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# Assessment of The Efficacy and Safety of Dihydroartemisinin-Piperaquine for Intermittent Preventive Treatment of Malaria in Pregnancy: A Prospective Intervention Study in North-Central Nigeria

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**ABSTRACT**

**Introduction:** Sulfadoxine-pyrimethamine is the only antimalarial drug recommended for Intermittent preventive therapy in pregnancy (IPTp), however, its efficacy is declining due to increased malaria parasite resistance. This study assessed the efficacy and safety of dihydroartemisinin-piperaquine for IPTp. **Method:** A prospective observational study was conducted for twelve months in Nigeria. Five hundred and fifty eligible pregnant women were recruited and randomly assigned to either IPTp with dihydroartemisinin-piperaquine arm or IPTp with sulfadoxine-pyrimethamine arm. Designed data collection forms were used to collect relevant data. The participants were scheduled to receive three curative doses of either Sulfadoxine-pyrimethamine or dihydroartemisinin/piperaquine at an interval of not less than four weeks. Malaria rapid diagnostic tests and pack cell volume were conducted to detect malaria parasitemia and anemia respectively. The participants were followed to delivery and the pregnancy outcomes were assessed. Descriptive and inferential analyses were conducted and the significant level was set to be $P<0.05$. **Results:** The incidence of malaria parasitemia during pregnancy was significantly higher in the sulfadoxine-pyrimethamine arm, 3.83% than in the dihydroartemisinin-piperaquine arm 0.76% (P=0.036). However, the incidence of symptomatic malaria was higher in the dihydroartemisinin-piperaquine group (1.92%), than in the sulfadoxine-pyrimethamine group (0.38%), but showed no significant difference (P=0.122). The prevalence of a composite adverse pregnancy outcome showed no statistically significant difference between the two groups (P=0.288). **Conclusion:** The study revealed that in the region of low malaria parasite resistance to sulfadoxine-pyrimethamine, three regimens of Dihydroartemisinin-piperaquine for IPTp were effective, safe, and well-tolerated compared to three regimens of Sulfadoxine-pyrimethamine.

## INTRODUCTION

Sulfadoxine-pyrimethamine (SP) is currently the only antimalarial drug recommended by the WHO for Intermittent preventive treatment in pregnancy, [1] it is aimed at protecting pregnant women and their unborn babies against adverse consequences of malaria infection. However, its prophylactic efficacy is declining due to increased malaria parasite resistance. [2,3] A severe malaria infection during pregnancy is related to maternal anemia and unwanted birth outcomes, including spontaneous abortions, stillbirth, preterm birth, low birth weight (LBW), and early infant mortality.[4-8] Global malaria cases and death were estimated to be 229 million and 409,000 respectively in 2019. However, five countries in Africa were responsible for 51% of world malaria cases and 51% of death due to malaria. Nigeria alone contributed 27% and 23% to Africa malaria cases and death, respectively. [9] World Health Organization (WHO) recommends using insecticidal treated nets and intermittent preventive treatment with SP in malaria-endemic areas to prevent malaria infection during pregnancy and reduce the risk of adverse birth outcomes. However, public health concerns about the declining benefit of these interventions due to the widespread malaria parasite resistance to the Pyrethroid insecticides used in insecticidal treated nets and Sulfadoxine-pyrimethamine in a malarial endemic region. [10, 11] Observational studies from East Africa suggested that the use of SP as intermittent preventive treatment during pregnancy provided minimal or no benefit.

[12,13] A few controlled trials have evaluated alternatives to Sulfadoxine-pyrimethamine, including amodiaquine and mefloquine, for intermittent preventive treatment during pregnancy; however, they have not shown convincing evidence of higher efficacy, and the drugs had an intolerable side-effect profile. [14,15] Presently there is no alternative antimalarial drug recommended for intermittent preventive therapy. Therefore, there is an urgent need for alternative antimalarial agents for malaria prophylaxis during pregnancy to achieve the global target of protecting pregnant women and their unborn babies against high-risk adverse consequences of malaria infection. Artemisinin-based combination therapies (ACTs) are now the standard treatment for malaria in Africa; A comparison study of four ACTs {Artesunate-mefloquine, Artesunate-amodiaquine, Artemether-lumefantrin, and Dihydroartemisinin-piperaquine (DP)} for the treatment of malaria in pregnancy in Africa showed that DP had the best efficacy and prolonged post-treatment prophylactic effect, which

supports its suitability for intermittent preventive treatment of malaria in pregnancy (IPTp) in the region of high transmission. [16]

However, data about their repeated use as malaria preventive therapy during pregnancy are limited, especially in the region of low malaria resistance to SP. Dihydroartemisinin-piperaquine is an attractive alternative to SP for intermittent preventive treatment of malaria in pregnancy because it is highly productive in eliminating malaria parasites. In addition, the long half-life of piperaquine provides longer post-treatment prophylaxis of at least four weeks. [17]

Five randomized control trials were conducted in the African region with a high record of malaria transmission and resistance to SP to evaluate the use of Dihydroartemisinin-piperaquine for the prevention of malaria in pregnancy. One trial [18] compared intermittent preventive treatment in pregnancy (IPTp) with monthly dihydroartemisinin-piperaquine plus daily trimethoprim-sulfamethoxazole in HIV-infected pregnant women. The study concluded that the addition of IPTp with monthly DP to trimethoprim-sulfamethoxazole appeared to be safe and well-tolerated but did not provide additional protection against malaria [18]. Two trials [19, 20] included a group where women were screened for malaria with rapid diagnostic tests at scheduled intervals when found positive, a full course of DP was administered, this strategy is known as intermittent screening and treatment in pregnancy (ISTp). The trials' outcomes suggested that IST with DP was not superior to intermittent preventive treatment in pregnancy with Sulfadoxine-pyrimethamine (IPTp-SP) and was inferior for some results. Another two trials [19, 21] compared intermittent preventive treatment in pregnancy with Dihydroartemisinin-piperaquine (IPTp-DP) versus intermittent preventive treatment in pregnancy with Sulfadoxine-pyrimethamine (IPTp-SP), in one of these, both drugs were given every 4–6 weeks and in the other trial, sulfadoxine-pyrimethamine was given every eight weeks, and Dihydroartemisinin-piperaquine was given every four weeks or every eight weeks. In both trials, IPTp-DP was found to be superior to IPTp-SP for the prevention of malaria during pregnancy and at delivery; however, there were no differences in the risk of low birth weight or preterm birth. One trial [22] compared IPTp-DP versus IPTp-SP participants in both arms were given full courses of DP and SP every month, commencing from early second trimesters up to delivery in line with the WHO recommendation. The trial also assessed QTc prolongation in all women. The trial outcomes showed that incidence of malaria during pregnancy, the prevalence of placenta malaria, and symptomatic malaria were

significantly lower in IPTp-DP than IPTp-SP, these findings were similar to the outcomes of earlier trials conducted in Kenya [19] and Uganda [20].

In all five trials, DP was found to be as safe and well-tolerated as intermittent preventive therapy of malaria in pregnancy. The outcomes of three trials involving DP showed that intermittent preventive treatment in pregnancy with dihydroartemisinin-piperaquine was more efficacious in reducing malaria incidence during pregnancy than intermittent preventive therapy with Sulfadoxine-pyrimethamine.[19,21,22] WHO Malaria Policy Advisory Committee concluded that intermittent preventive treatment in pregnancy with Dihydroartemisinin-piperaquine merits further study, but that Sulfadoxine-pyrimethamine should remain the recommended drug for intermittent preventive treatment in pregnancy until there is conclusive evidence that alternative regimens are safe and improve birth outcomes. [23]

The earlier trials on IPTp-DP were limited to the region of high malaria transmission and high malaria parasite resistance to SP. None or few were carried out in areas of low malaria parasite resistance to Sulfadoxine-pyrimethamine. In this study, we compared the efficacy and safety of scheduled three doses regimens of dihydroartemisinin-piperaquine for intermittent preventive treatment in pregnancy versus scheduled three doses regimens sulfadoxine-pyrimethamine among pregnant women that attended antenatal care (ANC) in a tertiary health care facility located in an area of low malaria parasite resistance to Sulfadoxine-pyrimethamine. This will provide early additional information on the efficacy and safety of DP as IPT antimalarial in the region of low malaria parasite resistance to Sulfadoxine-pyrimethamine.

## MATERIALS AND METHODS

### Study setting

The study was conducted in Federal Medical Centre Keffi, a tertiary health facility in the north-central part of Nigeria. The Hospital is located at 52 kilometers distance from Abuja, the nation's capital. The facility has a manpower capacity of more than 2500 spread across different categories of health care professionals. In addition, the facility has two hundred and fifty-four (254) beds across other medical words in the Hospital.

**Study design**

The study was a prospective intervention **conducted** between September 2019 to October 2020. Five hundred and fifty (550) eligible pregnant women were recruited and randomly assigned to the two study arms.

**Study population/sample size**

All Pregnant women who attended Antenatal Care at the study facility and satisfied inclusion criteria were eligible and considered to participate in the study. The participants were grouped into intermittent preventive therapy of malaria in pregnancy with Sulfadoxine-pyrimethamine (IPTp-SP) (control arm) and intermittent preventive therapy of malaria in pregnancy with Dihydroartemisinin-piperaquine (IPTp-DP) (Test arm).

To test the hypothesis that the use of IPTp-DP would be associated with a 50% reduction in the incidence of malaria parasitemia, symptomatic malaria, and composite adverse outcomes compared with IPTp-SP taken within early second and third trimesters at the interval of not less than four (4) weeks, we assumed that the risk of these outcomes would be 20% in the IPTp-SP group based on previous data [22] and calculated that a sample size of 260 for each study arm (with 10% allow for a loss to follow-up during pregnancy) would be needed for the study to have 80% power to detect 50% reduction in malaria parasitemia, symptomatic malaria and composite adverse outcome with a statistical significance level of 0·05.

Pregnant women who were HIV-negative with gestational age between 13-24 weeks, age 16 years and above, leaving within 30 km radius from the study facility, and agreed to be followed-up to delivery were included. However, those with a history of adverse effects to DP or SP, chronic medical conditions requiring frequent medical attention were excluded.

**Ethical consideration**

Ethical and administrative approvals were sought and obtained from the Health Research Ethics Committee (HREC) of Federal medical Centre Keffi and heads of departments (obstetrics and gynecology, nursing, medical laboratory services, pharmaceutical services, and health information unit) of the facility, respectively (Ref. number: FMC/KF/HREC/289/18).

**Data collection instruments/ recruitment procedure**

Data collection forms were designed and used to collect relevant data from the pregnant women at the enrolment stage, follow-up schedules, and in addition, clinical talks were conducted during antenatal clinics at the study facility. During the health talks emphasis was made on the aim and objectives of the study, the importance of the research work, the advantage of the study to the participants, the society at large, and the rules guiding the study. Pregnant women who satisfied the inclusion criteria and voluntarily agreed to participate in the study signed or thumb-printed the consent forms. All eligible pregnant women who consented were recruited consecutively at the antenatal clinics (ANCs) until each group's required samples size was obtained.

**Enrollment/ Data collection procedure**

Eligible pregnant women were enrolled and randomly assigned (1:1) to either the control or the test groups of the study. All the participants were assigned study numbers, issued a study card, and had their baseline characteristics assessed and documented. The first assessment involves the collection of demographic data, obstetric history {Gestational age (GA) at enrollment, last menstrual period (LMP), expected delivery day (EDD), gravidity, parity}, previous medication history, etc. into enrolment form. Similarly, Baseline pack cell volume (PCV), malaria rapid diagnostic test (mRDT) results, ownership of insecticide-treated net (ITN); uses of ITN, subjects' contact numbers, and residential addresses were collected. Data were collected in collaboration with other research team members (Obstetric and gynecologists, Nurses, Medical laboratory scientists, Pharmacists, Medical health information managers, and six (6) research assistants). Health talks were delivered to pregnant women at every ANC clinic during the study. Each enrolled subject with gestational age (13 to 24) weeks, either at enrollment or at a subsequent visit, were given either Sulfadoxine-pyrimethamine (SP) (25mg/500mg)(Maldox$^{R}$ Emzor pharmaceutical product, NAFDAC number: 04-2911, batch number: R747X and expiration date: November 2021) three (3) tablets as a single dose or dihydroartemisinin-piperaquine (DP) (40mg/320mg) (Fanmed$^{R}$ Maydon Pharmaceutical product, NAFDAC number: B4-2194, batch number: FN7001-FN7002 and expiration date: January 2021 consisted of eight (8) tablets and were taken three (3) tablets each at 0 hours, 24 hours and two (2) tablets at 48hours consecutively. The full doses of Sulfadoxine-Pyrimethamine (SP) and the first doses of Dihydroartemisinin-Piperaquine (DP) were given under directly observed therapy (DOT) at the study clinic. All

recruited subjects were scheduled to receive three standard doses regimens of either DP or SP (i.e., IPTp1, IPTp2 & IPTp3) during the pregnancy at an interval of not less than four (4) weeks. The first daily doses of Dihydroartemisinin-Piperaquine (DP) (40mg/320mg) were administered to the IPTp-DP group under directly observed therapy in the clinic. The participants were properly counseled on how and when to take second and third subsequent doses at home.

**Laboratory procedure**

Malaria rapid diagnosis test (mRDT) kits (SD BIO LINE $^{(R)}$ Standard diagnostic, INC) were used to test for malaria parasitemia. Fresh blood samples of subjects were collected and tested for the presence of malaria parasites. These procedures were observed at the enrollment stage, subsequent visits, and the third trimester's last week. The test kits were labeled correctly with the subjects' study numbers and hospital numbers for proper tracking and recording. The medical laboratory assistants carried out the sample's collections while certified Medical laboratory scientists performed the tests. The results reading is done five to seven minutes after adding the buffer to the blood drop on the RDT test kit. Similarly, tests for Pack cell volume (PCV) were conducted. Fresh blood samples were collected into properly labeled sample collection bottles, the blood was mixed properly and then filled into the capillary tube up to two-thirds and the unfilled end was sealed with plasticine. The capillary tube was fixed in the microhematocrit centrifuge and covered. The centrifuge was then set at 12,000 revolutions per minute (rpm) and spun for five (5) minutes, the results were read using microhematocrit and recorded in percentages. These procedures were observed for all the samples collected at the baseline (enrolment) and the final (last week of the third trimester).

**Follow-up visit procedure:**

At each scheduled follow-up visit, all enrollees were assessed for malaria parasitemia by rapid diagnostic test (RDT), self-reporting side effects, adverse events, history of other drugs used between the last visit and the current visit, and relevant data were collected into data collection form, these procedures were consistently observed, and the enrollees were followed-up to delivery. The routine follow-up visits were scheduled every four (4) weeks. Bulk short message services (SMS) were used consistently to remind subjects of their follow-up schedules. This was sustained through the period of the study. Throughout the entire

follow-up visit, the Participants were encouraged to come for delivery at the study facility. Those who presented fresh complaints were referred to physicians for proper assessment and documented. Similarly, the participants were regularly counseled on the need to report any adverse events to the investigator/Physicians and to avoid self-medication during the study. Regular Phone calls follow-up were made to participants that were not seen on the scheduled antenatal clinic day. Pregnant women who delivered at home or Hospitals other than the study facility were traced correctly with the contact addresses. Data about their deliveries were collected accordingly. Adverse events were assessed and graded according to standardized criteria (National Institutes of Health, Division of AIDS table for grading the severity of adult and Paediatric adverse events) at every visit to the study clinic. [24]

**Outcomes**

The primary outcomes were the incidence of malaria parasitemia by RDT after administration of doses of study drugs, symptomatic malaria, and prevalence of anemia (pack cell volume <30%). Secondary outcomes were risk of a composite of adverse birth outcomes; these include low birth weight (<2.5kg), preterm birth (<37 weeks gestational age), spontaneous abortion (delivery at <28 weeks gestational age), stillbirth (infant born deceased at ≥28 weeks gestational age), poor or good Appearance, Pulse, Grimace, Activity and Respiration (APGAR) score, neonatal death (infant death within the first 28 days of life) and presence of any congenital malformation. In addition, tolerability assessments which included vomiting and other adverse effects were recorded following the administration of study drugs. Finally, pregnancy outcomes of the subjects followed to delivery were assessed and documented accordingly.

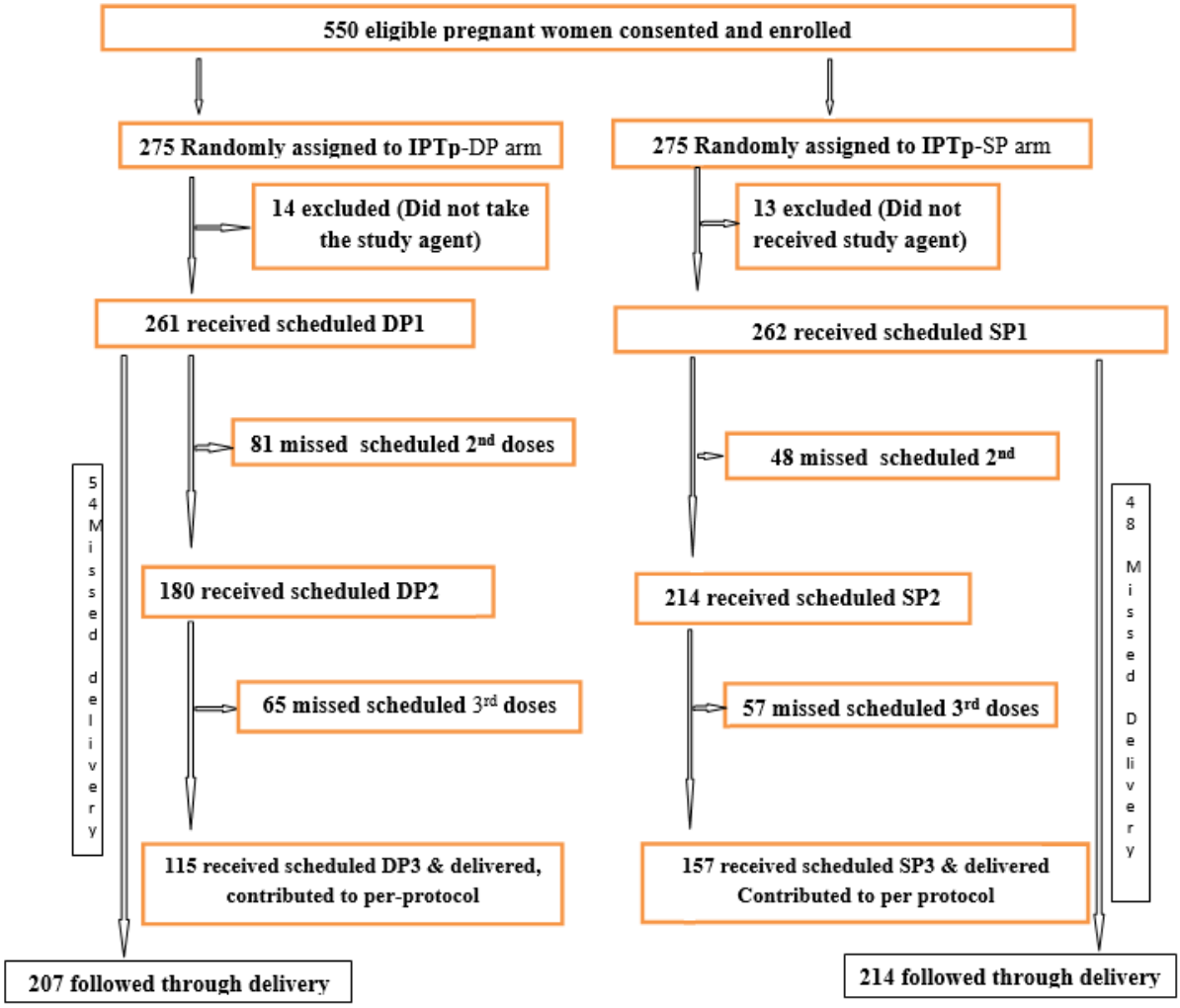


***Figure 1: Study profile***

IPTp-SP=*Intermittent preventive treatment for malaria in pregnancy with Sulfadoxine-pyrimethamin*e. IPTp-DP= *Intermittent preventive treatment for malaria in pregnancy with Dihydroartemisinin-piperaquine. The number of recruited subjects per clinic day was controlled to a maximum of 20 for an effective follow-up protocol.*

**Statistical analysis**

Descriptive and inferential analyses were done using IMB SPSS version 20. All analyses were performed in the modified intention-to-treat population, including all participants who received either SP or DP and had an outcome of interest that could be evaluated. Categorical variables were compared using the chi-square test. Means of anemia in the study groups were compared using a paired sample t-test. A comparison of incidence measures using a negative binomial regression model was done. Incidence risk ratios (IRR) were defined as the incidence risk of malaria parasitemia in the IPTp-DP group divided by the incidence risk in

the IPTp-SP group. The modification excluded subjects who were withdrew from the study before the administration of study agents

**RESULTS**

A total of 421 (77%) of 550 enrolled pregnant women were followed through delivery (214 in the IPTp-SP group and 207 in the IPTp-DP group). Thus, 394 (72%) of 550 participants received two to three total doses of the study agents (i.e., 180 of DP and 214 of SP) (figure 1).

Table 1. shows that 310 (56%) of 550 participants attended tertiary education. 34 (12%) of 275 and 11(4%) of 275 were tested positive to malaria parasites at enrolment in test and control arms, respectively. Furthermore, the mean pack cell volumes (PCV) of the participants in IPTp-DP and IPTp-SP were 32.1 and 32,0 respectively.

Table 2. Obstetric characteristics of participants at baseline reflected that; A total of 402 (72%) of 550 were enrolled at (13-24) weeks gestational age. A total of 69 (25%) of 275 and 61 (22%) of 275 were primigravidae in IPTp-DP and IPTp-SP arms, respectively. Meanwhile, 30 (14%) and 33(15%) of previous miscarriages recorded were observed in IPTp-DP and IPTp-SP arms, respectively.

Table 3. shows that 34 and 12 malaria parasitemia were recorded at enrolment in IPTp-DP and IPTp-SP respectively, similarly, 2 and 10 cases of malaria parasitemia during pregnancy were detected in IPTp with DP and IPTp with SP. The prevalence of anemia in IPTp-SP and IPTp-DP arms were 7 and 15 respectively. Meanwhile, a comparison of anemia cases at enrolment and last week of the pregnancy shows statistically significant differences within the test group ($p<0.001$) and control group ($p<0.001$).

Table 4. shows that the incidence of symptomatic malaria during pregnancy was significantly higher 5/261(1.9%) in the Dihydroartemisinin-piperaquine group compared to 2/262(0.8%) in the Sulfadoxine-pyrimethamine group. However, the incidence of malaria parasitemia detected with rapid diagnostic test (RDT) kit was significantly lower 2/261(0.8%) in the Dihydroartemisinin-piperaquine group relative to 10/262 (3.9%) in the Sulfadoxine-pyrimethamine group. In addition, the risk of maternal anemia during pregnancy was also significantly higher 15/261(5.8%) in the Dihydroartemisinin-piperaquine group than 7/252(2.7%) in the Sulfadoxine-pyrimethamine group.

A total of 421(77 %%) participants were followed through delivery (207 in the IPTp-SP group and 214 in the IPTp-DP group), and 417 (99%) delivered live births. About 102(20%) of 523 missed delivery, with the proportion of 54 participants in IPTp-DP and 48 participants in IPTp-SP). (Figure 1). Among 417 pregnant women who delivered, 15 (3.6%) did not give birth at the Hospital, with the proportion of 6 (1.4%) in Dihydroartemisinin-piperaquine and 9 (2.2%) in Sulfadoxine-pyrimethamine study arms. Only two women gave birth to twins with no evidence of complications.

Table 5. Depicted that the occurrence of composite adverse pregnancy outcome did not differ significantly between the intervention groups, (50 [24%] of 207) women in the IPTp-DP group as compared with (54 [25%] of 214) women in IPTp-SP group; {IRR 0.971, (95%CI 0.772-1.220) P=0.822}. Furthermore, none of the risks of individual adverse pregnancy outcomes (low birth weight, preterm birth, post-term delivery, miscarriage, stillbirth, and APGAR scores) shows a statistically significant difference between the two arms of the study.

A total of 70 adverse events associated with drugs tolerability were recorded in the treatment groups, with greater occurrence (51) reported in participants in intermittent preventive treatment in pregnancy with the Dihydroartemisinin-piperaquine group (table 6). In addition, the composite adverse events showed a statistically significant difference between the treatment arms P <0.001. (table 6). The first dose of Dihydroartemisinin-piperaquine was well tolerated by most pregnant women: twelve (12) and two (2) pregnant women had a single episode of vomiting after the first and subsequent doses, respectively (table 6). Most of the risks of individual adverse events differ significantly between groups (vomiting, weakness, and dizziness) (table 6). There was 10 grade two adverse events associated with vomiting. (table 6).

**Table 1. Sociodemographic characteristics of participants**

| Items | IPTp-DP | | IPTp-SP | | *P*-value |
|---|---|---|---|---|---|
| **Age (Year)** | (n) | (%) | (n) | (%) | |
| Mean age (year) | 29.2 | | 29.7 | | **0.999** |
| **Categories of age** | | | | | **1** |
| <18 | 1 | 0.36 | 1 | 0.36 | |
| ≥18 | 274 | 99.64 | 274 | 99.63 | |
| Total | 275 | 100 | 275 | 100 | |
| **Educational status** | | | | | **0.975** |
| Non-formal | 3 | 1.09 | 3 | 1.09 | |
| Primary | 12 | 4.36 | 11 | 4 | |
| Secondary | 103 | 37.45 | 108 | 39.27 | |
| Tertiary | 157 | 57.1 | 153 | 55.64 | |
| Total | 275 | 100 | 275 | 100 | |
| **Occupation** | | | | | **<0.001** |
| Farmer | 6 | 2.18 | 15 | 5.45 | |
| Applicant | 26 | 9.45 | 114 | 41.45 | |
| Student | 38 | 13.82 | 69 | 25.09 | |
| House wife | 42 | 15.27 | 4 | 1.45 | |
| Civil servant | 70 | 25.45 | 40 | 14.55 | |
| Business | 93 | 33.83 | 33 | 12 | |
| Total | 275 | 100 | 275 | 100 | |
| Detected Malaria parasite at enrolment by RDT | 34 | 12 | 11 | 4 | **<0.001** |
| Mean PCV at enrolment | 32.1 | | 32.0 | | **0.999** |

*IPTp-DP= Intermittent preventive therapy with dihydroartemisinin/piperaquine, IPTp-SP= Intermittent preventive therapy with Sulfadoxine/pyrimethamine, PCV=Pack cell volume*

**Table 2. Obstetrics characteristics of participants at baselines**

| **Items** | **IPTp-DP** | | **IPTp-SP** | | |
|---|---|---|---|---|---|
| | (n) | (%) | (n) | (%) | **P-value** |
| **Gestational age at enrolment** | | | | | |
| Mean gestational age (week) | 18.6 | | 17.6 | | **0.999** |
| First trimester | 70 | 25.45 | 58 | 17.8 | **2.084** |
| Second trimester | **197** | 71.64 | 205 | 77.65 | |
| Third trimester | 8 | 2.91 | 12 | 4,55 | |
| Total | 275 | 100 | 275 | 100 | |
| **Gravidity** | | | | | **0.252** |
| Primigravidae | 69 | 25.09 | 61 | 22.18 | |
| Secondigravidae | 65 | 23.61 | 82 | 29.82 | |
| Multigravidae | 141 | 51.3 | 132 | 48 | |
| Total | 275 | 100 | 275 | 100 | |
| **Parity** | | | | | **0.954** |
| 1-2 | 138 | 66.67 | 140 | 66.67 | |
| 3-4 | 48 | 23.53 | 53 | 25.24 | |
| 4-6 | 13 | 6.37 | 15 | 5.24 | |
| >6 | 7 | 3.43 | 6 | 2.86 | |
| **Mode of delivery** | | | | | **0.022** |
| Caesarian section | 21 | 10.45 | 37 | 18.5 | |
| Vaginal | 180 | 89.55 | 163 | 81.5 | |
| Total | 201 | 100 | 200 | 100 | |
| **Previous pregnancy outcome** | | | | | **0.774** |
| Miscarriage | 30 | 14.02 | 33 | 15.94 | |
| Pre term delivery | 2 | 0.93 | 4 | 1.93 | |
| Term delivery | 173 | 80.84 | 162 | 78.26 | |
| Still birth | 9 | 4.21 | 8 | 3.86 | |
| Total | 214 | 100 | 207 | 100 | |

*IPTp-DP= Intermittent preventive therapy with dihydroartemisinin/piperaquine, IPTp-SP= Intermittent preventive therapy with Sulfadoxine/pyrimethamine*

**Table 3. Comparison of malaria parasitemia and PCV at enrolment and during pregnancy within the study arms**

| Incidence of malaria | IPTp-DP | | | IPTp-SP | | |
|---|---|---|---|---|---|---|
| | At enrolment | during pregnancy | P-value | At enrolment | during pregnancy | P-value |
| Symptomatic malaria | 0/261 | 5/261 | **0.061** | 0/262 | 1/262 | **1** |
| Detection of malaria parasitaemia by RDT | 34/261 | 2/261 | **<0.001** | 12/262 | 10/262 | **0.828** |
| Mean PCV % | 31.7 | 31.9 | **0.697** | 31.7 | 32.7 | **0.159** |
| Anaemia (PCV <30%) | 37/261 | 15/261 | **0.001** | 35/262 | 7/262 | **<0.001** |

*IPTp-DP= Intermittent preventive therapy with dihydroartemisinin/piperaquine, IPTp-SP= Intermittent preventive therapy with Sulfadoxine/pyrimethamine, PCV=Pack cell volume*

**Table 4. Comparison of incidence of malaria during pregnancy between IPTp-DP and IPTp-SP**

| Incidence of malaria | IPTp-DP | IPTp-SP | IRR | 95% CI | P-value |
|---|---|---|---|---|---|
| Symptomatic malaria | 5/261 | 1/262 | 5.109 | 0.590 – 42.669 | **0.122** |
| Detection of malaria parasitaemia by RDT | 2/261 | 10/262 | 0.201 | 0.044 – 0.908 | **0.036** |
| Anaemia (PCV <30%) | 15/261 | 7/262 | 2.151 | 0.892 – 5.189 | **0.086** |

*IPTp-DP= Intermittent preventive therapy with dihydroartemisinin/piperaquine, IPTp-SP= Intermittent preventive therapy with Sulfadoxine/pyrimethamine, PCV=Pack cell volume*

**Table 5. Safety profiles**

| Outcome assessed at delivery | IPTp-DP | IPTp-SP | IRR | 95% CI | *P*-value |
|---|---|---|---|---|---|
| Composite adverse pregnancy outcomes | 50/207 | 54/214 | 0.971 | 0.772 - 1.220 | **0.822** |
| Low birth weight | 11/207 | 9/196 | 1.075 | 0.715 - 1.617 | **0.821** |
| Preterm delivery | 10/207 | 15/214 | 0.804 | 0.493 - 1.313 | **0.412** |
| Post term delivery | 4/207 | 7/214 | 0.734 | 0.334 - 1.615 | **0.544** |
| Poor APGAR score at 1mins | 14/127 | 10/115 | 1.125 | 0.784 - 1.616 | **0.668** |
| Poor APGAR score at 5mins | 2/127 | 2/115 | 0.952 | 0.355 - 2.556 | **1** |
| Miscarriage | 4/261 | 7/262 | 0.724 | 0.330 - 1.591 | **0.544** |
| Still birth | 4/207 | 4/214 | 1.017 | 0.505 - 2.048 | **1** |
| Neonatal death | 1/207 | 0/205 | 1.995 | 1.812 - 2.197 | **1** |

*IPTp-DP= Intermittent preventive therapy with dihydroartemisinin/piperaquine, IPTp-SP= Intermittent preventive therapy with Sulfadoxine/pyrimethamine, APGAR=Appearance, Pulse, Grimace, Activity and Respiration*

**Table 6. Tolerability and safety outcomes**

| | IPTp-DP (N=261) | IPTp-SP (N=262) | IRR | 95% CI | P- value |
|---|---|---|---|---|---|
| **Incidence of vomiting** After administration of the first dose in the study facility | 12/261 | 1/262 | 1.891 | 1.579-2.264 | **0.002** |
| After administration of second or third dose at home | 2/295 | 0/365 | 2.246 | 2.062 - 2.446 | **0.199** |
| **Incidence of adverse events** | | | | | |
| Composite adverse events | 51 | 19 | 2.695 | 1.637 – 4.434 | <0.001 |
| Headache | 2 | 9 | 0.359 | 0.102-1.263` | **0.063** |
| Itching | 5 | 1 | 1.683 | 1.165 - 2.432 | **0.122** |
| Weakness | 13 | 3 | 1.661 | 1.292 - 2.136 | **0.011** |
| Body rashes | 1 | 0 | 2.008 | 1.842 - 2.188 | **0.499** |
| Nausea | 5 | 1 | 1.683 | 1.165 - 2.432 | **0.122** |
| Leg cramp | 1 | 1 | 1 | 0.250 - 4.017 | **1** |
| Restless | 1 | 0 | 2.008 | 1.842 - 2.188 | **0.499** |
| Andresen | 0 | 1 | 0 | Undefined | **1** |
| Dizziness | 9 | 1 | 1.832 | 1.464 - 2.294 | **0.011** |
| Polyuria | 0 | 1 | 0 | Undefined | **1** |
| Individual Grade 2 adverse effect (severe 5-7 in a day) | | | | | |
| Vomiting | 10 | 0 | 2.044 | 1.871 - 2.234 | **0.001** |

## DISCUSSION

The outcome of this clinical study shows that three repeated regimens of Dihydroartemisinin-piperaquine (DP) as intermittent preventive therapy in pregnancy (IPTp) was associated with

an 80% reduction in malaria parasitemia during pregnancy than intermittent preventive therapy in pregnancy with Sulfadoxine-Pyrimethamine (IPTp-SP). IPTp-DP demonstrated better efficacy in preventing malaria infection during pregnancy than IPTp-SP (IRR 0.329; 95% CI, 0.093-1.136) P=0.034).). However, the incidence of symptomatic malaria during pregnancy was higher in IPTp-DP than IPTp-SP, but there was no statistically significant difference between the two arms (IRR1.683, 95%CI, 1.165 - 2.432; **P= 0.122**). This finding is similar to that reported by previous studies conducted in Kenya, Uganda, and Tanzania in terms of the incidence of malaria parasitemia during pregnancy. [19,21,22,25] However, this is different from their finding regarding the occurrence of symptomatic malaria, which was reported to be higher in IPT-SP than IPT-DP. The occurrence of malaria parasitemia with RDT at enrollment was notably higher in the DP group than in the SP group. Comparing malaria parasitemia detected at enrolment with that recorded during pregnancy, DP reduced malaria infection by more than 90%, while SP reduced it by less than 20%. These results further suggested that IPTp-DP is more efficacious in preventing malaria during pregnancy than IPTp-SP. The significant reduction of malaria parasitemia during pregnancy in the IPTp-DP arm could be due to the long malaria prophylactic activity related to the long piperaquine elimination half-life.[26] Among the currently recommended ACT piperaquine component in DP has the longest elimination half-life of up to 30 days. In addition, it provides long post-treatment protection against malaria infection. [26] Similarly, the high burden of malaria parasitemia recorded in the IPTp-SP arm might be associated with malaria parasite resistance to SP in the study setting.

Comparing the two study groups there were no significant differences in the risks of individual adverse birth outcomes; similarly, composites adverse pregnancy outcomes of Low birth weight (LBW), spontaneous abortion, preterm delivery, APGAR score, neonatal death between the two intervention arms showed no statistically significant difference (IRR=0.971, 95%CI=0.772-1.220, P=0.822). These findings suggest that IPTp-DP is as safe as IPTp-SP for the prevention of malaria in pregnancy. Though the prevalence of low birth weight and preterm birth were found to be higher in IPT-DP and IPT-SP respectively, these did not differ significantly between the two study arms. This finding is consistent with earlier studies that showed that IPTp-DP did not improve adverse pregnancy outcomes when compared with IPTp-SP.[21,22] However, our finding differs from the trial conducted in Tanzania which revealed that monthly IPTp-DP significantly reduced low birth weight (LBW) when compared with monthly IPTp-SP. [25] The observed significant reduction in

risk of malaria parasitemia associated with IPTp-DP did not corroborate well with the observed high risk for LBW in this area of low malaria parasite resistance to SP. Similarly, a lower prevalence of low birth weight recorded in the IPT-SP group might be connected with sulfadoxine-pyrimethamine potential to improve birth outcomes independent of its antimalarial activity. Sulfadoxine–pyrimethamine is known to possess broad-spectrum antimicrobial activity, and its repeated uses might have conferred some protection against undetected bacterial infections of the reproductive tract and sexually transmitted diseases during the pregnancies.[27,28]

Comparison of the occurrence of maternal anemia between IPTp-DP arm and IPTp-SP arm indicated that three complete courses of SP as IPT reduces maternal anemia than three complete courses of DP as IPT during pregnancy, but the difference did not show a statistically significant difference (IRR 1.389; 95%CI, 1.030-1.873; P= 0.086). This outcome differs from that of studies conducted in Kenya [19] and Uganda [21] which reported that IPTp-SP is associated with a higher prevalence of anemia than IPTp-DP. However, malaria is a high-risk factor for anemia in pregnancy in sub-Saharan Africa. Other causes of anemia, include inadequate nutrition, non-adherence to routine Antenatal supplementation during pregnancy, these might have played a marginal role in the observed increase in anemia in the IPTp-DP group. Most importantly the high prevalence of anemia at enrolment In the IPTp-DP arm might have contributed to this observation.

The study findings further showed that IPTp-DP is associated with only two macerated and two macrosomia-delivered babies; however, there is no record of any congenital malformation. Similarly, only one macerated baby and no congenital malformation were observed in IPT-SP. The assessment of the level of compliance to the scheduled three intermittent preventive treatments with Dihydroartemisinin-piperaquine shows that greater than 65% of the participants received two (2) and three (3) regimens dihydroartemisinin-piperaquine during the assessment. Two episodes of twins were recorded in IPTp-DP, and one woman died after 72hrs of delivery at home in the IPTp-DP group. The death was assessed to be due to post-partum hemorrhage and not related to the intervention drugs.

Safety, tolerability, and side effects are issues of concern when repeated use of drugs is being assessed for prophylactic purposes during pregnancy. No clinically significant differences were observed in the risk of adverse pregnancy outcomes between the IPTp-DP and IPTp-SP groups in this study. A systematic review, [29] reported no safety issues associated with

Dihydroartemisinin–piperaquine when used for the treatment of malaria and when administered monthly to control malaria in young children and adults.[30-32] Intermittent preventive therapy with dihydroartemisinin-piperaquine was associated with higher vomiting, dizziness, and weakness than intermittent preventive therapy with Sulfadoxine-pyrimethamine. However, composite side effects between the study arms showed a statistically significant difference (IRR 2.695; 95%CI, 1.637-4.434; P= 0.001). Though, higher adverse events were recorded in the IPT-DP group than IPT-SP group, most of the side effects recorded were normal side effects associated with the DP as reported by the manufacturer of the drug [33] Therefore, It can be concluded that DP is well-tolerated during repeated regimens as an antimalarial for intermittent preventive treatment in pregnancy.

## LIMITATION

This study does not assess the prevalence of placenta malaria and the prolongation of the QT interval. In addition, only the first doses of dihydroartemisinin-piperaquine were administered under directly observed therapy because the subjects had to take the second and third doses at home. failure to take the second and third doses administered at home could influence the outcomes in a dihydroartemisinin-piperaquine group compared to SP doses that were given under directly observed therapy in the clinic. The study was carried out in a setting with low malaria resistance to SP; therefore the findings might not be generalizable to areas with higher resistance.

## CONCLUSION

In this area of low malaria resistance to SP, our finding showed that three regimens of IPTp-DP reduced malaria parasitemia by more than 75% compared to IPTp-SP; however, the composite of adverse pregnancy outcomes between the two arms showed no statistically significant difference. These findings suggested that IPTp-DP is effective, safe, and well-tolerated compared with IPTp-SP. This study further affirmed that Dihydroartemisinin-piperaquine is a better alternative to Sulfadoxine-pyrimethamine for intermittent preventive treatment of malaria during pregnancy (IPTp). In addition, this research work provides early evidence to support the use of IPTp-DP as an alternative to IPTp-SP, in areas with a low level of malaria parasite resistance to Sulfadoxine-pyrimethamine.

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## REFERENCES

1. World Health Organization. Updated WHO policy recommendation: intermittent preventive treatment of malaria in pregnancy sulfadoxine-pyrimethamine (IPTp-SP). 3/05/2018. Available from: https://www.mhtf.org/document/updated-who-policy-

2. Feng G, Simpson JA, Chaluluka E, Molyneux ME, Rogerson SJ. The decreasing burden of malaria in pregnancy in Malawian women and its relationship to use of intermittent preventive therapy or ??? Bed nets. PLoS ONE. 2010;5:e12012

3. Harrington WE, Mutabingwa TK, Kabyemela E, Fried M, Dufy PE. Clin Infect Dis. 2011;53:224–30.

4. Desai M, Ter Kuile FO, Nosten F, et al. Epidemiology and burden of malaria in pregnancy. March The Lancet Infectious Diseases. 2007; 7(2):93-104. DOI:10.1016/S1473-3099(07)70021-X

5. Bader E, Alhaj AM, Hussan AA, Adam I. Malaria and stillbirth in Omdurman Maternity Hospital. Sudan Int J Gynaecol Obstet. 2010;109:144–6.

6. McGregor IA. Epidemiology, malaria, and pregnancy. Am J Trop Med Hyg. 1984;33:517–25.

7. McGregor IA, Wilson ME, Billewicz WZ. Malaria infection of the placenta in The Gambia, West Africa; its incidence and relationship to stillbirth, birth weight, and placental weight. *Transactions of The Royal Society of Tropical Medicine and Hygiene.* 1983; 77(2): 232–44. https://doi.org/10.1016/0035-9203(83)90081-0

8. Brabin BJ. An analysis of malaria in pregnancy in Africa. Bull World Health Organ. 1983; 61:1005–16.

9. World Health Organization. (2020). World malaria report.4/7/2019. Available from: http://www.who.int/malaria/publications/world-malaria-report-2020/en

10. Gutman J, Kalilani L, Taylor S, et al. The A581G mutation in the gene encoding Plasmodium falciparum dihydropteroate synthetase reduces the effectiveness of sulfadoxine-pyrimethamine preventive therapy in Malawian pregnant women. J Infect Dis. 2015; 211: 1997–2005.

11. Ranson H, N'Guessan R, Lines J, Moiroux N, Nkuni Z, Corbel V. Pyrethroid resistance in African anopheline mosquitoes: what are the implications for malaria control? Available from:https://pubmed.ncbi.nlm.nih.gov/20843745/

12. Gutman J, Mwandama D, Wiegand RE, Ali D, Mathanga DP, Skarbinski J. Effectiveness of intermittent preventive treatment with sulfadoxine-pyrimethamine during pregnancy on maternal and birth outcomes in Machinga district, Malawi. J Infect Dis. 2013;208:907-16.
13. Arinaitwe E, Ades V, Walakira A, et al. Intermittent preventive therapy with sulfadoxine-pyrimethamine for malaria in pregnancy: a cross-sectional study from Tororo, Uganda. PLoS One. 2013;8(9): e73073.
14. Clerk CA, Bruce J, Affipunguh PK, et al. A randomized, controlled trial of intermittent preventive treatment with sulfadoxine-pyrimethamine, amodiaquine, or the combination in pregnant women in Ghana. J Infect Dis. 2008; 198:1202-11.
15. González R, Mombo-Ngoma G, Ouedraogo S, et al. Intermittent preventive treatment of malaria in pregnancy with mefloquine in HIV-negative women: a multicentre randomized controlled trial. PLoS Med. 2014;11(9):e1001733.
16. Evid Based Med. (2016). First published as 10.1136/embed-2016-110438. Available from. http://ebm.bmj.com
17. The Four Artemisinin-Based Combinations (4ABC) Study Group. A Head-to-Head Comparison of Four Artemisinin-Based Combinations for Treating Uncomplicated Malaria in African Children: A Randomized Trial. PLOS Medicine. 2011 ; 8(11): e1001119. https://doi.org/10.1371/journal.pmed.1001119
18. Natureeba P, Ades V, Luwedde F, et al. Lopinavir/ritonavir-based antiretroviral treatment (ART) versus efavirenz-based ART for the prevention of malaria among HIV-infected pregnant women. J Infect Dis. 2014; 210: 1938–45.
19. Desai M, Gutman J, L'lanziva A, et al. Intermittent screening and treatment or intermittent preventive treatment with dihydroartemisinin-piperaquine versus intermittent preventive treatment with sulfadoxine-pyrimethamine for the control of malaria during pregnancy in western Kenya: an open-label, three-group, randomized controlled superiority trial. Lancet. 2015; 386: 2507–19.
20. Madanitsa M, Kalilani L, Mwapasa V, et al. Scheduled intermittent screening with rapid diagnostic tests and treatment with dihydroartemisinin-piperaquine versus intermittent preventive therapy with sulfadoxine-pyrimethamine for malaria in pregnancy in Malawi: An open-label randomized controlled trial. PLoS Med. 2016;13:e1002124.
21. Kakuru A, Jagannathan P, Muhindo MK, et al. Dihydroartemisinin– piperaquine for the prevention of malaria in pregnancy. N Engl J Med. 2016; 374: 928–39.
22. Richard K, Teddy O, Kakuru A, ae al. Monthly sulfadoxine-pyrimethamine versus dihydroartemisinin-piperaquine for intermittent preventive treatment of malaria in pregnancy: a double-blind, randomized, controlled superiority trial. Lancet. 2019; 393: 1428–39.
23. WHO Malaria Policy Advisory Committee and Secretariat. Malaria Policy Advisory Committee to the WHO: conclusions and recommendations of eighth biannual meeting (September 2015). Malar J. 2016; 15: 117.
24. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0. Washington, DC: U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS, 2014. Available from: http://rsc.techres.com/Document/safetyandpharmacovigilance/DAIDS_AE_Grading_Table_v2_NOV2014.pdf
25. Mlugu EM, Omary M, Appolinary ARK, Aklillu E. Effectiveness of Intermittent Preventive Treatment With Dihydroartemisinin Piperaqunine Against Malaria in Pregnancy in Tanzania. Clinical pharmacology & therapeutics. 2021;0 doi:10.1002/cpt.2273
26. Pekyi AA, Ampromfi H, Tinto M. et al. Four artemisinin-based treatments in African pregnant women with malaria. N. Engl. J. Med. 2016;374: 913–927. DOI: 10.1056/NEJMoa1508606
27. Chico RM, Cano J, Ariti C, et al. Influence of malaria transmission intensity and the 581G mutation on the efficacy of intermittent preventive treatment in pregnancy: systematic review and meta-analysis. Trop Med Int Health. 2015;20: 1621–33
28. Chico RM, Chaponda EB, Ariti C, Chandramohan D. Sulfadoxine–pyrimethamine exhibits dose-response protection against adverse birth outcomes related to malaria and sexually transmitted and reproductive tract infections. Clin Infect Dis. 2017; 64: 1043–51.

29. Atinuke O, Babasola OO,|Olabisi O, |Ekpereonne E, Martin M. A systematic review and meta-dihydroartemisinin piperaquine versus sulphadoxine-pyrimethamine for malaria prevention in pregnancy. Int J Gynecol Obstet. 2019;1–13. DOI: 10.1002/ijgo.12835
30. Bigira V, Kapisi J, Clark TD, et al. Protective efficacy and safety of three antimalarial regimens for the prevention of malaria in young Ugandan children: a randomized controlled trial. PLoS Med. 2014;11(8):e1001689
31. Zani B, Gathu M, Donegan S, Olliaro PL, Sinclair D. Dihydroartemisinin-piperaquine for treating uncomplicated Plasmodium falciparum malaria. Cochrane Database Syst Rev. 2014; 1:CD010927.
32. Nankabirwa JI, Wandera B, Amuge P, et al. Impact of intermittent preventive treatment with dihydroartemisinin-piperaquine on malaria in Ugandan schoolchildren: a randomized, placebo-controlled trial. Clin Infect Dis. 2014;58:1404-12.
33. Chris CO, Joshua FA, Olubiyi FA, Oldipo-Clegg LO, Ifeoma CO. Emdex. Drug information. 2014/2015 Edition. Lagos Nigeria. Emdex Limited;2015.