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MAJOR ARTICLE

Protective Effect of Indoor Residual Spraying of Insecticide on Preterm Birth Among Pregnant Women With HIV Infection in Uganda: A Secondary Data Analysis

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Background. Recent evidence demonstrated improved birth outcomes among human immunodeficiency virus (HIV)–uninfected pregnant women protected by indoor residual spraying of insecticide (IRS). Evidence regarding its impact on HIV-infected pregnant women is lacking.

Methods. Data were pooled from 2 studies conducted before and after an IRS campaign in Tororo, Uganda, among HIV-infected pregnant women who received bed nets, daily trimethoprim-sulfamethoxazole, and combination antiretroviral therapy at enrollment. Exposure was the proportion of pregnancy protected by IRS. Adverse birth outcomes included preterm birth, low birth weight, and fetal or neonatal death. Multivariate Poisson regression with robust standard errors was used to estimate risk ratios.

Results. Of 565 women in our analysis, 380 (67%), 88 (16%), and 97 (17%) women were protected by IRS for 0%, >0% to 90%, and >90% of their pregnancy, respectively. Any IRS protection significantly reduced malaria incidence during pregnancy and placental malaria risk. Compared with no IRS protection, >90% IRS protection reduced preterm birth risk (risk ratio, 0.35; 95% confidence interval, .15–.84), with nonsignificant decreases in the risk of low birth weight (0.68; .29–1.57) and fetal or neonatal death (0.24; .04–1.52).

Discussion. Our exploratory analyses support the hypothesis that IRS may significantly reduce malaria and preterm birth risk among pregnant women with HIV receiving bed nets, daily trimethoprim-sulfamethoxazole, and combination antiretroviral therapy.

Keywords. IRS; HIV; malaria; preterm birth; Uganda.

Malaria during pregnancy poses serious risks for both the pregnant woman and her fetus. In sub-Saharan Africa, malaria during pregnancy is thought to be the cause of 10%–25% of maternal deaths, low birth weight in 1 million infants, and 110 000 neonatal deaths per year; for which preterm birth remains the leading cause [1–3]. The World Health Organization currently recommends that all pregnant women living in malaria-endemic areas receive long-lasting insecticide-treated nets, intermittent preventive treatment with sulfadoxine-pyrimethamine (IPTp-SP), and prompt and effective treatment of malaria [4, 5]. However, in some areas, especially areas of high malaria burden, coverage of bed nets and IPTp-SP has been shown to be low, despite high antenatal care attendance [4, 6].

The risks for complications from malaria infection are substantially higher among pregnant women with untreated human immunodeficiency virus (HIV) infection. Coinfection with HIV and malaria has been associated with a higher risk of placental malaria, severe anemia, and adverse birth outcomes than among women without HIV infection [4, 7, 8]. Thus, for HIV-infected pregnant women living in malaria-endemic areas, the World Health Organization guidelines recommend combination antiretroviral therapy (cART) and daily trimethroprim-sulfamethoxazole (TMP-SMX) prophylaxis [9]. In addition to protecting against HIV-related infections, TMP-SMX has been shown to protect against malaria [10, 11], but for HIV-infected pregnant women taking daily TMP-SMX, IPTp-SP is contraindicated owing to overlapping toxic effects with this regimen [5, 12].

Beginning in December 2014, the US President's Malaria Initiative and the Ugandan Ministry of Health implemented a district-wide indoor residual spraying (IRS) campaign using bendiocarb, a carbamate insecticide, at approximately 6-month intervals in Tororo District of eastern Uganda [13]. The campaign sustained a household targeted coverage of >90% [14], and after the first round of the IRS campaign, clear reductions in malaria morbidity and transmission rates were observed [15].

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An observational study of HIV-uninfected pregnant women published in 2016 found that the risk of low birth weight, preterm birth, and fetal or neonatal deaths were markedly lower among women protected by the IRS campaign during their pregnancy [16]. Given these findings, we sought to investigate whether this effect would also be observed among HIV-infected pregnant women taking daily TMP-SMX and cART and protected by bed nets.

METHODS

Study Site

Tororo is a rural district in eastern Uganda, highly endemic for malaria. Before the implementation of IRS, malaria transmission was stable and year-round, with relatively little seasonal variation and a reported annual entomological inoculation rate of 310 infectious bites per year in 2012. According to the 2011 AIDS Indicator Survey, the estimated prevalence of HIV was 6.1% among pregnant women [17, 18]. In December 2014, IRS was first implemented throughout Tororo District, using bendiocarb [13]. Subsequent rounds of IRS have been conducted at approximately 6-month intervals [15]. After 3 rounds of IRS within a 14-month period, the incidence of childhood malaria reduced by 87% (3.25 to 0.63 episodes per person-year) and the density of female *Anopheles* mosquitoes was reduced by 71% [15].

Description of Parent Studies

Tororo has been the study site for the Prevention of Malaria and HIV Disease (PROMOTE) Pregnant Women and Infant trials since 2009. One of the goals of these trials has been to establish efficacious regimens for malaria chemoprevention and HIV treatment for pregnant women living in malaria-endemic regions.

We analyzed data from 2 PROMOTE parent studies, PROMOTE–Protease Inhibitors (PROMOTE-PIs; ClinicalTrials.gov, NCT00993031) [19] and PROMOTE–Birth Cohort 2 (PROMOTE-BC2; NCT02282293) [20], which were conducted before or after the initiation of IRS in December 2014, respectively. Participants from both trials were pregnant women ≥16 years of age with an estimated gestational age of 12–28 weeks, HIV-1 positive, and living within 30 km of the study clinic. All women received cART, daily TMP-SMX prophylaxis, and bed nets at enrollment. Our analysis included participants from both studies who were followed through to delivery and had singleton deliveries.

The PROMOTE-PIs study was an open-label, randomized controlled trial of HIV-infected pregnant women who received either protease inhibitor (PI)–based antiretroviral therapy (ART) (lopinavir-ritonavir) or nonnucleoside reverse-transcriptase inhibitor–based ART (efavirenz). Between December 2009 and September 2012, a total of 389 ART-naive women were enrolled into the PROMOTE-PIs trial (Figure 1). The PROMOTE-BC2 study was a double-blinded, randomized placebo-controlled trial of HIV-infected pregnant women who received either TMP-SMX plus placebo or TMP-SMX plus monthly dihydroartemisinin-piperaquine (DP) for the prevention of malaria during pregnancy. DP or placebo was administered every 4 weeks between 16 and 40 gestational weeks. Between December 2014 and October 2015, a total of 200 women were enrolled into the PROMOTE-BC2 trial (Figure 1). All PROMOTE-BC2 participants were treated with efavirenz-based ART but switched to a PI-based regimen if clinically indicated.

Written informed consent was obtained from all participants in both studies in their preferred language. Both studies were approved by the Makerere University School of Biomedical Sciences Research and Ethics Committee, the Uganda National

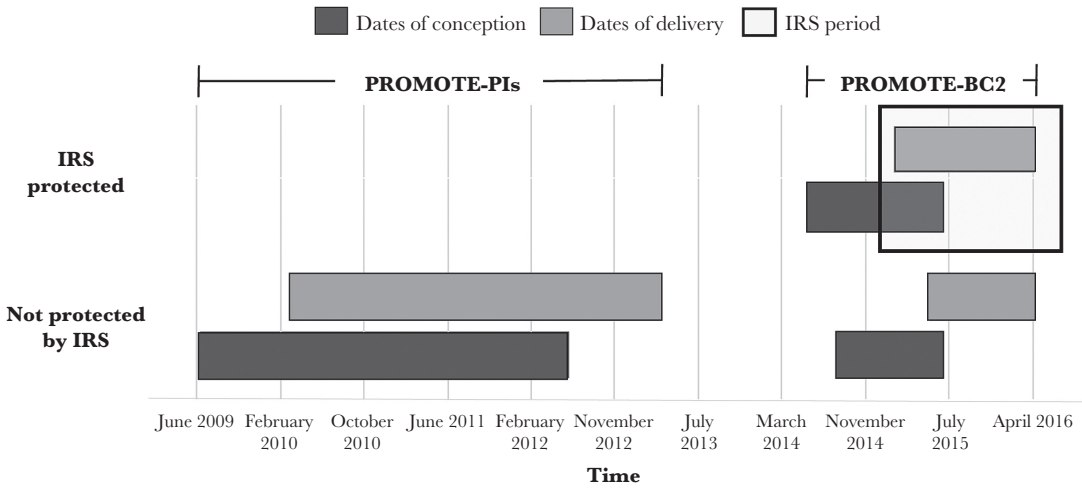

Figure 1. Timeline of the PROMOTE–Protease Inhibitors (PROMOTE-PIs) and PROMOTE–Birth Cohort 2 (PROMOTE-BC2) trials relative to IRS exposure. IRS, indoor residual spraying.

Council for Science and Technology, and the University of California San Francisco Committee for Human Research.

Study Procedures and Follow-up

Detailed description of participant recruitment, eligibility, and study procedures are described elsewhere [19, 20]. Briefly, in both trials, pregnant women were recruited from Tororo District Hospital antenatal clinic, The AIDS Support Organization (an HIV clinic in Tororo), and other surrounding health facilities. At enrollment, each woman received a bed net, underwent a standardized examination, completed a brief questionnaire, and provided a blood sample. Women received all medical care at a designated study clinic open 7 days per week. Monthly routine visits were conducted, including collection of dried blood spots. Women were encouraged to deliver at Tororo District Hospital, though women who delivered at home were visited by study staff at the time of delivery or soon afterward. A standardized assessment was conducted immediately after birth, including evaluation of birth weight and collection of placental samples.

Laboratory Methods

Peripheral blood was collected if women presented with fever during pregnancy, and placental blood was collected from all women at delivery. Thick and thin blood smears were stained with 2% Giemsa and read independently by 2 microscopists. A smear was considered negative if no malaria parasites were detected after a review of 100 high-power fields. Discordant results were resolved by a third microscopist. CD4 cell count and HIV-1 RNA load were measured at enrollment and monitored throughout follow-up.

Placental specimens were collected within 30 minutes of delivery. Placental blood was collected from an incision from the maternal surface and tested for malaria parasites using microscopy and polymerase chain reaction (PCR) or loop-mediated isothermal amplification (LAMP) (Eiken Chemical). Placental tissues were processed for histological evidence of placental malaria, as described elsewhere [19], including examination of malaria parasites and hemozoin pigment in intervillous fibrin and macrophages. Further details on methods for detecting placental malaria have been described elsewhere [19, 20].

Measurement of IRS Exposure

A woman was considered protected by IRS if her house or adjacent households were sprayed. When a house was sprayed, the date was marked on the door of each household by spray technicians, and this information was used to calculate the duration of IRS protection. The primary exposure variable was the proportion of a woman's pregnancy during which she was protected by IRS (duration of IRS protection during pregnancy/duration of pregnancy).

The date that IRS was considered protective against malaria infection was calculated based on the actual date of spraying plus 14 days to account for the average incubation period of *Plasmodium falciparum*. The duration of IRS protection was calculated by subtracting the date when IRS was considered protective from the date of delivery. The total duration of pregnancy was calculated by subtracting the date of conception (estimated by means of ultrasonography) from the date of delivery. The distribution of proportion of pregnancy protected by IRS is provided in Supplementary Figure S1. We further categorized IRS protection into 3 levels: 0%, >0% to 90%, and >90%. These categories were created after first selecting those with no IRS protection (0%) and then dividing the remaining observations into 2 categories (>0% to 90% and >90%) based on the distribution of study outcomes across the full range of IRS protection by visual inspection using lowess smoothing. The exposure variable was collapsed into a binary variable (ie, 0% vs >0%) if no outcome events were observed at either the >0% to 90% or the >90% level.

Study Outcomes

Assessment of malaria outcomes included the incidence of symptomatic malaria (defined as fever and positive thick blood smear) during pregnancy and risk of placental malaria measured using microscopy, LAMP/PCR, and histopathology. For histopathology, active infection was defined as the detection of malaria parasites in placental tissue and past infection defined as pigment observed in the fibrin or monocytes. Birth outcomes assessed included premature delivery (defined as gestational age <37 weeks), low birth weight (defined as <2500 g), and fetal or neonatal death. Methods to assess gestational age at enrollment are described elsewhere [21]. Fetal or neonatal death was defined as a composite outcome that included spontaneous abortions (delivery of a nonviable fetus at <28 weeks of gestational age), stillbirths (delivery of a nonviable fetus at ≥28 weeks gestational age), and death of a live-born infant within 28 days after birth.

Statistical Analysis

All analyses were performed using Stata 14.0 software (StataCorp). Baseline characteristics were compared between exposure groups using the χ^2-test for categorical variables and *t* tests or Mann-Whitney tests for continuous variables, depending on the degree of normality of underlying distributions.

A directed acyclic graph was used to guide decisions on covariate adjustment for each set of outcomes (Supplementary Figure S2). Potential confounders were included in our adjusted models. Socioeconomic status was measured using the mother's education and the household wealth index, estimated using principal components analysis of common household items [22]. Poisson regression models were used to calculate incidence rate ratios between exposure groups. Our final model comparing malaria incidence rates was adjusted for education, household wealth, gravidity, receipt of intermittent preventive

treatment with DP (IPTp-DP), and maternal age at conception. Poisson regression models with robust standard errors were used to estimate risk ratios of binary outcomes [23], including placental malaria and birth outcomes.

Final models assessing the differences in placental malaria between levels of IRS protection were adjusted for education, household wealth, gravidity, receipt of DP, maternal age at conception, and reported bed net ownership at enrollment. Final birth outcome models were adjusted for education, household wealth, receipt of DP, baseline CD4 cell count, baseline viral load, maternal age at conception, reported baseline bed net ownership, protease inhibitor use, and gravidity. Gestational age at enrollment was not included as a covariate in our models, because it did not confound the relationship between IRS protection and malaria or adverse birth outcomes. In addition, indicators of malaria infection were not adjusted for in the final birth outcomes models, because these were intermediate steps in the causal pathway (Supplementary Figure S2).

All continuous variables were tested for nonlinearity by fitting a 5-knot restricted cubic spline to each model. The restricted cubic spline terms were tested for nonlinearity at the $P < .05$ level using the *testparm* command in Stata software. Marginal risks for each level of exposure (ie, the potential risk of the outcome assuming that all individuals received the same level of IRS protection) are presented in our analyses and computed from our adjusted models using marginal standardization. Predicted probabilities from adjusted models were tested for trends across levels of IRS protection using the *nptrend* command in Stata software, an extension of the nonparametric, Wilcoxon rank sum test. For all analyses above, differences were considered statistically significant at $P < .05$.

Data were missing for household wealth (n = 20), maternal education (n = 1), baseline CD4 cell count (n = 13), HIV-1 load (n = 6), and date of birth (n = 6). Data were also missing for diagnosis of placental malaria with microscopy (n = 67; 12%), LAMP/PCR (n = 83; 15%), and histopathology (n = 54; 10%). To account for this, missing data were assumed to be missing at random and accounted for using multiple imputation with a series of chained regression equations. We imputed 100 data sets with 1000 iterations of each, accounting for 10-iteration burn-in. Results from analyses of complete data and analyses from imputed data were similar, and only analyses using imputed data sets are reported here.

RESULTS

Characteristics of the Sample Population

A flow diagram of all women included in our analysis is presented in Figure 2. Women with nonsingleton pregnancies (n = 12) and those withdrawn before delivery (n = 12) were excluded. Women were enrolled only once in each parent study, but 22 women (3.9%) were enrolled separately into both studies.

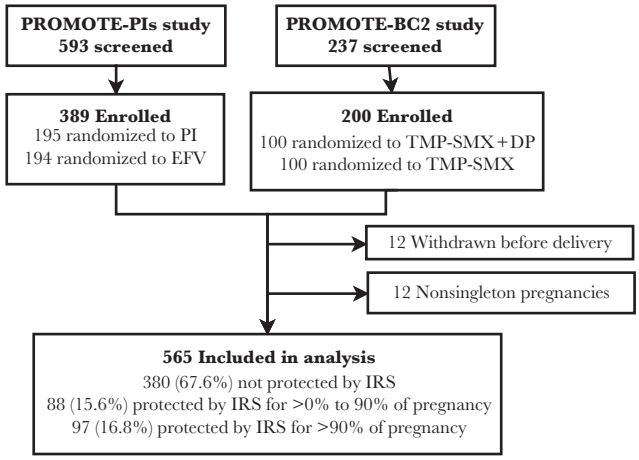

Figure 2. Flow diagram representing the study's inclusion criteria for human immunodeficiency virus (HIV)–infected pregnant women in the PROMOTE–Protease Inhibitors (PROMOTE-PIs) and PROMOTE–Birth Cohort 2 (PROMOTE-BC2) studies conducted in Tororo, Uganda. DP, dihydroartemisinin-piperaquine; EFV, efavirenz; IRS, indoor residual spraying; PI, protease inhibitor; TMP-SMX, trimethoprim-sulfamethoxazole.

The general characteristics of the study sample by levels of IRS protection are presented in Table 1. Of the 565 women included in our analysis, 380 (68%), 88 (16%), and 97 (17%) were protected by IRS for 0%, >0% to 90%, and >90% of their pregnancy, respectively (Figure 2).

All women enrolled in the PROMOTE-PIs trial delivered ≥20 months before IRS was implemented in Tororo District. Women from the PROMOTE-BC2 trial who were not protected by IRS (n = 13) did not reside within Tororo District, but were included in the study because their households were still within the catchment area. The remaining 93%of women in the PROMOTE-BC2 trial (185 of 198) were protected by IRS for various durations of their pregnancy. Among women with any IRS protection, the median proportion of protection was 92% (interquartile range, 65%–100%). Compared with women not protected by IRS, women protected by IRS for >90% of their pregnancy were more likely to have no formal education ($P = .02$), be wealthier ($P = .001$), receive monthly doses of IPTp-DP ($P < .001$), report owning a bed net at study enrollment ($P < .001$), have a higher baseline CD4 cell count ($P < .001$), have a lower baseline HIV-1 load ($P < .001$), and be enrolled earlier in their pregnancy ($P < .001$). Gravidity and maternal age were similar across levels of IRS protection.

Effect of IRS on Malaria Outcomes

Associations between IRS protection and malaria outcomes are presented in Table 2 and Table 3. Seventy episodes of symptomatic malaria were observed in 14% of women with no IRS protection (52 of 380), compared with 1 episode observed in a woman with >0% to 90% IRS protection ($P < .001$) and none observed among women with >90% IRS protection ($P < .001$). The incidence rate of symptomatic malaria was 93% lower in

Table 1. Characteristics of Study Participants by IRS Exposure[a]

Characteristic	Proportion of Pregnancy Protected by IRS			*P* Value[b]
	0% (n = 380)	>0% to 90% (n = 88)	>90% (n = 97)	
Parent study, No. (%)				
PROMOTE-PIs	367 (96.6)	0 (0.0)	0 (0.0)	<.001
PROMOTE-BC2	13 (3.4)	88 (100.0)	97 (100.0)	
Only neighboring houses sprayed, No. (%)	NA	9 (10.2)	13 (13.4)	.51
Level of education, No. (%)				
None	53 (14.0)	12 (13.6)	28 (28.9)	.02
Primary school	248 (65.3)	53 (60.2)	53 (54.6)	
Secondary school or higher	78 (20.5)	23 (26.1)	16 (16.5)	
Household wealth, No. (%)				
Low	133 (35.0)	23 (26.1)	23 (23.7)	.001
Middle	114 (30.0)	27 (30.7)	41 (42.3)	
High	113 (29.7)	38 (43.2)	33 (34.0)	
Gravidity, No. (%)				
Primagravida	24 (6.3)	9 (10.6)	7 (7.2)	.36
Secundigravida	41 (10.7)	11 (12.9)	14 (14.4)	
Multigravida	318 (83.0)	65 (76.5)	76 (78.4)	
Assigned malaria chemoprevention regimen, No. (%)				
Daily TMP-SMX	374 (97.7)	46 (54.1)	46 (47.4)	<.001
Daily TMP-SMX plus monthly IPTp-DP	9 (2.4)	39 (45.9)	51 (52.6)	
Any use of PI during follow-up, No. (%)	186 (48.6)	8 (9.1)	6 (6.2)	<.001
Baseline bed net ownership, No. (%)	222 (58.4)	77 (87.5)	89 (91.8)	<.001
Baseline CD4 cell count, median (IQR), cells/μL	402 (274–504)	523 (361–658)	514 (390–610)	<.001
Baseline HIV RNA, median (IQR), $\log_{10}$ copies/mL	4.2 (3.3–4.8)	2.3 (1.3–3.7)	2.8 (0–4.1)	<.001
Maternal age at conception, mean (SD), y	29.2 (5.5)	29.4 (6.1)	29.9 (6.6)	.56
Gestational age at enrollment, median (IQR), wk	21.0 (17.7–24.6)	21.2 (18.3–24.9)	18.3 (14.8–21.1)	<.001

Abbreviations: HIV, human immunodeficiency virus; IPTp-DP, intermittent preventive treatment (in pregnancy) with dihydroartemisinin-piperaquine; IQR, interquartile range; IRS, indoor residual spraying; NA, ; PI, protease inhibitor; PROMOTE-BC2, PROMOTE–Birth Cohort 2 study; PROMOTE-PIs, PROMOTE–Protease Inhibitors study; SD, standard deviation; TMP-SMX, trimethoprim-sulfamethoxazole.

[a]Column percentages may not add up to 100% owing to missing data.

[b]Significance levels determined using Fisher exact or χ^2 tests, where appropriate

women with >0% IRS protection (0.01 episodes per person-year) than in unprotected women (0.41 episodes per person-year).

The risk of placental malaria detected by microscopy was 89% lower for women protected by IRS for >0% of their pregnancy than for women not protected by IRS (marginal risk of the outcome among exposed vs unexposed, 0.4% vs 3.9%). Compared with women with no IRS protection, the risk of placental malaria detected by LAMP/PCR was 83% lower in women protected by IRS for >0% to 90% of their pregnancy (10.2% vs 1.8%) and 92% lower in women with >90% IRS protection (10.2% vs 0.9%). The risk of placental malaria detected through histopathology was 88% lower in women protected by IRS for >0% to 90% of their pregnancy (31.3% vs 3.9%) and 80% lower in women with >90% IRS protection (31.3% vs 6.3%). Among placental tissues assessed at delivery (n = 511), active infection was observed in 7.2% of the women who were not protected by IRS (24 of 332), 1.2% of those with >0% to 90% IRS protection (1 of 84), and none of those with >90% protection (0 of 95). Past infections were observed in 25.0% of women not protected by IRS (83 of 332), 2.4% of those with >0% to 90% IRS protection

Table 2. Associations Between IRS Exposure and Incidence of Symptomatic Malaria Assessed During Pregnancy

IRS Exposure Category	Events (IR)[a]	Crude IRR (95% CI)	*P* Value	Adjusted IRR (95% CI)[b]	*P* Value
0%	70 (0.41)	Reference group	…	Reference group	…
>0% to 90%	1 (0.03)	0.03 (.004–.21)	<.001	0.07 (.009–.48)	.007
>90%	0 (0)				

Abbreviations: CI, confidence interval; IR, incidence rate; IRR, IR ratio; IRS, indoor residual spraying.

[a]Defined as episodes per person-year.

[b]Adjusted for education, household wealth, gravidity, receipt of intermittent preventive treatment with dihydroartemisinin-piperaquine, and maternal age at conception. Both the reported crude and adjusted IRRs refer to the collapsed IRS exposure categories of >0 to 90% and >90% to equate >0 to 100%.

Table 3. Associations Between IRS Exposure and Placental Malaria Assessed at Delivery

IRS Exposure Category by Outcome	No. (%)	Crude RR (95% CI)	*P* Value	Adjusted RR (95% CI)[a]	*P* Value
Placental malaria by microscopy					
0%	10 (3.1)	Reference group	…	Reference group	…
>0% to 90%	1 (1.2)	0.17 (.02–1.38)	.10	0.11 (.04–.20)	<.001
>90%	0 (0)				
Placental malaria by LAMP/PCR					
0%	25 (8.3)	Reference group	…	Reference group	…
>0% to 90%	2 (2.4)	0.30 (.07–1.23)	.095	0.17 (.05–.61)	.007
>90%	1 (1.1)	0.15 (.02–1.05)	.056	0.08 (.01–.54)	.009
Placental malaria by histopathology					
0%	107 (32.2)	Reference group	…	Reference group	…
>0% to 90%	3 (3.6)	0.12 (.04–.37)	<.001	0.12 (.04–.36)	<.001
>90%	5 (5.3)	0.19 (.08–.44)	<.001	0.20 (.08–.47)	<.001

Abbreviations: CI, confidence interval; IRS, indoor residual spraying; LAMP, loop-mediated isothermal amplification; PCR, polymerase chain reaction; RR, risk ratio.

[a]Adjusted for education, household wealth, gravidity, receipt of intermittent preventive treatment with dihydroartemisinin-piperaquine, maternal age at conception, and reported bed net ownership at baseline. Both the reported crude and adjusted IRRs refer to the collapsed IRS exposure categories of >0 to 90% and >90% to equate >0 to 100%.

(2 of 83), and 5.3% of those with >90% IRS protection (5 of 95). Overall, results were similar in sensitivity analyses excluding women who received monthly IPTp-DP (Supplementary Table S1).

Effect of IRS on Birth Outcomes

Associations between levels of IRS protection and the risks of adverse birth outcomes are presented in Table 4. Overall, IRS protection was associated with reduced risks of preterm birth, low birth weight, and fetal or neonatal death. A dose-response relationship was observed across all levels of birth outcomes ($P_{trend} < .001$). IRS protection >90% was associated with a significant, 65% reduction in preterm birth risk as compared with women with no IRS protection (17.1% vs 6.0%). The risks of low birth weight and fetal or neonatal death in women with >90% IRS protection were lower than in women with no IRS protection (11.4% vs 16.9% and 1.5% vs 6.1%, respectively), though these findings did not reach statistical significance. In addition, similar trends were found in sensitivity analyses excluding women who received monthly IPTp-DP (Supplementary Table S2) and excluding women from the PROMOTE-PIs study (Supplementary Table S3).

DISCUSSION

In Tororo, Uganda, IRS has led to marked declines in malaria transmission and incidence of malaria [15]. In our study, the incidence of symptomatic malaria and placental malaria were significantly reduced among HIV-infected pregnant women protected by IRS. IRS was associated with a significant reduction in preterm birth risk among women protected by IRS for >90% of their pregnancy. Reductions in low birth weight and fetal or neonatal death were observed among women protected for >90% of their pregnancy, although these findings did not reach statistical significance. Notably, these findings were

Table 4. Associations Between IRS Exposure and Adverse Birth Outcomes

IRS Exposure Category by Birth Outcome	No. (%)	Crude RR (95% CI)	*P* Value	Adjusted RR (95% CI)[a]	*P* Value
Preterm birth					
0%	65 (17.1)	Reference group	…	Reference group	…
>0% to 90%	11 (12.5)	0.73 (.40–1.33)	.30	0.76 (.35–1.65)	.49
>90%	6 (6.2)	0.36 (.16–.81)	.01	0.35 (.15–.84)	.02
Low birth weight					
0%	70 (18.5)	Reference group	…	Reference group	…
>0% to 90%	15 (17.1)	0.92 (.55–1.53)	.74	1.27 (.69–2.36)	.44
>90%	9 (9.3)	0.50 (.26–.97)	.04	0.68 (.29–1.57)	.36
Fetal or neonatal death					
0%	20 (5.3)	Reference group	…	Reference group	…
>0% to 90%	5 (5.7)	1.08 (.42–2.80)	.88	0.78 (.22–2.72)	.70
>90%	2 (2.1)	0.39 (.09–1.65)	.20	0.24 (.04–1.52)	.13

Abbreviations: CI, confidence interval; IRS, indoor residual spraying; RR, risk ratio.

[a]Adjusted for education, household wealth, receipt of intermittent preventive treatment with dihydroartemisinin-piperaquine, baseline CD4 cell count, baseline human immunodeficiency virus type 1 RNA load, maternal age at conception, reported baseline bed net ownership, protease inhibitor use, and gravidity.

observed among HIV-infected pregnant women concurrently receiving bed nets, daily TMP-SMX and cART, suggesting that IRS may have additional benefits in women receiving these interventions. We also observed an inverse relationship between increasing levels of IRS protection and the risk of both malaria and adverse birth outcomes, suggesting that IRS may have dose-dependent effects.

These findings are consistent with an earlier study conducted by our group among HIV-uninfected pregnant women [16]. In that study, IRS was implemented after approximately half of the women had been enrolled, and the maximum duration of pregnancy under the protection of IRS was 43%. Compared with women who had no IRS protection, those protected by IRS for >20% to 43% of their pregnancy had lower risks of preterm birth (17.2% vs 1.5%), low birth weight (20.9% vs 3.1%), and fetal or neonatal deaths (7.5 vs 0%) [16]. Compared with HIV-infected women, effect sizes seen among uninfected women were greater in magnitude and statistically significant across all similarly measured birth outcomes, despite a shorter duration of IRS protection. Thus, it is possible that an interaction between HIV and malaria may still persist among women receiving cART, though data on this is conflicting [24, 25].

The studies included in the current analysis were not designed to answer our research question a priori and subject to several limitations. One limitation is that our study was observational and may have be prone to residual confounding. For example, only women enrolled in the first study receive PIs, which have previously been associated with small but significant increases in adverse birth outcomes [26–30]. In our study, however, PI use was not associated with an increased risk of preterm birth [21]. We also may have overestimated our results had there been secular declines in malaria and adverse birth outcomes independent of the IRS campaign. Data from the General Population Cohort, a population-based cohort in rural Uganda, suggest that the prevalence of adverse birth outcomes remained fairly stable or slightly increased between 1996 and 2013 [31], though we found no data on birth outcomes during the 2014–2016 period. We also assessed the effects of IRS by limiting our analysis to women of the PROMOTE-BC2 trial and found similar patterns of reduction. Although these findings did not reach statistical significance, they suggest that our conclusions were not driven by secular trends. Statistical power was another limitation of our study. This is evident in the relatively large confidence intervals around our parameter estimates. Thus, it is possible that IRS may reduce the risk of low birth weight and neonatal death but our study was not powered to detect it. Future studies evaluating the effect of IRS are needed to validate our exploratory findings.

Our results support the hypothesis that IRS may be beneficial for HIV-infected pregnant women living in areas of high malaria burden. In our study, we found that the risks of placental malaria detected with histopathology (32.2%), preterm birth (17.1%), low birth weight (18.5%), and fetal or neonatal death (5.3%) were particularly high among HIV-infected pregnant women not protected by IRS, despite their having received bed nets, daily TMP-SMX, and cART. The high prevalence of these adverse birth outcomes suggests that current interventions are insufficient to achieve the target of Sustainable Development Goal 3.2 to reduce neonatal mortality rates and mortality rates in children <5 years old by 2030 in malaria-endemic regions. In 2015, 45.1% of global deaths among children <5 years old occurred during the neonatal period, for which the leading cause was preterm birth [32]. In women infected with *P. falciparum* during pregnancy, a recent analysis showed that 26% of all neonatal deaths were mediated through preterm birth [33]. Our findings suggest that IRS protection among HIV-infected pregnant women early in their pregnancy may reduce the risk of preterm birth, which could potentially translate into the substantial reductions in neonatal mortality rates required to meet the target indicators of Sustainable Development Goal 3.2.

Although IRS can be cost-intensive and requires a large amount of human resources, investment in IRS could lead to substantial gains in improving maternal and neonatal health outcomes, especially in areas of intense malaria transmission where the prevalence of preterm births is particularly high. Future studies evaluating the impact of IRS should also consider these outcomes in their cost-benefit and cost-effectiveness analyses. Understanding these downstream effects may assist in integrating efforts between the malaria, HIV, and maternal-child health communities, which may ultimately lead to considerable improvements in outcomes among HIV-infected pregnant women and their children in sub-Saharan Africa.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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