Int Health* **2004**; 9:651–60.
- Programme National de Lutte contre le Paludisme. NLP. Rapport annuel d'activités 2010. Lomé, Togo: Direction Generale de la Sante Direction des Soins de Sante Primaires, **2010**.
- World Health Organization. Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults. Recommendations for a public health approach 2006. Available at: <http://www.who.int/hiv/pub/guidelines/ctxguidelines.pdf>. Accessed 4 February 2013.
- Joint United Nations Programme on HIV/AIDS. Provisional WHO/UNAIDS Secretariat recommendations on the use of cotrimoxazole prophylaxis in adults and children living with HIV/AIDS in Africa, **2000**. Available at: [http://data.unaids.org/publications/IRC-pub04/recommendation\\_en.pdf](http://data.unaids.org/publications/IRC-pub04/recommendation_en.pdf). Accessed 4 February 2013.
- Eliaszewicz M, Flahault A, Roujeau JC, Chosidow O, Caumes E. Prospective evaluation of risk factors of cutaneous drug reactions to sulfonamides in patients with AIDS. *J Am Acad Dermatol* **2002**; 47:40–6.
- Kanya MR, Gassasira AF, Achan J, et al. Effects of trimethoprim-sulfamethoxazole and insecticide-treated bednets on malaria among HIV-infected Ugandan children. *AIDS* **2007**; 21:2059–66.
- Sandison TG, Homsy J, Arinaitwe E, et al. Protective efficacy of cotrimoxazole prophylaxis against malaria in HIV exposed children in rural Uganda: a randomised clinical trial. *BMJ* **2011**; 342:d1617.



12. Mermin J, Ekwaru JP, Lietchy C, et al. Effect of co-trimoxazole prophylaxis, antiretroviral therapy, and insecticide-treated bednets on the frequency of malaria in HIV-1 infected adults in Uganda: a prospective cohort study. *Lancet* **2006**; 367:1256–61.
13. WHO/Roll Back Malaria. Malaria and HIV interactions and their implications for public health policy. Report of a technical consultation. Geneva, Switzerland: WHO, **2005**. Available at: <http://whqlibdoc.who.int/publications/2005/9241593350.pdf>. Accessed 4 February 2013.
14. Kapito-Tembo A, Meshnick SR, van Hensbroek MB, Phiri K, Fitzgerald MMwapasa V. Marked reduction in prevalence of malaria parasitemia and anemia in HIV-infected pregnant women taking cotrimoxazole with or without sulfadoxine-pyrimethamine intermittent preventive therapy during pregnancy in Malawi. *J Infect Dis* **2011**; 203: 464–72.
15. Runsewe-Abiodun I, Ogunfowora O, Fetuga B. Neonatal malaria in Nigeria—a 2 year review. *BMC Pediatrics* **2006**; 6:19.
16. Campbell JD, Moore D, Degerman R, et al. HIV-infected Ugandan adults taking antiretroviral therapy with CD4 counts >200 cells/μL who discontinue cotrimoxazole prophylaxis have increased risk of malaria and diarrhea. *Clin Infect Dis* **2012**; 54:1204–11.
17. World Health Organization. World malaria report 2012. Malaria country profiles. Togo: African Region. Available at: [http://www.who.int/malaria/publications/country-profiles/profile\\_tgo\\_en.pdf](http://www.who.int/malaria/publications/country-profiles/profile_tgo_en.pdf). Accessed 4 February 2013.
18. Eliades MJ, Wolkon A, Morgah K, et al. Burden of malaria at community level in children less than 5 years of age in Togo. *Am J Trop Med Hyg* **2006**; 75:622–9.
19. World Health Organization. Global report on antimalarial drug efficacy and drug resistance: 2000–2010. Available at: [http://whqlibdoc.who.int/publications/2010/9789241500470\\_eng.pdf](http://whqlibdoc.who.int/publications/2010/9789241500470_eng.pdf). Accessed 4 February 2013.
20. Iyer JK, Milhous WK, Cortese JF, Kublin JG, Plowe CV. *Plasmodium falciparum* cross-resistance between trimethoprim and pyrimethamine. *Lancet* **2001**; 358:1066–7.
21. Iriemenam NC, Shah M, Gatei W, et al. Temporal trends of sulphadoxine-pyrimethamine (SP) drug-resistance molecular markers in *Plasmodium falciparum* parasites from pregnant women in western Kenya. *Malar J* **2012**; 11:134.
22. Cottrell G, Mary JY, Barro D, Cot M. Is malarial placental infection related to peripheral infection at any time of pregnancy? *Am J Trop Med Hyg* **2005**; 73:1112–18.
23. van Eijk AM, Ayisi JG, Ter Kuile FO, et al. HIV, malaria, and infant anaemia as risk factors for postneonatal infant mortality among HIV-seropositive women in Kisumu, Kenya. *J Infect Dis* **2007**; 196:30–7.
24. Newman PM, Wanzira H, Tumwine G, et al. Placental malaria among HIV-infected and uninfected women receiving anti-folates in a high transmission area of Uganda. *Malar J* **2009**; 8:254.
25. Nkhoma ET, Kalilani-Phiri L, Mwapasa V, Rogerson SJ, Meshnick SR. Effect of HIV infection and *Plasmodium falciparum* parasitemia on pregnancy outcomes in Malawi. *Am J Trop Med Hyg* **2012**; 87:29–34.
26. Walter J, Mwiya M, Scott N, et al. Reduction in preterm delivery and neonatal mortality after the introduction of antenatal cotrimoxazole prophylaxis among HIV-infected women with low CD4 cell counts. *J Infect Dis* **2006**; 194:1510–8.
27. Msamanga GI, Taha ET, Young AM, et al. Placental malaria and mother-to-child transmission of human immunodeficiency virus-1. *Am J Trop Med Hyg* **2009**; 80:508–15.
28. Villamor E, Msamanga G, Aboud S, Urassa W, Hunter DJ, Fawzi WW. Adverse perinatal outcomes of HIV1infected women in relation to malaria parasitemia in maternal and umbilical cord blood. *Am J Trop Med Hyg* **2005**; 73:694–7.
29. Nanche D, Lahuerta M, Bardaji A, et al. Mother-to-child transmission of HIV-1: association with malaria prevention, anaemia and placental malaria. *HIV Med* **2008**; 9:757–64.
30. Bulterys PL, Chao A, Dalai SC, et al. Placental malaria and mother-to-child transmission of human immunodeficiency virus-1 in rural Rwanda. *Am J Trop Med Hyg* **2011**; 85:202–6.
31. Ter Kuile FO, Steketee RW, Hamer DH, et al. Two-dose versus monthly intermittent preventive treatment of malaria with sulfadoxine-pyrimethamine in HIV-seropositive pregnant Zambian women. *J Infect Dis* **2007**; 196:1574–6, 1585–94.