

EFFICACY OF SULFADOXINE-PYRIMETHAMINE FOR PREVENTION OF PLACENTAL MALARIA IN AN AREA OF KENYA WITH A HIGH PREVALENCE OF MALARIA AND HUMAN IMMUNODEFICIENCY VIRUS INFECTION

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Abstract. A fever case management (CM) approach using sulfadoxine-pyrimethamine (SP) was compared with two presumptive intermittent SP treatment regimens in the second and third trimesters in pregnant primigravidae and secundigravidae in an area of intense *Plasmodium falciparum* malaria transmission in western Kenya. The investigation evaluated efficacy of the antimalarial regimens for prevention of placental malaria and examined the effect of human immunodeficiency virus (HIV) infection on antimalarial drug efficacy and adverse drug reactions. Twenty-seven percent (93 of 343) of pregnant women in the CM group had placental malaria compared with 12% (38 of 330; $P < 0.001$) of women who received two doses of SP and compared with 9% (28 of 316; $P < 0.001$) of women who received monthly SP. Fourteen percent (49 of 341) of women in the CM group delivered low birth weight (LBW) infants compared with 8% (27 of 325; $P = 0.118$) of women who received two doses of SP and compared with 8% (26 of 331; $P = 0.078$) of women who received monthly SP. Seven percent (7 of 99) of the HIV-negative women on the two-dose SP regimen had placental malaria compared with 25% (10 of 39; $P = 0.007$) of HIV-positive women on the same regimen; the rate of placental malaria in HIV-positive women was reduced to 7% (2 of 28; $P = 0.051$) for women on the monthly SP regimen. Less than 2% of women reported adverse drug reactions, with no statistically significant differences between HIV-positive and HIV-negative women. Intermittent treatment with SP is safe and efficacious for the prevention of placental malaria in pregnant primigravidae and secundigravidae in sub-Saharan Africa. While a two-dose SP regimen may be effective in areas with low HIV seroprevalence, administration of SP monthly during the second and third trimesters of pregnancy should be considered in areas of high HIV seroprevalence to prevent the effects of maternal malaria on the newborn.

In sub-Saharan Africa, pregnant women are more likely than their non-pregnant counterparts to become infected with *Plasmodium falciparum* malaria and have a higher density of parasitemia.^{1,2} In areas of high *P. falciparum* transmission, infection in pregnant women is frequently asymptomatic but can lead to parasite sequestration and altered placental integrity.^{3–5} Placental malaria is a risk factor for low birth weight (LBW),^{6–8} presumably through decreased nutrient transport across the placenta. Additionally, malaria parasitemia may contribute to maternal anemia,^{9,10} also a risk factor for LBW.¹¹ Low birth weight is the single greatest risk factor for neonatal and infant mortality.¹² In areas with high *P. falciparum* malaria transmission, where women may have substantial acquired antimalarial immunity, women in their first and second pregnancies are most at risk of malaria^{8,13} and of malaria-associated LBW.^{1,12,13}

In these same sub-Saharan African settings, human immunodeficiency virus (HIV) infection has become increasingly prevalent in women of reproductive age.^{14–16} Recent studies suggest that HIV infection may diminish a pregnant woman's capacity to control *P. falciparum* infection¹⁷ and thus may lead to decreased efficacy of antimalarial interventions. The presence of placental malaria in HIV-positive women may also increase the risk of vertical transmission of HIV.¹⁸ In addition, infection with HIV may predispose the woman to adverse events associated with sulfa-containing antimalarials. Adverse drug reactions (ADRs),¹⁹ including fatal ones,²⁰ have been reported in HIV-positive persons using sulfadoxine-pyrimethamine (SP) for prophylaxis against *Pneumocystis carinii* pneumonia. Case-fatality rates for ADRs, particularly severe cutaneous adverse reactions, have been reported to be higher after administration of drugs with

long elimination half-lives, such as SP, compared with drugs with shorter half-lives.²¹

Because of the consequences of *P. falciparum* infection during pregnancy, the World Health Organization recommends that women living in malarious areas receive chemoprophylaxis during pregnancy.²² The choice of an efficacious and safe regimen has, however, become increasingly challenging because of widespread chloroquine (CQ) resistance. In 1992, Schultz and others²³ demonstrated that two treatment doses of SP, administered once in the second and once in the third trimester, was efficacious in decreasing placental malaria in an area where persons receive, on average, 50 infective mosquito bites/year. Important remaining questions include whether such a two-dose SP regimen would be sufficiently efficacious in an area with even higher malaria transmission and where malaria transmission is less seasonal than at the Malawi study site and, additionally, whether SP would be effective in an area with a high prevalence of HIV infection.

In western Kenya, where women receive 200–300 infective mosquito bites/year,²⁴ the standard of care at the time of this study was to provide fever case management (CM), that is, antimalarial treatment for febrile episodes accompanied by parasitemia during pregnancy. In this investigation we compared CM to two presumptive intermittent SP-treatment regimens. The objectives of the study were to determine the efficacy of the different regimens in the prevention of placental malaria, to examine for adverse effects associated with SP use, and to assess the effect of HIV infection on antimalarial efficacy and ADRs.

METHODS

Study site. The study was conducted from December 1994 through July 1996 in Kisumu District in western Ke-

nya. Malaria transmission (principally *P. falciparum*, present in approximately 98% of cases, with low levels of *P. malariae* or *P. ovale*)²⁵ is highest at the end of the long rainy season which usually extends from mid-April through June. Chloroquine resistance is prevalent, with approximately 75% of *P. falciparum* infections demonstrating RII/RIII responses to a standard CQ regimen.²⁶

Enrollment. Women were enrolled in the antenatal clinics (ANCs) of the two large government hospitals, New Nyanza Provincial General Hospital and Kisumu District Hospital, in Kisumu District. Women in their first and second pregnancies presenting to the antenatal clinics who were between 16- and 26-weeks gestation were invited to participate. The study protocol was approved by institutional review boards at the Kenya Medical Research Institute (KEMRI) and at the Centers for Disease Control and Prevention (CDC).

After explanation of study procedures and collection of signed informed consent, enrolled women completed the routine ANC registration, including an abdominal/pelvic examination performed by the clinic nurse midwife. A questionnaire was administered to collect data on demographics, socioeconomic status (SES) (based on house construction), malaria symptoms, and antimalarial drug use. Addresses and contact information was collected to aid in follow-up procedures. Women who reported prior ADRs to sulfa-containing medications, or to any unknown antimalarial medication, were excluded from the study. Height, weight, and temperature were measured. A fingerstick blood sample was drawn for hemoglobin testing and for a malaria thick blood smear. Urine was collected for qualitative analysis for 4-aminoquinolones and sulfa compounds. When funding became available in June 1995, HIV counseling and testing was offered to all women enrolled.

Women were systematically assigned to receive one of three regimens using a rotating assignment based on day of clinic visit: 1) two-dose SP, with treatment doses (1,500 mg of sulfadoxine and 75 mg of pyrimethamine) at enrollment and again early in the third trimester; 2) monthly SP, with treatment doses at enrollment and then monthly through 34 weeks of gestation; or 3) CM, with SP given only to women presenting with a recent history of fever and parasitemia. Women on the CM regimen were given a treatment dose of SP if they complained of fever within the last seven days and had documented fever (axillary temperature $\geq 37.5^{\circ}\text{C}$) with any parasite count or undocumented fever and peripheral parasitemia $\geq 5,000$ parasites/ μl . All participating women were asked not to self-administer antimalarials in addition to study medication; instead they were asked to return to the study team for evaluation any time they experienced symptoms of malaria between scheduled visits. Women were given 200 mg of ferrous sulfate and 5 mg of folic acid for administration daily during their pregnancies.

Follow-up. At two and four weeks after enrollment and then monthly until delivery, women were asked about malaria symptoms and potential side effects of SP treatment, and a temperature and blood smear were taken. Hemoglobin was remeasured in the beginning of the third trimester. Women with illness or severe anemia detected at any time were referred to the hospital staff for medical care. Once available, women were offered confidential HIV testing, with pre-and post-test counseling either during their preg-

nancy or at delivery. The HIV counseling was performed by trained counselors who were fluent in the local languages (Dholuo and Kiswahili). Sulfadoxine-pyrimethamine was not administered at intervals of less than one month. The ANC records were checked before each dose to ensure that SP was not given in the last month of pregnancy. A study team member observed the ingestion of all scheduled antimalarials. Women were encouraged to deliver in the hospital and the study team assisted with transportation when needed.

Delivery. Study women presenting to the hospital for delivery were asked about recent malaria symptoms and any complications of the pregnancy. Following delivery, thick blood smears were made from maternal capillary (fingerstick) blood, the maternal side of the placenta, and from the umbilical cord. Newborns were weighed on a digital scale, accurate to the nearest gram, within 24 hr of delivery. Gestational age was determined by physical and neurologic examination, using a modified standardized Dubowitz method.²⁷ Urine was collected for antimalarial drug testing.

Infant follow-up. General health status, including examination for scleral icterus, was assessed in all newborns between three and seven days of life and again at six weeks of age. Any infant showing signs of illness was referred to the hospital or clinic and the study team assisted with transportation when needed. An attempt was made to determine the cause of any neonatal deaths by questioning the mother about premortal symptoms.

Laboratory investigations. Thick blood smears were stained with Giemsa and examined for malaria parasites. Parasites and leukocytes were counted in the same fields until 300 leukocytes or 500 parasites were counted. Parasite densities were estimated using an assumed leukocyte count of 6,000 leukocytes/ mm^3 of blood. The limit of detection was approximately 10 parasites/ mm^3 . A HemoCue[®] hemoglobin detection system (HemoCue AB, Angelholm, Sweden)²⁸ was used to measure hemoglobin. A modified Saker-Solomons test²⁹ and the method of Mount and others,³⁰ respectively, were used for the measurement of 4-aminoquinolones and sulfa compounds. Testing for HIV was done by an enzyme immunoassay (EIA) screening (Genetic System Corporation, Redmond, WA), a repeat EIA if a sample was positive, and confirmatory Western blot testing (Cambridge Biotech, Worcester, MA) if positive on both EIAs.

Definitions. Parasitemia (in peripheral, placental, or cord blood) was defined as the presence of asexual stage parasites in thick smears. Newborns weighing less than 2,500 grams were considered to be of LBW. Neonates assessed as < 37 weeks gestation at birth (using the Dubowitz score) were classified as premature. Women with hemoglobin levels less than 11 g/dL and 7 g/dL were considered to have anemia and severe anemia, respectively. Severe cutaneous adverse reactions were defined as erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis.

Statistical analysis. An intent-to-treat analysis included all women enrolled in the study. Participating women who had a placental blood smear examined and a singleton neonate's birth weight measured at hospital delivery were included in analyses of parasitemia and birth weight, respectively. Results from all study women who delivered singleton newborns were included in birth outcome and neonatal survival analyses. Women in the CM group who never re-

TABLE 1
Characteristics of women enrolled in the study*

Characteristic	Case management (n = 736)	Two-dose SP group (n = 680)	Monthly SP group (n = 661)	Total (n = 2,077)
Age (years) (\pm SD)	19.7 (\pm 3.0)	19.6 (\pm 3.1)	19.6 (\pm 2.9)	19.6 (\pm 3.0)
Member of Luo tribe (%)	73.9	74.6	74.6	74.3
Primigravida (%)	62.3	65.4	62.1	63.5
Education (% who completed primary school)	73.6	72.1	74.9	73.5
SES (% low/middle)	81.0	80.4	81.8	81.1
Married (%)	71.4	74.4	74.7	73.4
Height <150 cm (%)	1.2	0.6	1.1	1.0
Weight <50 kg (%)	5.3	5.5	5.4	5.4
Reported fever in week before enrollment (%)	38.9	36.5	36.5	37.3
Hemoglobin (g/dL) (\pm SD)	9.6 (\pm 1.9)	9.6 (\pm 1.9)	9.7 (\pm 1.9)	9.6 (\pm 1.9)
Blood smear positive (%)	44.9	45.6	45.2	45.2
HIV(+) [†] (%)	26.9	30.0	23.7	26.9

* SP = sulfadoxine-pyrimethamine; SES = socioeconomic status; HIV = human immunodeficiency virus.

[†] n = 577 (2-dose = 196, monthly = 169, case management = 212).

ceived SP were excluded from the analyses of maternal ADRs.

Differences between means were tested using one-way analysis of variance. Differences between proportions were evaluated by the chi-square or Fisher's exact tests. Logistic regression analysis using a backward selection technique was used to investigate the effect of multiple risk factors (identified from the univariate calculations of crude odds ratios) on the presence/absence of placental malaria. Since inclusion of HIV serostatus (only 577 women had HIV test results) substantially reduces the number of usable observations, regression models were derived with and without this variable. Comparisons between treatment groups were performed using a multiple comparison *t*-test to control for the increased probability of declaring false significance when testing many hypotheses on the same data set. Statistical tests were run using SAS software (SAS Inst., Cary, NC). *P* values \leq 0.05 were considered statistically significant.

RESULTS

Study population. A total of 2,077 women were enrolled in the study: 680 (33%) in the two-dose SP, 661 (32%) in the monthly SP, and 736 (35%) in the CM groups. No significant differences in age, ethnicity, parity, education, socioeconomic or marital status, maternal height or weight, HIV seropositivity, enrollment hemoglobin level, reported history of fever in the week before enrollment, or malaria parasitemia at enrollment were seen among women in the different treatment groups (Table 1).

Six hundred ninety-nine women (34%) were lost to follow-up during pregnancy because they moved out of the study area or failed to return for follow-up and the study team was unable to locate their houses. Three hundred (14%) did not deliver in the hospital while 1,078 (52%) delivered

in the hospital. Nine hundred eighty-nine (92%) of the 1,078 who delivered in the hospital had placentas collected; 713 (72%) of the 989 had been in the study for at least 60 days and had completed their assigned treatment regimen: 204 (66%) in the two-dose SP group, 209 (68%) in the monthly SP group, and 300 (92%) in the CM group. Eighty percent of women in an ANC who were offered HIV counseling and testing accepted it. Five hundred seventy-seven (28%) of 2,077 women enrolled had HIV test results; 389 (36%) of the 1,078 women delivering in the hospital had both placental and HIV test results.

Among women enrolled for a minimum of 60 days and delivering in the hospital, the mean duration of participation was 113 days. Eleven percent of all CM women received at least one dose of SP during the study. The mean interval between SP doses in the two-dose group was seven weeks (range = 4–19 weeks). Among women in the monthly group, only 20% received more than three doses of SP (17% received four doses and 3% received five doses).

Women who completed the study were more likely to be primigravidae, to have completed primary school, to be of higher SES, to weigh more than 50 kg at enrollment, and less likely to have malaria parasitemia at enrollment than women who did not deliver in hospital.

Efficacy of regimens. Peripheral parasitemia was identified in 45% of women at enrollment and rates were similar in the three treatment groups (Figure 1). Two weeks after enrollment, parasitemia was observed in less than 2% of all women in the two-dose SP and monthly SP groups, compared with 38% in the CM group (*P* < 0.001). Less than 4% of 531 women who were parasitemic at enrollment and were treated remained parasitemic at their second visit. Nineteen percent or more women in the CM group were parasitemic at each follow-up visit. The highest prevalences of parasitemia in the two-dose SP and monthly SP groups

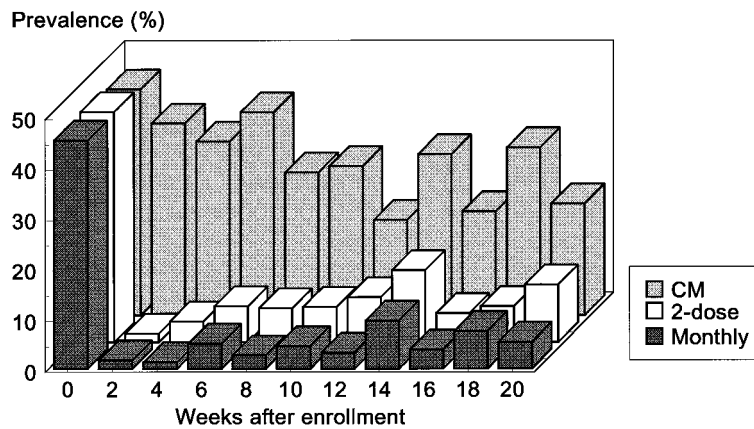


FIGURE 1. Peripheral parasitemia among women in different treatment groups during the course of study. CM = case management.

occurred at 13–14 weeks after enrollment and were 14% and 10% respectively.

In the CM group, only 20–35% of parasitemic women at each follow-up visit complained of recent fever. Compared with the CM group, in which 23–30% of the women reported fever at follow-up visits, 13–19% of the women in the monthly SP group and 15–22% of the women in the two-dose SP group reported fever at follow-up visits.

At delivery, compared with women in the CM group, women in the two-dose SP and monthly SP groups were less likely to have peripheral and placental malaria. Although differences in the incidence of LBW did not reach statistical significance, the mean birth weight of infants born to mothers in the two-dose SP and monthly SP groups was higher than that of those born to women in the CM group (Table 2). In addition, women in the monthly SP group were less likely than women in the CM group to have third trimester anemia. No significant differences were seen in the proportion of women in the three treatment groups with severe anemia, umbilical cord blood parasitemia, premature deliv-

ery, spontaneous abortion, stillbirth, or who delivered live newborns that died in the neonatal period.

Adverse events. Maternal. After the first dose of SP, there were no significant differences in the proportion of women reporting ADRs in the two-dose SP and monthly SP groups and women in the CM group who received SP (2.3%, 1.4%, and 3.3%, respectively). Overall, 1.9% and 0.3% of the women reported ADRs after the first dose and after subsequent doses, respectively. Adverse reactions included nausea, vomiting, rash, pruritus, and fatigue. One patient complained of oral lesions (without skin lesions) after taking the medication; these had resolved by the time of follow-up. Seven (0.6%) of 1,086 women were not given more SP because of ADRs (rash or oral lesions). No severe cutaneous adverse reactions were observed in 2,276 treatment episodes among 1,086 women.

Neonatal. Neonatal icterus was observed in 15% of the newborns examined between three and seven days of age (15% of those in the two-dose SP group, 14% of those in the monthly SP group, and 17% of those in the CM group).

TABLE 2
Anemia and delivery outcomes among women in different treatment groups*

Characteristic	Case management (n = 472)	Two-dose SP group (n = 432)	Monthly SP group (n = 431)
Third trimester Hb (g/dL) (\pm SD) [†]	9.9 (\pm 1.7)	10.2 (\pm 1.7)	10.4 (\pm 1.8)
Third trimester anemia (% Hg/11) [‡]	73.7	68.0	63.9
Third trimester severe anemia (% Hg < 7)	4.8	3.0	2.6
Maternal peripheral parasitemia (%) [§]	27.0	9.8	6.7
Placental malaria (%) [§]	27.1	11.5	8.9
Cord blood parasitemia (%)	3.2	2.1	0.6
Singleton BW (\pm SD) [¶]	3,079 (\pm 585)	3,183 (\pm 534)	3,198 (\pm 528)
LBW (%)	14.4	8.3	7.8
Premature delivery (<37 weeks) (%)	12.2	10.3	12.0
Spontaneous abortion (%)	2.3	1.1	2.0
Stillbirth (%)	2.1	2.6	3.7
Neonatal deaths (%)	1.2	1.3	0.3

* SP = sulfadoxine-pyrimethamine; Hb = hemoglobin; BW = birth weight; LBW = low birth weight; CM = case management.

[†] Between two-dose SP and CM ($P = 0.012$) and between monthly SP and CM ($P < 0.001$).

[‡] Between monthly SP and CM ($P = 0.017$).

[§] Between two-dose SP and CM ($P < 0.001$) and between monthly SP and CM ($P < 0.001$).

[¶] Between two-dose SP and CM ($P = 0.041$) and between monthly SP and CM ($P = 0.014$).

TABLE 3
Anemia and delivery outcomes by treatment group and HIV serostatus*

Outcome	Case management			Two-dose			Monthly		
	HIV+ (n = 40)	HIV- (n = 111)	P	HIV+ (n = 39)	HIV- (n = 99)	P	HIV+ (n = 28)	HIV- (n = 85)	P
Hb (g/dL) (±SD)	9.3 (±1.7)	9.9 (±1.7)	0.047	9.9 (±2.2)	10.4 (±1.6)	0.156	10.1 (±1.5)	10.4 (±2.1)	0.466
Anemia (% Hb < 11)	83.7	70.6	0.103	79.1	60.0	0.031	73.1	62.6	0.330
Maternal peripheral parasitemia (%) [†]	40.0	21.6	0.024	18.0	8.1	0.094	3.6	8.2	0.404
Placental malaria (%) [‡]	45.0	22.9	0.008	25.6	7.1	0.003	7.1	9.6	0.690
Singleton birth weight (grams) (±SD)	3,066 (±478)	3,150 (±522)	0.388	3,177 (±556)	3,239 (±542)	0.550	3,204 (±524)	3,296 (±479)	0.387
LBW (%)	13.2	9.4	0.519	13.2	5.1	0.110	10.7	5.7	0.360

* HIV = human immunodeficiency virus; Hb = hemoglobin; LBW = low birthweight; SP = sulfadoxine-pyrimethamine; CM = case management.

[†] HIV-positive women: monthly SP vs CM ($P = 0.001$). HIV-negative women: two-dose SP vs CM ($P = 0.024$) and monthly SP vs CM ($P = 0.062$).

[‡] HIV-positive women: monthly SP vs CM ($P = 0.002$). HIV-negative women: two-dose SP vs CM ($P = 0.007$) and monthly SP vs CM ($P = 0.076$).

Maternal consumption of at least one dose of SP, taking SP within 30 days of delivery, or detectable levels of sulfa compounds in maternal urine at delivery were not associated with icterus in the neonate.

Nine deaths (0.9%) occurred among 970 newborns (home- or hospital-delivered) followed through the neonatal period (1.3%, 0.3%, and 1.2% of neonates in the two-dose SP, monthly SP and CM groups, respectively). Of five neonates who had a history of convulsions before death (a possible sign of kernicterus), only one had neonatal jaundice; the cause of death in this neonate was reported as pneumonia.

Effect of HIV on efficacy and adverse events. *Drug efficacy.* Of the 577 women for whom HIV test results were available, 155 (27%) were HIV-positive. At enrollment, 57% of HIV-positive women were parasitemic compared with 39% of HIV-negative women ($P < 0.001$). Two weeks after enrollment, parasitemia was observed in less than 3% of both HIV-positive and HIV-negative women in the two-dose SP and monthly SP groups, compared with 52% and 36% of HIV-positive and HIV-negative women, respectively, in the CM group ($P < 0.001$ and $P < 0.001$, respectively). One (2%) of 49 HIV-positive women and three (3%) of 92 HIV-negative women who were parasitemic at enrollment and were treated remained parasitemic at their second follow-up visit. Seventeen to fifty-eight percent of HIV-positive women and 11–67% of HIV-negative women in the CM group were parasitemic at each follow-up visit. After enrollment, the highest prevalences of parasitemia in the two-dose SP group occurred at 9–10 weeks of follow-up in HIV-positive women (33%) and at 5–6 weeks of follow-up in HIV-negative women (20%). In the monthly SP group, highest prevalences of peripheral parasitemia occurred at 11–12 weeks of follow-up in HIV-positive women (5%) and at 9–10 weeks of follow-up (17%) in HIV-negative women. There were no differences between the treatment groups in proportions of women reporting fever at follow-up visits among either HIV-positive or HIV-negative women, nor differences in the pro-

portions of HIV-positive and HIV-negative women complaining of fever at follow-up visits.

Compared with HIV-negative women in the CM group, HIV-positive women had significantly lower third trimester hemoglobin levels (Table 3). In the two-dose and monthly SP groups, there was no significant difference in the prevalence of anemia between HIV-positive and HIV-negative women.

For HIV-positive women, the prevalence of peripheral parasitemia at delivery was lower in the monthly (4%) compared with the CM group (40%; $P = 0.001$). For HIV-negative women, the prevalence of peripheral parasitemia at delivery was lower in the two-dose SP and monthly SP groups (both 8%) groups compared with the CM group (40%; $P = 0.024$ and $P = 0.062$, respectively). Within treatment groups, a significant difference was seen only in the CM group, where a higher proportion of HIV-positive women (40%) had peripheral parasitemia, compared with HIV-negative women (22%; $P = 0.024$). Among HIV-positive women, the prevalence of placental malaria was lower in the monthly SP group (7%) compared with the CM group (45%; $P = 0.002$). Among HIV-negative women, the prevalence of placental malaria was similar in the two-dose SP (7%) and monthly SP (10%) groups, and higher in the CM group (22%; $P = 0.007$ and $P = 0.076$, respectively). Within treatment groups, a significant difference was seen in both the two-dose and CM groups, where a higher proportion of HIV-positive compared with HIV-negative women had placental malaria (26% versus 7%; $P = 0.003$, respectively, in the two-dose group and 45% versus 23%; $P = 0.008$, respectively, in the CM group). No significant difference was seen in the prevalence of placental malaria between HIV-positive and HIV-negative women receiving monthly SP.

If prevalences of placental malaria are stratified by both parity and HIV serostatus, a higher proportion of HIV-positive compared with HIV-negative primigravidas had peripheral (24% versus 14%, respectively; $P = 0.043$) and placen-

TABLE 4
Maternal characteristics associated with placental malaria in univariate analysis*

Characteristic	n	% placental malaria	Crude OR	95% CI	P
Treatment group					
Two-dose SP	330	11.5	0.35	0.23, 0.53	<0.001
Monthly SP	316	8.9	0.26	0.22, 0.48	<0.001
Case management	343	27.1	Ref	Ref	
Total number of doses taken					
None					
One	305	27.2	Ref		
Two	218	17.0	0.55	0.34, 0.86	0.006
Three or more	272	9.9	0.29	0.18, 0.48	<0.001
	194	6.2	0.18	0.08, 0.34	<0.001
Primary language					
Luo	715	17.6	1.56	1.04, 2.35	0.033
Other	274	12.0	Ref		
Enrollment hemoglobin					
<11 g/dL	645	17.7	1.92	1.16, 3.18	0.010
≥11 g/dL	199	10.0	Ref		
Enrollment blood smear					
Positive	410	21.0	2.11	1.47, 3.04	<0.001
Negative	510	11.2	Ref		
HIV serostatus					
Positive	107	28.0	2.44	1.43, 4.19	<0.001
Negative	291	13.8	Ref		

* OR = odds ratio; CI = confidence interval; SP = sulfadoxine-pyrimethamine; Ref = referent; HIV = human immunodeficiency virus.

tal malaria (28% versus 14%, respectively; $P = 0.013$) at delivery. In secundigravidas, the difference between HIV-positive and HIV-negative women only reached statistical significance for placental malaria (29% versus 12%, respectively; $P = 0.025$).

To more fully evaluate the reasons for the differences in the efficacy of the treatment regimens among HIV-positive compared with HIV-negative women, we examined the prevalences of placental malaria according to the total number of doses of SP received among women who had been in the study for at least 60 days and were compliant with their treatment regimen. Prevalences of placental malaria in women receiving two doses of SP compared with three or more doses of SP were 19% versus 0% ($P = 0.068$), respectively for HIV-positive women, and 8% versus 7%, respectively, for HIV-negative women.

Although differences were seen in mean birth weight and proportion of LBW between the monthly SP group compared with the two-dose SP and CM groups among HIV-positive women, and between the monthly SP and two-dose SP groups, compared with the CM group among HIV-negative women, these differences did not reach statistical significance. This is likely because the sample size of women for whom HIV test results were known limited our power to detect this difference. There were no significant differences in the proportion of premature deliveries, spontaneous abortion or stillbirths, or neonatal deaths, when stratified by HIV serostatus.

Maternal adverse drug reactions. After the first dose of SP, 3.2% of HIV-positive women reported ADRs compared with 0.4% of HIV-negative women. There were no significant differences in the proportion of women reporting ADRs in the three treatment groups (two-dose SP, monthly SP, and

treated CM groups). No women reported ADRs after subsequent doses. Two (2%) of 94 HIV-positive and none of 230 HIV-negative women had SP withheld because of ADRs (rash or oral lesions). No severe cutaneous adverse reactions were observed in 193 treatment episodes among 94 HIV-positive women and 502 treatment episodes among 230 HIV-negative women.

Characteristics associated with placental parasitemia.

Univariate analysis. Maternal characteristics associated with placental malaria (Table 4) included treatment group, total number of SP doses taken, ethnic group, hemoglobin level at enrollment, peripheral parasitemia at enrollment, and HIV serostatus. Additional characteristics examined but not found to be significant included age, parity (comparing only first and second pregnancies), compliance with treatment regimen, maternal weight at enrollment, duration of time in study, and time between last dose of SP and delivery.

Multivariate analysis. Maternal characteristics associated with placental malaria in multivariate analysis (Table 5) included total number of doses taken, peripheral parasitemia at enrollment, and HIV serostatus. Because sample size was reduced from 875 to 309 when HIV serostatus was included in the model (many women were not HIV tested), the model was also run without HIV serostatus. When HIV serostatus was excluded, characteristics associated with placental malaria were total number of doses of SP, peripheral parasitemia at enrollment, and ethnic group (belonging to the Luo tribal group).

DISCUSSION

In primigravidae and secundigravidae in western Kenya, a setting of intense malaria transmission and high prevalence

TABLE 5

Maternal characteristics associated with placental parasitemia in multivariate analysis* (n = 309)

Characteristic	% placental malaria	Adjusted OR	95% CI	P
Total number of doses taken				
None		Ref		
One	27.4	0.35	0.15, 0.82	0.016
Two	17.9	0.19	0.07, 0.49	<0.001
Three or more	8.2	0.07	0.02, 0.32	<0.001
	3.3			
Enrollment blood smear				
Positive	24.1	3.71	1.79, 7.68	<0.001
Negative	8.5	Ref		
HIV serostatus				
Positive	24.7	2.43	1.19, 4.95	0.015
Negative	11.8	Ref		

* OR = odds ratio; CI = confidence interval; Ref = referent; HIV = human immunodeficiency virus.

of HIV infection, we observed that intermittent treatment with either monthly dosing or two doses of SP in the second or third trimester of pregnancy were well tolerated and were effective in reducing the frequency of placental malaria. Overall, compared with women receiving the standard of care (CM using standard treatment with SP for fever illness and parasitemia), women receiving a presumptive intermittent treatment regimen experienced an approximate three-fold reduction in placental malaria. The prevalence of parasitemia among women receiving one of the intermittent SP regimens was 9–11%, comparable with rates measured in similar trials using effective antimalarials in pregnant women.^{23,31} However, HIV infection in these pregnant women was accompanied by somewhat higher rates of malaria infection and poorer response to antimalarial treatment.

Our previous work in western Kenya, which is consistent with the literature on malaria symptoms in pregnant women in highly endemic areas,³² has shown that a history of fever during pregnancy does not identify all pregnant women with placental malaria; 30% of women with placental malaria reported no fever at any time during pregnancy (Parise M, unpublished data). Because parasitemic women are frequently asymptomatic, not surprisingly, the use of SP for presumptive treatment was significantly better than CM.

Our observed reduction in placental malaria with presumptive intermittent SP regimens was heralded by consistently low rates of peripheral parasitemia during the second and third trimester antenatal clinic visits, again, consistent with previous studies.²³ Two weeks after enrollment, only 3.7% of the women who had been parasitemic at enrollment remained parasitemic, providing evidence that SP remains an effective drug in these women with a high degree of acquired immunity.

The HIV-positive women had a higher prevalence of peripheral parasitemia at enrollment and although a single initial dose of SP had a marked impact on peripheral parasitemia, its efficacy in clearing placental malaria was diminished in the presence of HIV infection. Steketee and others also noted higher prevalences of peripheral and placental parasitemia in HIV-positive compared with HIV-negative

pregnant women in rural Malawi.¹⁷ This difference was most marked in multigravidae, with HIV-positive multigravidae having placental malaria rates similar to primigravidae unless they received effective antimalarial therapy. One possible explanation proposed was that HIV infection interferes with the maintenance of immune recognition of malaria that develops following the first malaria-exposed pregnancy, such that HIV-positive secundigravidae and multigravidae lose this pregnancy-specific acquired immunity. In Malawi, no significant difference was seen in rates of placental malaria between HIV-positive and HIV-negative primigravidae, presumably because neither HIV-positive nor HIV-negative primigravidae had yet acquired the necessary pregnancy-specific immunity and so both groups exhibited a similar high rate of malaria infection.

It is possible that in the very high malaria transmission area in western Kenya that women receive so many infective mosquito bites that even a mild degree of impaired immunity in HIV-positive women, of any parity, could cause them to have difficulty in clearing both peripheral and placental parasitemia, and thus higher prevalences of parasitemia were also seen in HIV-positive compared with HIV-negative primigravidae. This hypothesis is supported by the finding that, while the two-dose SP regimen was efficacious in HIV-negative women, the prevalence of placental malaria in HIV-positive women (25.6%) with this regimen remained high. The HIV-positive women required at least three doses of SP to decrease prevalences of placental malaria to acceptable levels. One possible explanation for the impaired response to intermittent SP treatment seen among HIV-positive women is that the response to antimalarial drugs depends on both drug efficacy and host immunity and, during pregnancy, HIV infection impairs host immunity to malaria. In persons with a high degree of acquired antimalarial immunity, such as adults who have lived for long periods in high malaria transmission areas, drugs with poor efficacy (i.e., CQ in areas with high levels of CQ resistance) may be sufficient to clear parasitemia, whereas young children in these areas, who have not yet acquired sufficient immunity, may have high mortality rates when treated with CQ compared with more efficacious regimens.³³ If low-level resistance to SP is beginning to develop in this area, it will first be seen in those with impaired immunity, including HIV-positive pregnant women.

Another potential reason for the impaired efficacy of SP in HIV-positive women is impaired drug absorption or increased metabolism. Although other investigators have found high sulfamethoxazole levels in patients with acquired immunodeficiency syndrome being treated for *Pneumocystis carinii* pneumonia,³⁴ suggesting normal absorption of sulfonamides, no study has directly compared the pharmacokinetics in HIV-positive and HIV-negative patients.

Because not all participants completed their assigned therapy, the group of women who were in the study for at least 60 days and who completed their assigned course of therapy (i.e., were compliant) were also evaluated; women in the CM group were included in this latter analysis if they had been in the study for at least 60 days. Participation in the study for at least 60 days would allow the monthly SP group to receive three doses of medication, which would allow for differentiation of this group from the two-dose SP group,

and would provide a period of time for fetal growth when the placenta would theoretically be parasite-free under the protective antimalarial. Evaluation of the group of women who were in the study for 60 days and were compliant with their treatment regimen demonstrate essentially equivalent findings as the intent-to-treat analysis.

Steketee and others demonstrated that an efficacious antimalarial (mefloquine) that decreased the prevalence of placental malaria also decreased the incidence of LBW in a large cohort study in Malawi.³⁵ Because of the large sample sizes required to sufficiently examine the effect of a single factor on LBW and because of the demonstrated association between malaria and LBW, our study was designed to use placental malaria rates as a surrogate measure for LBW risk.

To minimize confusion at the clinic level, the allocation of subjects to treatment groups was performed in a systematic fashion based on clinic day rather than by randomized assignment. During the 16 months of study enrollment (December 1994 through March 1996) this was not expected to introduce any selection bias. As shown in Table 1, there were no differences in the characteristics of women in the different treatment groups.

Despite extensive attempts at follow-up, loss to follow-up was a concern in this investigation and occurred in part because of the highly mobile nature of this peri-urban study population. We had expected that many women would deliver at home (which eliminates the opportunity to collect the placenta and accurately measure the baby's birth weight) based on a community survey that we had previously conducted in Kisumu District where the rate of home delivery was 48% (Parise M, unpublished data). The extent to which women lost to follow-up differ from hospital-delivering women in terms of our main study outcomes, placental parasitemia and low birth weight, cannot be examined from the available data. However, since there were no differences in the rates of women lost to follow-up among the treatment groups, this is unlikely to have altered study results.

Sulfadoxine-pyrimethamine was well tolerated, with no statistically significant differences in the frequency of ADRs among HIV-positive women when compared with HIV-negative women. More importantly, even among HIV-positive women, the rate of ADRs reported remained very low (3%). No severe cutaneous adverse reactions were noted, but given their estimated incidence of one in 5,000–8,000 users, with fatal reactions in one per 11,000–25,000 users,³⁶ it is not surprising that none were seen in a study of this size. Several women were not given a second dose of SP because of reported rash after the first dose, and this aspect of the study protocol may have reduced any risk of severe cutaneous adverse reactions. As African countries move toward the use of SP for prevention of malaria in pregnant women,³⁷ and for first-line treatment of uncomplicated malaria,³⁸ it will be essential to establish mechanisms to limit repeat dosing of SP among women experiencing rash or oral lesions and to set up surveillance systems to monitor for severe ADRs. In areas with high *P. falciparum* malaria transmission, the benefit of SP in reducing malaria-associated LBW and thus, infant mortality, appears to outweigh the risk for rare, albeit serious, SP-related ADRs.

The most common concern expressed in the literature regarding the use of SP during pregnancy is a theoretical one

that its use in late pregnancy may displace bilirubin from albumin in the neonate and thus, contribute to kernicterus. This concern stems from one study that demonstrated an increased incidence of kernicterus in neonates treated with a sulfonamide, in combination with several other drugs,³⁹ but this occurrence has not been confirmed in subsequent studies.^{40,41} There has been only one case series of nine infants with hyperbilirubinemia, including one who had kernicterus⁴² after administration of sulfa drugs to the mother. Numerous other trials have failed to show adverse reactions in neonates born to mothers taking sulfonamides during pregnancy,^{43,44} including studies of women who received sulfa drugs throughout pregnancy.^{45–47} The current study showed no evidence that SP taken by the mother during pregnancy is harmful to the newborn. The incidence of neonatal icterus was lower than the 60% incidence observed in full-term newborns in nurseries.⁴⁸ The neonatal death rate, 14.4 deaths per 1,000 live births (95% confidence interval = 7.9, 24.1), is lower than that reported for Kenya (27.0 per 1,000).⁴⁹

The results of this investigation, coupled with those from the study of the efficacy of SP in pregnant Malawian women,²³ provide strong evidence that intermittent treatment with SP during pregnancy is safe and efficacious for the prevention of placental malaria in pregnant primigravidae and secundigravidae in sub-Saharan Africa. While two doses of SP provided sufficient protection in HIV-negative women even in this very high *P. falciparum* transmission area, HIV-positive women required at least three doses of SP to sufficiently clear their infections. Given that it is not yet feasible to provide informed HIV testing to all pregnant women in many circumstances in malaria-endemic developing countries, we suggest that a monthly SP regimen be provided in areas with high HIV seroprevalence in women of child-bearing age. In areas where women tend to seek health care in the middle-to-late second trimester, as in our study site, a relatively small proportion of women would actually receive more than three doses and total exposure to SP would be relatively low. Findings of high placental malaria rates in HIV-positive multigravidae raise the question of whether antimalarial interventions should be extended to this group; further studies are needed in this area.

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