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# Dosage of Sulfadoxine–Pyrimethamine and Risk of Low Birth Weight in a Cohort of Zambian Pregnant Women in a Low Malaria Prevalence Region

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*Abstract.* In Lusaka, Zambia, where malaria prevalence is low, national guidelines continue to recommend that all pregnant women receive sulfadoxine–pyrimethamine (SP) for malaria prophylaxis monthly at every scheduled antenatal care visit after 16 weeks of gestation. Human immunodeficiency virus (HIV)–positive women should receive co-trimoxazole prophylaxis for HIV and not SP, but many still receive SP. We sought to determine whether increased dosage of SP is still associated with a reduced risk of low birth weight (LBW) in an area where malaria transmission is low. Our secondary objective was to determine whether any association between SP and LBW is modified by receipt of antiretroviral therapy (ART). We analyzed data routinely collected from a cohort of HIV-positive pregnant women with singleton births in Lusaka, Zambia, between February 2006 and December 2012. We used a log-Poisson model to estimate the risk of LBW by dosage of SP and to determine whether the association between SP and LBW varied by receipt of ART. Risk of LBW declined as the number of doses increased and appeared lowest among women who received three doses (adjusted risk ratio [ARR] = 0.78; 95% confidence interval [CI] = 0.64–0.95). In addition, women receiving combination ART had a higher risk of delivering an LBW infant compared with women receiving no treatment or prophylaxis (ARR = 1.18; 95% CI = 1.09–1.28), but this risk was attenuated among women who were receiving SP (risk ratio = 1.09; 95% CI = 0.99–1.21). SP was associated with a reduced risk of LBW in HIV-positive women, including those receiving ART, in a low malaria prevalence region.

## INTRODUCTION

In Zambia, the prevalence of human immunodeficiency virus (HIV) among pregnant women is 22%,[1] and malaria infection accounts for approximately 30% of outpatient visits nationally, but varies considerably by region.[2,3] HIV-infected pregnant women have reduced antimalarial immunity[4] and, when infected, higher burdens of the malaria parasite.[5–9] Malaria-infected pregnant women have increased CD4+ cell activation, upregulation of proinflammatory cytokines, and increased HIV RNA viral loads.[5,10] Considerable efforts have been made to combat malaria burden in Zambia, and while there has been a resurgence of malaria in the country, in Lusaka Province, malaria transmission is very low with < 1% parasite prevalence.[2]

Distinct guidelines for the treatment and prophylaxis of HIV and malaria infection, particularly for pregnant women, may not be appropriate for the overlap in these epidemics. For example, Zambian guidelines recommend malaria prophylaxis with sulfadoxine–pyrimethamine (SP) for all pregnant women during the course of pregnancy given monthly at each scheduled antenatal care (ANC) visit starting at 16 weeks of gestation to achieve a total of three of more doses.[3,11,12] HIV-positive women are recommended to receive co-trimoxazole (CTX) prophylaxis and not SP, but many still receive SP with or without CTX.[13] SP is a folic acid antagonist that disrupts replication of the malaria parasite and is not recommended for HIV-infected pregnant women on CTX prophylaxis, owing to the redundant mechanism of action leading to increased toxicity.[11,14] In 2013, Zambia adopted the "Option B+ strategy," which recommends that all HIV-infected pregnant women start antiretroviral therapy (ART) during pregnancy and continue it for life, regardless of their CD4 count.[13] These recommendations have resulted in a large number of HIV-positive women in sub-Saharan Africa, and specifically in Zambia, who are receiving both ART and SP during pregnancy. Although guidelines recommend that HIV-positive women who are pregnant receive CTX without SP, real-world application of HIV and malaria guidelines in pregnancy suggests that HIV-positive women are receiving both ART and SP, with or without CTX.[15]

SP has been associated with a decreased risk of low birth weight (LBW) among pregnant women in general[16–18] and among HIV-infected pregnant women in specific.[19] A Cochrane review of trials comparing dosing regimens found that infants born to HIV-positive pregnant women receiving three or more doses of SP weighed more than those born to mothers receiving two doses.[19] However, one trial in Ndola, Zambia, found no difference between those receiving the standard two doses of SP compared with three or more doses.[20] All prior studies have been in malaria-endemic areas and none have considered how simultaneous receipt of both ART and SP in HIV-positive pregnant women may influence risk of LBW.

In our study population in Lusaka, Zambia, a low malaria burden area, current national antenatal guidelines continue to recommend that HIV-infected pregnant women, except those receiving CTX prophylaxis, receive three or more doses of SP in pregnancy. The primary objective of this study was to determine whether increased dosage of SP is still associated with a reduced risk of LBW in an area where malaria transmission is low. The secondary objective was to determine whether any association between SP and LBW is modified by administration of antiretroviral therapy (ART).

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## MATERIALS AND METHODS

Lusaka, Zambia, is city of 2 million people with 25 public health sector facilities, including the University Teaching Hospital, which provide ANC and delivery services to pregnant women. We conducted analysis of data collected prospectively through the Zambia Electronic Perinatal Record System (ZEPRS). ZEPRS is a patient-linked electronic health record system that serves all pregnant women receiving pregnancy care in the Lusaka Urban District.[1] Data are collected from patients on demographic characteristics, medical history, and ANC, and delivery information for both the mother and infant.[1]

Our primary analysis included singleton births to HIV-positive women with an initial ANC visit between February 1, 2006 and December 31, 2012. Women who were HIV seronegative or whose status was unknown, who delivered outside of the ZEPRS catchment area, who delivered multiple gestation, and who had missing information on infant birth weight or gestational age were excluded. The outcome of LBW was defined as an infant weighing < 2,500 g.[21] The number of doses of SP received was recorded at each ANC visit at a ZEPRS clinic. Our exposure was defined categorically as the maximum number of doses of SP received during any ANC visit over the course of the pregnancy. Women at the ZEPRS facilities can receive up to three doses of SP. Gestational age was assessed by last menstrual period. Hypertension was defined as any diagnosis of hypertension during ANC or delivery, and hemoglobin was measured at first ANC visit. Although CTX prophylaxis is recommended for all HIV-positive women and SP is not recommended for women receiving CTX, we were unable to determine which women in our cohort were receiving CTX prophylaxis; ART was defined as initiation of a combination antiretroviral regimen with a goal of viral suppression, as described in World Health Organization (WHO) guidelines.[13]

We compared maternal and newborn characteristics of HIV-positive pregnant women by number of SP doses received during ANC. Frequencies and percentages were reported for categorical measures. Medians with the interquartile range were reported for continuous measures. We used the Cochran–Mantel–Haenszel nonzero correlation coefficient, row mean score statistic or Kruskal–Wallis test to test differences between number of SP doses received and ordinal, nominal, or continuous variables, respectively. We fit a log-Poisson regression model to estimate the risk of LBW by dose of SP.[22]

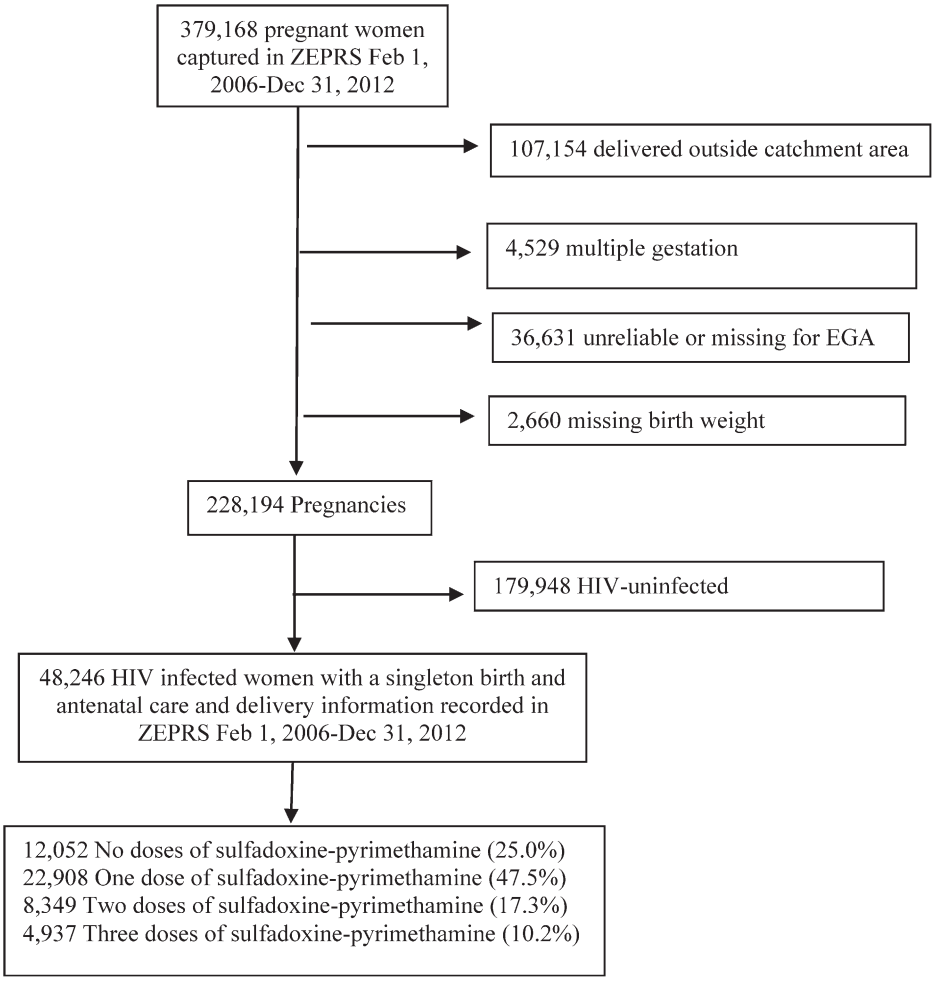


FIGURE 1. Flow diagram of inclusion criteria for a Zambian cohort of pregnant women from the Zambia Perinatal Electronic Record System in Lusaka, Zambia (February 2006–December 2012).

TABLE 1

Characteristics of a Zambian cohort of HIV-positive pregnant women by dose of SP from the ZEPRS in Lusaka, Zambia (February 2006–December 2012)

| | Dose of SP | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | None | | One dose | | Two doses | | Three doses | | |
| Characteristics | *N* (%) | Median (IQR) | *N* (%) | Median (IQR) | *N* (%) | Median (IQR) | *N* (%) | Median (IQR) | *P* value |
| Maternal age (years) | 12,052 | 27 (23, 31) | 22,908 | 27 (23, 31) | 8,349 | 27 (24, 31) | 4,937 | 27 (24, 32) | < 0.01+ |
| < 20 | 981 (8.1) | | 1,812 (7.9) | | 570 (6.8) | | 324 (6.6) | | < 0.01* |
| 20–34 | 9,710 (80.6) | | 18,556 (81.0) | | 6,843 (82.0) | | 4,036 (81.8) | | |
| ≥ 35 | 1,361 (11.3) | | 2,540 (11.1) | | 936 (11.2) | | 577 (11.7) | | |
| Parity | 12,052 | 1 (0, 3) | 22,908 | 2 (0, 3) | 8,349 | 2 (1, 3) | 4,937 | 2 (1, 3) | < 0.01+ |
| 0 | 3,479 (28.9) | | 5,850 (25.5) | | 1,946 (23.3) | | 1,101 (22.3) | | |
| ≥ 1 | 8,573 (71.1) | | 17,058 (74.5) | | 6,403 (76.7) | | 3,836 (77.7) | | |
| BMI (kg/m$^2$) | 7,940 | 23.3 (21.4, 25.8) | 16,117 | 23.5 (21.6, 26.0) | 5,262 | 23.5 (21.6, 26.0) | 2,905 | 23.8 (21.7, 26.7) | < 0.01+ |
| < 18.5 | 290 (3.7) | | 437 (2.7) | | 138 (2.6) | | 86 (3.0) | | < 0.01* |
| 20–30 | 7,134 (89.8) | | 14,481 (89.8) | | 4,697 (89.3) | | 2,545 (87.6) | | |
| ≥ 30 | 516 (6.5) | | 1,199 (7.4) | | 427 (8.1) | | 274 (9.4) | | |
| Prior LBW | 388 (3.2) | | 784 (3.4) | | 327 (3.9) | | 216 (4.4) | | < 0.01‡ |
| Prior stillbirth | 233 (1.9) | | 393 (1.7) | | 177 (2.1) | | 107 (2.2) | | 0.12‡ |
| Hypertension during ANC or delivery | | | | | | | | | |
| No | 9,406 (93.2) | | 19,317 (94.1) | | 7,424 (91.7) | | 4,307 (88.3) | | < 0.01‡ |
| Yes | 683 (6.8) | | 1,208 (5.9) | | 673 (8.3) | | 572 (11.7) | | |
| Baseline hemoglobin | 8,699 | 11.1 (10.2, 12.0) | 18,036 | 11.1 (10.1, 12.0) | 6,579 | 11.2 (10.2, 12.1) | 3,733 | 11.3 (10.3, 12.2) | < 0.01+ |
| ≥ 10 g/dL | 7,048 (74.4) | | 14,474 (75.4) | | 5,469 (76.6) | | 3,185 (76.7) | | < 0.01* |
| ≥ 8–9 g/dL | 1,441 (15.2) | | 3,164 (16.5) | | 981 (13.7) | | 491 (11.8) | | |
| < 8 g/dL | 210 (2.2) | | 398 (2.1) | | 129 (1.8) | | 57 (1.4) | | |
| No. of ANC visits | 12,052 | 1 (1, 2) | 22,908 | 1 (1, 2) | 8,349 | 2 (2, 3) | 4,937 | 3 (3, 4) | < 0.01+ |
| 1 | 8,671 (71.9) | | 16,228 (70.8) | | 123 (1.5) | | 62 (1.3) | | < 0.01* |
| 2 | 1,984 (16.5) | | 4,231 (18.5) | | 5,218 (62.5) | | 335 (6.8) | | |
| 3 | 962 (8.0) | | 1,800 (7.9) | | 2,111 (25.3) | | 2,549 (51.6) | | |
| > 3 | 435 (3.6) | | 649 (2.8) | | 897 (10.7) | | 1,991 (40.3) | | |
| CD4 count at first ANC visit | 8,941 | 373 (249, 521) | 17,814 | 368 (246, 517) | 6,410 | 368 (246, 521) | 3,715 | 366 (241, 516) | 0.46+ |
| < 200 | 1,439 (16.1) | | 2,974 (16.7) | | 1,046 (16.4) | | 620 (16.7) | | 0.30* |
| 200–250 | 2,647 (29.7) | | 5,258 (29.6) | | 1,914 (29.9) | | 1,130 (30.5) | | |
| 350–500 | 2,323 (26.0) | | 4,646 (26.1) | | 1,649 (25.8) | | 937 (25.2) | | |
| ≥ 500 | 2,512 (28.2) | | 4,899 (27.6) | | 1,783 (27.9) | | 1,024 (27.6) | | |
| Gestational age | 12,052 | 37 (35, 39) | 22,908 | 37 (34.0, 39.0) | 8,349 | 38 (36, 40) | 4,937 | 39 (37, 40) | < 0.001+ |
| Stillbirth | 332 (2.8) | | 655 (2.9) | | 188 (2.3) | | 86 (1.7) | | < 0.001‡ |
| Type of ART | | | | | | | | | |
| No treatment or AZT/NVP prophylaxis | 8,409 (69.8) | | 16,727 (73.0) | | 5,800 (69.5) | | 3,350 (67.9) | | 0.001‡ |
| Combination ART | 3,643 (30.2) | | 6,181 (27.0) | | 2,549 (30.5) | | 1,587 (32.1) | | |
| EGA at first ANC (weeks) | | | | | | | | | < 0.001* |
| < 14 weeks | 1,204 (10.0) | | 595 (2.6) | | 444 (5.3) | | 382 (7.7) | | |
| 14–24 weeks | 6,143 (51.0) | | 10,834 (47.3) | | 4,699 (56.3) | | 3,281 (66.5) | | |
| > 24 weeks | 4,705 (39.0) | | 11,479 (50.1) | | 3,206 (38.4) | | 1,274 (25.8) | | |

ANC = antenatal care; ART = antiretroviral therapy; AZT = Zidovudine; BMI = body mass index; EGA = estimated gestational age; HIV = human immunodeficiency virus; IQR = interquartile range; LBW = low birth weight; NVP = nevirapine; SP = sulfadoxine–pyrimethamine; ZEPRS = Zambia Electronic Perinatal Record System; *N* = 48, 246.

*Cochran–Mantel–Haenszel nonzero correlation coefficient for two ordinal variables.

+Kruskal–Wallis test.

‡Cochran–Mantel–Haenszel row mean scores differ statistic for nominal by ordinal variable

The log-Poisson model approximates a log binomial.[22] Generalized estimating equations with an unstructured correlation structure estimated robust 95% confidence intervals (CIs) that accounted for repeat deliveries over the study period. Covariates were included in multivariable analysis that were deemed clinically meaningful and that were significant in univariable analysis. Our final model was adjusted for age, parity, hypertension, body mass index (BMI), hemoglobin, prior LBW infant, receipt of ART, CD4+ lymphocyte count, and number of ANC visits. Correlation between parity and prior LBW was examined but was not high (0.184). Clinical diagnosis of malaria (3.2%) (without laboratory confirmation) was not significantly associated with LBW (risk ratio [RR] = 1.04; 95% CI = 1.90–1.21), did not substantially change the coefficients for dose of SP (< 10%), and a likelihood ratio test comparing models with and without the variable was not significant ($\chi^2 = 0.33$, $P = 0.564$, df = 1). Therefore, malaria diagnosis was not included in the final model due to the large number of missing data (24%). We added an interaction term between SP and ART to the adjusted model to estimate the association between ART and LBW infant stratified by receipt of any SP (yes/no). We compared the fit of the adjusted model with and without an interaction term using a log-likelihood ratio test for multiplicative interaction. We also calculated the attributable proportion of LBW infants prevented by the additive interaction between SP and ART, adjusting for all other covariates.[23] Because women who present for a first antenatal visit later in pregnancy may have fewer opportunities to receive three doses of SP, we performed a subanalysis by restricting the cohort to those HIV-infected women whose first ANC occurred at or before 22 weeks gestation. In a final analysis, we compared our results to a model restricted to HIV-uninfected women from the original cohort. SP has been shown to have an effect in both HIV-uninfected and infected women, and we hoped to determine whether our results from a low prevalence area were similar between these populations. Subanalyses were adjusted for all covariates included in the final adjusted model. All analyses were conducted with SAS version 9.3 (SAS Institute, Cary, NC).

## RESULTS

A total of 48,246 mother–infant pairs met eligibility criteria and were included in the analysis cohort. Most women were excluded because they were HIV uninfected/unknown (*N* = 179,948) or did not have delivery information available (*N* = 107,154; Figure 1). Among HIV-positive women included in our study cohort, the majority received one dose of SP (*N* = 22,908; 47.5%) or no doses (*N* = 12,052; 25.0%). The remainder received either two (*N* = 8,349; 17.3%) or three doses of SP (*N* = 4,937; 10.0%).

Women receiving more doses of SP were less likely to have a teen pregnancy, and more likely to have higher parity, higher BMI, higher hemoglobin concentration, more ANC visits, and to have had a prior LBW or a diagnosis of hypertension during ANC or pregnancy (Table 1). Number of doses of SP did not correspond directly with number of ANC visits with some women reporting more doses than ANC visits. Among women who did not receive (*N* = 8,671; 71.9%) or received only one dose (*N* = 16,228; 70.8%), most women had only one ANC visit. Approximately 40% of women (*N* = 1,991) who received three doses of SP had more than three ANC visits. CD4+ T-lymphocyte counts did not vary by dose of SP.

The percentage of women who delivered an LBW infant decreased with each additional dose of SP. The lowest percentage of LBW was among women who received three (*N* = 401; 8.1%), followed by two (*N* = 920; 11.0%) doses of SP (Figure 2; Table 2). Gestational age at birth was slightly higher among women who received three doses

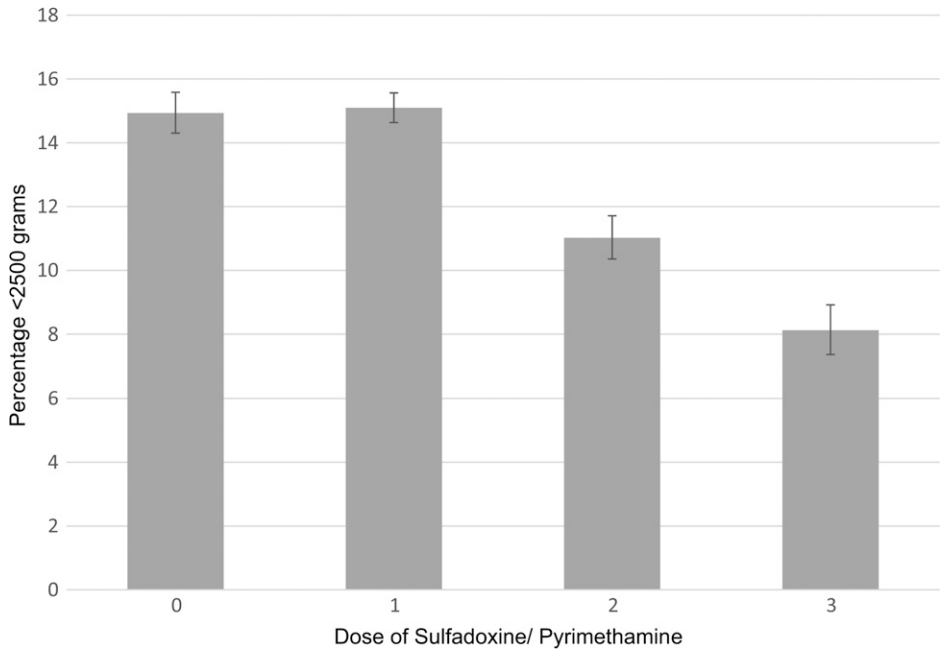


FIGURE 2. Percentage and 95% confidence intervals for low birth weight infants (< 2,500 g) by dose of sulfadoxine–pyrimethamine.

TABLE 2
Unadjusted and adjusted* RR and 95% CIs for the relationship between dose of SP and LBW in Lusaka, Zambia

| Characteristic | Unadjusted RR (95% CI) | Adjusted RR (95% CI) | Adjusted RR (95% CI) HIV uninfected (*N* = 179,948) | Adjusted RR (95% CI) EGA ≤ 22 weeks (*N* = 24,376) |
|---|---|---|---|---|
| Maternal Age | | | | |
| < 20 | 1.34 (1.24–1.44) | 1.29 (1.15–1.44) | 1.41 (1.32–1.51) | 1.16 (1.00–1.35) |
| 20–34 | 1 | 1 | 1 | 1 |
| > 35 | 1.06 (0.98–1.13) | 0.94 (0.84–1.06) | 1.07 (0.95–1.20) | 0.94 (0.79–1.12) |
| Parity, median | | | | |
| 0 | 1 | 1 | 1 | 1 |
| ≥ 1 | 0.81 (0.77–0.85) | 0.77 (0.71–0.83) | 0.63 (0.59–0.67) | 0.82 (0.74–0.91) |
| Hypertension in ANC or delivery | | | | |
| No | 1 | 1 | 1 | 1 |
| Yes | 1.30 (1.19–1.41) | 1.55 (1.38–1.74) | 1.67 (1.52–1.82) | 1.47 (1.26–1.72) |
| BMI | | | | |
| < 18.5 | 1.86 (1.67–2.09) | 1.89 (1.65–2.17) | 1.41 (1.23–1.60) | 1.85 (1.56–2.19) |
| 18.5–30 | 1 | 1 | 1 | 1 |
| > 30 | 0.56 (0.48–0.64) | 0.58 (0.49–0.70) | 0.68 (0.61–0.77) | 0.64 (0.49–0.82) |
| Dose of SP | | | | |
| None | 1 | 1 | 1 | 1 |
| One dose | 1.01 (0.96–1.06) | 0.98 (0.91–1.06) | 0.99 (0.92–1.06) | 1.00 (0.90–1.12) |
| Two doses | 0.74 (0.69–0.80) | 0.87 (0.76–1.00) | 0.95 (0.85–1.06) | 0.97 (0.82–1.14) |
| Three doses | 0.54 (0.49–0.60) | 0.78 (0.64–0.95) | 0.81 (0.70–0.93) | 0.78 (0.62–0.99) |
| CD4 count at first ANC visit | | | | |
| < 200 | 1.53 (1.42–1.66) | 1.40 (1.26–1.56) | – | 1.46 (1.26–1.69) |
| 200–350 | 1.18 (1.10–1.27) | 1.11 (1.01–1.22) | – | 1.16 (1.01–1.32) |
| 350–500 | 1.10 (1.02–1.18) | 1.06 (0.96–1.17) | – | 1.16 (1.02–1.33) |
| ≥ 500 | 1 | 1 | – | 1 |
| HGB | | | | |
| < 8 | 1.73 (1.52–1.98) | 1.47 (1.22–1.78) | 1.60 (1.22–2.09) | 1.43 (1.09–1.87) |
| 8–10 | 1.17 (1.09–1.25) | 1.15 (1.05–1.26) | 1.25 (1.11–1.41) | 1.23 (1.09–1.39) |
| > 10 | 1 | 1 | 1 | 1 |
| No. of ANC visits | | | | |
| 1 | 2.03 (1.82–2.26) | 2.09 (1.69–2.58) | 2.42 (2.02–2.90) | 2.23 (1.75–2.85) |
| 2 | 1.61 (1.44–1.81) | 1.63 (1.31–2.01) | 1.98 (1.66–2.36) | 1.83 (1.44–2.33) |
| 3 | 1.20 (1.05–1.36) | 1.29 (1.04–1.60) | 1.49 (1.26–1.77) | 1.46 (1.14–1.85) |
| > 3 | 1 | 1 | 1 | 1 |
| Type of ART | | | | |
| No treatment or AZT/NVP prophylaxis | 1 | 1 | – | 1 |
| Combination ART | 1.22 (1.17–1.28) | 1.18 (1.09–1.28) | – | 1.16 (1.04–1.28) |
| Prior LBW | | | | |
| No | 1 | 1 | 1 | 1 |
| Yes | 1.31 (1.22–1.41) | 1.41 (1.27–1.58) | 1.92 (1.74–2.12) | 1.43 (1.24–1.66) |

ANC = antenatal care; ART = antiretroviral therapy; BMI = body mass index; CI = confidence interval; EGA = estimated gestational age; HGB = hemoglobin; HIV = human immunodeficiency virus; LBW = low birth weight; RR = risk ratio; SP = sulfadoxine–pyrimethamine.
*Adjusted for age, parity, hypertension, BMI, hemoglobin, prior LBW infant, receipt of ART, CD4+ lymphocyte count, and number of ANC visits.

(39 weeks), and these women were the least likely to have a stillbirth (*N* = 86; 1.7%).

In unadjusted analysis, LBW was associated with age, parity, hypertension, CD4 count, hemoglobin concentration, number of ANC visits, type of ART, prior LBW, and number of doses of SP (Table 2). The risk of LBW in women receiving three doses was half of that faced by women receiving no doses (RR = 0.54; 95% CI = 0.49–0.60). In multivariable analysis, risk of LBW declined with number of doses received (one dose: adjusted risk ratio [ARR] = 0.98; 95% CI = 0.91–1.06, two doses: ARR = 0.87; 95% CI = 0.76–1.00, three doses: ARR = 0.78; 95% CI = 0.64–0.95). When restricted to women with an initial ANC visit at or before 22 weeks gestational age, results were similar. Risk of LBW declined with increased number of doses (one dose: ARR = 1.00; 95% CI = 0.90–1.12, two doses: ARR = 0.97; 95% CI = 0.82–1.14, three doses: ARR = 0.78; 95% CI = 0.62–0.99). Among HIV-uninfected women, the risk of LBW again declined with increased number of doses of SP (one dose: ARR = 0.99; 95% CI = 0.92–1.06, two doses: ARR = 0.95; 95% CI = 0.85–1.11, three doses: ARR = 0.81; 95% CI = 0.70–0.93).

In multivariable analysis, the risk of LBW among women receiving combination ART was 1.18 (95% CI = 1.09–1.28) times the risk in women not receiving ART (Table 3). When stratified by SP use, receipt of ART was not associated with LBW among women receiving SP (ARR = 1.09; 95% CI = 0.99–1.21) (Figure 3). Among women not receiving SP, women receiving suppressive ART had 1.31 (95% CI = 1.17–1.47) times the risk of LBW compared with women not receiving combination ART. A likelihood ratio test comparing adjusted models with and without an interaction term between SP and ART indicated a multiplicative interaction at an alpha level of 0.05 ($\chi^2$ = 4.61, df = 1, *P* = 0.03). The attributable proportion of LBW due to the additive interaction between SP and ART was –0.20 indicating that there are 20% fewer LBW infants due to the additive interaction between SP and ART. In other words, because some women were receiving both drugs, there were 20% fewer LBW infants in our population than would have been expected.

## DISCUSSION

In this population with a low malaria burden, we observed an inverse dose–response relationship between the number of doses of SP received and risk of LBW. Risk of LBW

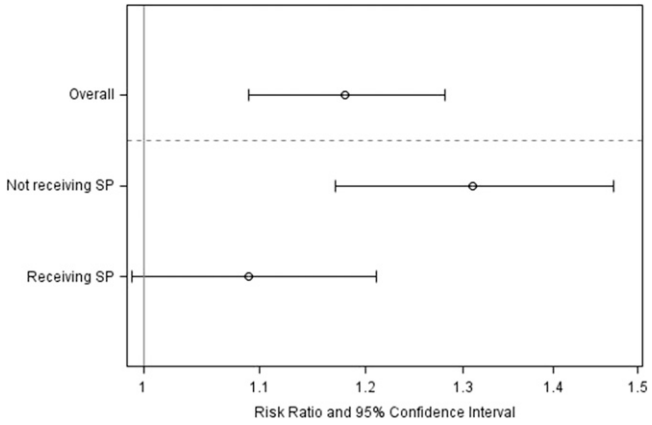


FIGURE 3. Adjusted risk ratios and 95% confidence intervals (CIs) for the relationship between antiretroviral therapy (ART) use and low birth weight–stratified receipt of sulfadoxine–pyrimethamine (SP). * *All adjusted for age, parity, hypertension during antenatal care (ANC) or delivery, body mass index, receiving ART, receiving SP, hemoglobin, baseline syphilis, CD4+ lymphocyte count, prior low birth weight, and number of ANC visits. Modeled using a log-Poisson model with robust standard errors to estimate the RR. **Likelihood ratio test comparing adjusted models with and without an interaction term between SP and ART: $\chi^2 = 4.61$, df = 1, P = 0.0318. ***Overall RR = 1.18 (95% CI = 1.09–1.28), not receiving SP = 1.31 (95% CI = 1.17, 1.47), receiving SP = 1.09 (95% CI = 0.99, 1.21). ****Interaction contrast ratio = (1.11 − [1.02 + 1.31 − 1]) = −0.22 (95% CI = −0.60, 0.16); additive attributable proportion = 0.22/1.11 = −0.20.

declined as number of doses increased and was lowest among women who received the recommended three doses. This pattern remained after restricting the sample to women who presented to care earlier and who were HIV uninfected. The majority of women (52%) received both ART and at least one dose of SP during ANC and 10.2% of women (*N* = 4,937) received the three doses of SP during pregnancy. In addition, women receiving combination ART had a higher risk of delivering an LBW infant, but this risk was attenuated among women who were simultaneously receiving SP. SP reduces risk of LBW in HIV-positive women, including those receiving ART. Because the malaria prevalence in Lusaka is very low, we hypothesize that it is unlikely that these apparent benefits can be solely ascribed to SP's antiplasmodial effect.

SP is used for prophylaxis because it eliminates parasites that persist asymptomatically as they emerge from the liver.[25] However, there is no consensus about the specific mechanism by which SP increases birth weight.[24] We observed an association between SP and LBW in a setting where few women are overtly infected with malaria. Our results suggest that SP may be treating or preventing another infection or interacting with the maternal immunological system thereby decreasing risk of LBW. Because CTX information was not available, it is also possible that CTX, which has a similar mechanism of action, is working through these pathways. Infections of both the upper and the lower genital tracts have been linked to increased risk of preterm birth and LBW. Antimicrobial treatment to treat infections has been shown to reduce risk of preterm birth.[25] It is possible that SP reduces LBW by reducing risk of infection and preterm birth. Further studies are needed to confirm these results and understand the mechanism for this relationship.

SP is contraindicated for women receiving CTX prophylaxis for HIV due to the redundant mechanism of action and potential for adverse toxicity events. WHO guidelines for the treatment of HIV recommend that all HIV-positive women receive CTX during pregnancy.[11] We were unable to determine whether women in our cohort were receiving both CTX and SP, but given the large number of women on SP in our study, it is possible that implementation of the recommendations is not optimal and some were receiving both drugs. Despite this limitation, a study in a comparable population in Malawi found that even among women who do receive both SP and CTX, there might be a beneficial reduction in anemia and malaria parasitemia.[15] Another study found that while SP should not be coadministered with CTX due to increased toxicity, women receiving CTX may still benefit from additional antimalarial prophylaxis.[26] Women receiving CTX should not be given SP; therefore, more research is needed to determine how CTX may factor into our findings and how other antimalarial drugs compare, particularly as CTX has also been associated with malaria and LBW.

A growing body of evidence supports the hypothesis that ART increases the risk of preterm birth in sub-Saharan Africa, perhaps through inflammation and/or immune activation.[27–33] ART may potentiate this risk through a similar mechanism.[27,28] Limited research exists regarding the interaction between antiretroviral and antimalarial drugs, but the protease inhibitor component of ART may have antimalarial properties by inhibiting parasite growth.[14,34,35] The antimalarial drugs chloroquine and hydroxychloroquine have also been shown to have antiretroviral activity in vitro and in vivo.[14] In our study cohort, a large percentage (*N* = 7,367; 53%) of women who were receiving ART were also receiving SP. Our results show an attenuated risk of LBW associated with ART in women who are simultaneously receiving SP. The mechanism for this relationship is unclear, but may be related to a reduced inflammatory response during pregnancy.[14] Although HIV-positive women should receive CTX and not SP, there are now a large number of HIV-pregnant women in sub-Saharan African who are receiving both SP and ART. Our study is the first study to examine whether receipt of SP for malaria prophylaxis modifies the risk of LBW associated with ART use. More studies are needed to confirm this association.

We acknowledge several limitations to our analysis. First, we are using clinical data collected at primary and tertiary care facilities in Zambia where missing data are common. Many of the women who were excluded were missing data on delivery because they did not return to a ZEPRS facility to deliver. Women who return to a facility may be more likely to have high-risk pregnancies or be different in other ways from women who deliver at home. However, a prior publication found that women with delivery information in ZEPRS did not differ in any clinically significant way from women without delivery information.[36] Second, we do not have complete information available about laboratory malaria diagnosis, CTX prophylaxis, socioeconomic status, or HIV RNA viral load and were unable to adequately examine or control for these factors. Third, there are women in our study with more doses of SP than ANC visits. This mismatch suggests that women had missed visits that were not recorded in the system or had other visits outside of ZEPRS facilities. Fourth, some women who present to

ZEPRS clinics travel from peri-urban areas around Lusaka where transmission of malaria is much higher.[37] Fifth, while we did control for CD4+ count in the model for the relationship between ART and LBW, there may still be some confounding by indication. Finally, ultrasound dating is not widely used in our setting and thus information about gestational age, including estimated gestational age at first ANC visit, is not particularly reliable.[38]

Alongside its primary benefit in malaria control, SP may have an additional secondary benefit of reducing risk of LBW in HIV-infected women, including those receiving ART. Among HIV-positive women, increased dosage of SP was associated with a decreased risk of LBW. The most robust association was seen among women who received the recommended three doses; however, many women present to ANC in advanced gestation and may not have sufficient time to receive three doses. Efforts are needed to encourage women to attend and present earlier to ANC. Further studies are also needed to better understand the mechanism for the relationship between SP and LBW in a low malaria prevalence setting, and determine how CTX prophylaxis for HIV versus SP affect risk of LBW in areas where SP is recommended.

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