



## Assessment of adherence to dihydroartemisinin-piperazine for intermittent preventive therapy in pregnant women in Keffi, Nasarawa state, Nigeria

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### Abstract

**Introduction:** Nonadherence to antimalarial for prophylactic use during pregnancy, can lead to undesirable effect such as treatment failure and adverse consequences of severe malaria to pregnant women and their unborn babies. This work was conducted to assess the level and patterns of adherence to repeated dose regimens of dihydroartemisinin-piperazine for intermittent preventive treatment in pregnant women.

**Methods:** A prospective intervention study was carried out for twelve months in Federal Medical Centre Keffi, Nigeria. The participants were HIV- negative pregnant women who consented and received three repeated regimens of dihydroartemisinin-piperazine for intermittent preventive therapy in pregnancy during clinical study. The subjects received first, second and third regimens at intervals of not less than four (4) weeks. The Four-item Morisky's Medication Adherence Scale (MMAS-4) was adopted and used to assess self-reported medication adherence. Respondents were considered highly adherent to the regimen if they responded negatively to all four questions.

**Results:** Among 115 subjects who received three regimens, High, moderate and low adherences to dihydroartemisinin-piperazine were 82(71.3%), 30(26.1%) and 3 (2.6%) respectively. The assessment revealed that forgetfulness (20.9%) and side effects (2.6%) were the most common factors contributing to nonadherence among the subjects. The level of adherence indicated that more than 60% of participants received second and third scheduled regimens of the study agent. However, the distribution of adherence among the gravidity showed no significant ( $P=0.201$ ) difference.

**Conclusion:** Majority of pregnant women who completed three full courses of dihydroartemisinin-piperazine were scored as highly adherent. Forgetfulness was the strongest factor associated with nonadherence. Thus, nonadherence should be seen as one of the potential barrier that must be overcome for intermittent preventive therapy with dihydroartemisinin-piperazine. Similarly, the success of this regimen will require proper counselling on medication use.

**Keywords:** malaria, dihydroartemisinin-piperazine, pregnant women, intermittent preventive therapy adherence

### Introduction

Malaria infection during pregnancy is the major cause of adverse pregnancy outcomes. Maternal and neonatal anaemia, low birth weight, loss of pregnancy and still birth are the leading consequences of malaria in mothers and their unborn babies. World health organization (WHO) recommends intermittent preventive treatment of malaria in pregnancy with sulfadoxine-pyrimethamine (IPTp-SP) [1]. However, there are reports suggesting that IPTp with SP is no longer effective, especially in East Africa, where resistance to this drug is widespread [2]. New interventions to prevent malaria during pregnancy are needed urgently [3]. WHO Malaria Policy Advisory Committee (MPAC) stated that dihydroartemisinin-piperazine (D/P) is a promising regimen for intermittent preventive therapy (IPTp) [4]. More research is needed to evaluate the impact of D/P for IPTp in preventing low birth weight and adherence to the required repeat 3-days regimens [5]. The success of the ongoing trial on dihydroartemisinin-piperazine for IPTp is restricted largely to pregnant women adherence to the multiple repeat doses and longer duration of therapy. Nonadherence to antimalarial use for the prevention of malaria during pregnancy, can lead to prophylactic failure and serious adverse consequences of severe malaria to pregnant women

and their unborn babies. Factors contributing to non-adherence include patient factors, nature of therapy, type of disorder being managed, and prevailing socioeconomic factors [6-8]. Patient factors that influence therapeutic adherence may be connected to lack or poor understanding of their health condition, not-involving them in their therapeutic decision-making process, lack of their participation in the counselling process and little or no medical literacy [9]. Non adherence to therapy could also be related to the patient's attitudes concerning treatment effectiveness, their past experiences with medication taken, and fear of unknown in respect to medication adverse events among others. Thus, improving patients' level of knowledge and understanding concerning their medical conditions and pharmacotherapy can equip them to adhere to drugs prescribed [10, 11, 12, and 13].

The aim of this study was to assess level and pattern of adherence to dihydroartemisinin-piperazine for intermittent preventive therapy among the pregnant women.

### Methods

A prospective intervention study was conducted from September, 2019 to October, 2020 in the Department of obstetrics and gynaecology, Federal Medical Centre Keffi,

Nasarawa state, Nigeria. Ethical and administrative approval were sought and obtained from the ethical and research health committee (ERHC) of the study facility. The targeted population was pregnant women of gestational age of 13 to 26 weeks and age  $\geq 16$  years who attended antenatal care at the study facility.

Pregnant women of age  $\geq 16$  years, HIV- negative, leaving within 30km from the study Centre and voluntarily agreed to deliver at the study Centre were included. However, pregnant women who were allergic to the study drug, had comorbid diseases that required multiple medications, HIV-positive and were excluded from the study.

### Recruitment procedure

Clinical talks were conducted during antenatal clinics at the study facility, pregnant women, who satisfied the inclusion criteria and agreed to participate, signed or thumb printed the consent forms were recruited into the study.

### Data collection instruments

Data collection forms were designed to capture desirable information at enrolment. Morisky Medication Adherence Scale (MMAS-4) with four (4) structured close ended questions was adopted and used to assess pregnant women's adherence to repeated three (3) doses regimens of Dihydroartemisinin-piperaquine (D/P) during the study.

### Data collection procedure

Health talks were delivered to pregnant women at every antenatal clinic during the study. Those who satisfied the inclusion criteria and agreed to participate were recruited. Each recruited subjects of gestational age (13 to 24) weeks, either at enrollment or at subsequent visit, were given dihydroartemisinin/piperaquine (D/P) (40mg/320mg) (Fanmed<sup>R</sup> Maydon Pharmaceutical product) consisting of eight (8) tablets and were to be taken three tablets each, at 0 hour, 24 hours and two tablets at 48hours consecutively. The first dose of Dihydroartemisinin/Piperaquine (D/P) was given under directly observed therapy at the study clinic. All recruited subjects were scheduled to receive three standard doses regimen of the study agent (i.e. IPTp1, IPTp2 & IPTp3) during the pregnancy at interval of not less than four (4) weeks.

### Adherence assessment

Morisky medical adherence scale (MMAS) with four (4) structured closed ended questions was adopted and used to assess pregnant women adherence to repeated doses of dihydroartemisinin-piperaquine (D/P) regimen for intermittent preventive treatment in pregnancy (IPTp). The subjects were assessed after completion of their third regimen (IPTp3). Self-reported method was adopted for the assessment. The participants responded to four questions.

1. Do you ever forget to take your antimalarial medicine?
2. Do you ever have problems remembering to take your antimalarial medicine?
3. When you feel you do not have malaria; do you sometimes stop taking your antimalarial?
4. Sometimes if you feel worse when you take your antimalarial, do you stop taking it?

Each YES answer had score of zero (0) while each NO answer had one (1) score. The total assessment was classified as low adherence (0-1), moderate adherence (2-3) and high adherence (4) and these were statistically analyzed.

### Results

A total of 261 pregnant women who satisfied the inclusion criteria were enrolled into the study. Two hundred and sixty (95.5%), 180(65.5%) and 115 (41.8%) received one regimen (D/P1), two regimens (D/P2) and three regimens (D/P3) respectively (figure 1).

Socio-demographic characteristics of participants showed that the mean age of participants was 29.2 years and 99.6% of them were of age greater than 18years. Greater percentage (57.5%) of the respondents had tertiary level of education, while 1.1% did not have formal education. However, 33.8% were business women (table 1).

Table 2. Obstetric characteristic of participants at baseline reflected that; A total of 197 (72%) of 275 were enrolled at (13-24) weeks gestational age. Among the total of 275 recruited 69 (25%) were primigravidae and 30 (14%) had previous record of miscarriage. Majority 173(80.8%) of the subjects had vaginal deliveries.

Among the four basic questions asked, more than 70% of participants answered no to all questions. Remembrance factor had the larger percentage 24(20.9%) of yes answer while the factor relating to "feeling worse when I take my antimalarial" had least percentage 4(2.6%) Table 3.

Table 4. Showed that high and low adherent scores were 82 (71.3%) and 3(2.6%) respectively. Similarly, out of the 82 participants that scored high adherence, 46%, 18% and 18% were Multigravidae, Secundigravidae and primigravidae respectively. Worthy of note was the distribution of adherence pattern between paucigravidae and multigravidae showed no significant difference (P= 0.201).

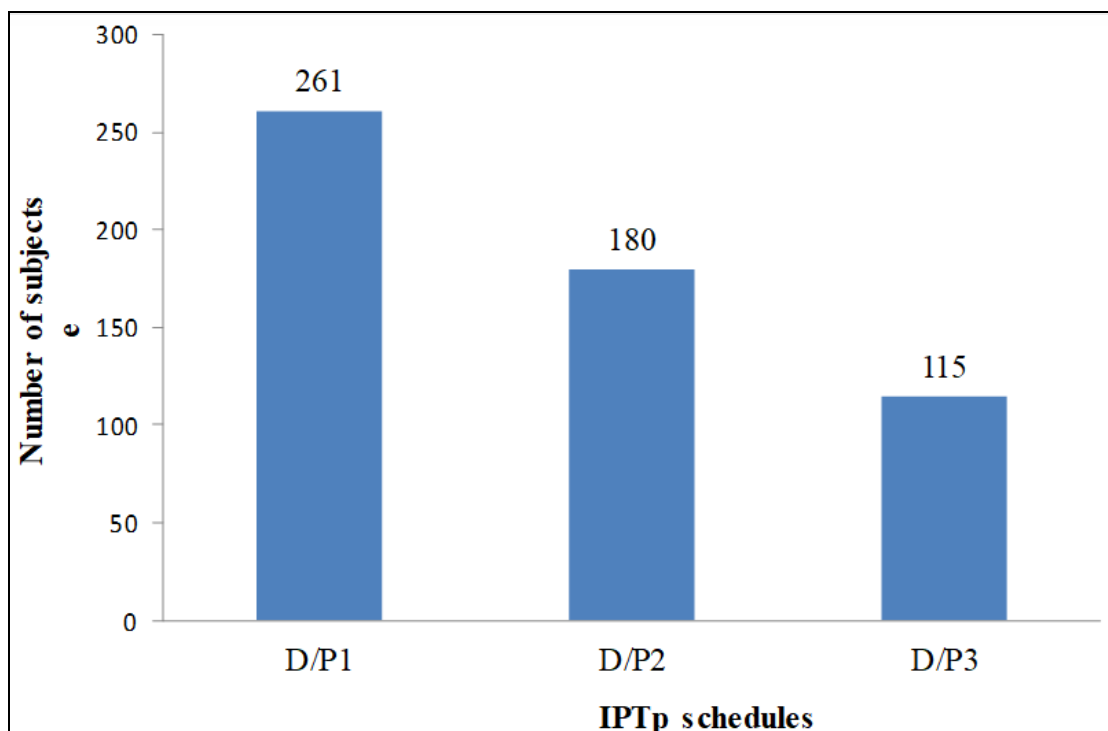
**Table 1:** Socio-demographic characteristics of participants at baseline

Items	n	(%)
Age(Year)	29.2	
Mean age (year)		
Categories of age (Year)		
0-18	1	0.36
>18	274	99.64
Total	275	100
Educational status		
No formal	3	1.09
Primary	12	4.36
Secondary	103	37.45
Tertiary	157	57.1
Total	275	100
Occupation		
Farmer	6	2.18
Applicant	26	9.45
Student	38	13.82
House wife	42	15.27
Civil servant	70	25.45
Business	93	33.82
Total	275	100
Detected Malaria parasite at enrolment by RDT	33	12

RDT=Rapid diagnostic test

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

Items	(n)	(%)
Mean gestational age (year)	18.6	
First trimester	70	25.45
Second trimester	197	71.64
Third trimester	8	2.91
Total	275	100
Gravidity		
Primigravidae)	69	25.09
Secundigravidae	65	23.64
Multigravidae	141	51.27
Total	275	100
Parity		
>6	7	3.43
1-2	138	66.67
3-4	48	23.53
4-6	13	6.37
Total	206	100
Mode of previous deliveries		
Caesarian section	21	10.45
Vaginal	180	89.55
Total	201	100
Previous pregnancy outcome		
Miscarriage	30	14.02
Pre term delivery	2	0.93
Term delivery	173	80.84
Still birth	9	4.21
Total	214	100



D/P = Dihydroartemisinin- piperazine, IPTp=Intermittent preventive therapy in pregnancy

**Fig 1:** Level of adherence to Dihydroartemisinin- piperazine regiments among the participants during schedules IPT

**Table 3:** Assessment for dihydroartemisinin-piperazine for IPTp

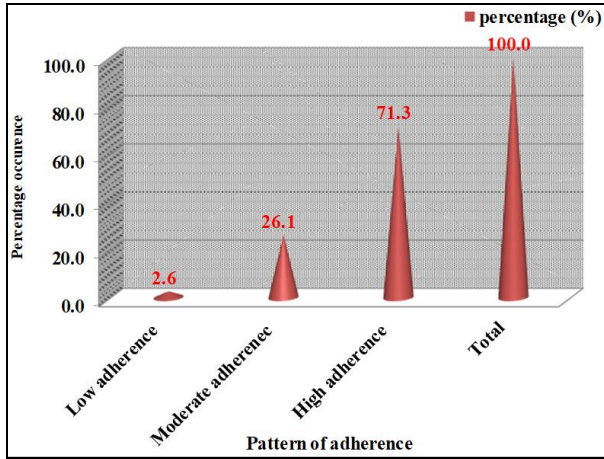
Morisky's instrument (MMAS-4) Questionnaires	Number of espondents (N=115)	
	Yes	No
1. Do you ever forget to take your antimalarial?	11 (9.6%)	104 (90.4%)
2. Do you ever have problems remembering to take your antimalarial?	24 (20.9%)	91 (79.1%)
3. When you feel you do not have malaria; do you sometimes stop taking your antimalarial?	4 (3.5%)	111 (96.5%)

No of participants who responded "No" to all four questions were considered 82 (71.3%) high adherent to IPTp-D/P  
 MMAS-4 = Four items Morisky's Medication adherence scale, IPTp = Intermittent preventive therapy in pregnancy

**Table 4:** Patterns of adherence to dihydroartemisinin-piperazine among the participants

Adherence patterns	Score	No	%
Low adherence	0-1	3	2.6
Moderate adherence	2-3	30	26.1
High adherence	4	82	71.3
Total		115	100

Scores: No answer=1, Yes answer=0,



**Fig 2:** Patterns of adherence to dihydroartemisinin-piperazine for intermittent preventive therapy among the participants

**Table 5:** Comparison of patterns of adherence among the gravidity

		Gravidity		$\chi^2$	P-value
Paucigravidae		Multigravidae			
Adherence Status				3.207	0.201
Low adherence		0	2		
Moderate adherence		17	13		
High adherence		36	46		

**Discussion**

Adherence to medication is the extent to which a person takes medicines as prescribed and instructed by the health care providers. It is a key factor for achieving desired therapeutic outcomes. Nonadherence to medication leads to increased ill-health and death. There are subjective and objective measurement tools available for medication adherence assessment. Objective measures of adherence include pharmacy refill records and pill counts. Subjective methods, such as a questionnaire, interview, or diary are commonly used to measure adherence. These methods are more flexible and practical than the objective methods, however, less reliable than objective methods because they are prone to recalls bias and social desirability bias. (14, 15). This work interviewed the participants with adopted questionnaires of Morisky's instrument that has been used in many adherence studies. Public health experts have attempted to improve adherence to antimalarial medications but the challenges persist in all methods, age group, gender and classes of drugs (15, 16).

There are studies conducted on adherence to other antimalarial from different parts of the world, but there are little or no studies conducted on adherence to dihydroartemisinin-piperazine as intermittent preventive therapy agent. This is because researches on this agent for the purpose IPTp are still ongoing in deferent parts of the world. This study revealed that the most common causes of noncompliance to dihydroartemisinin-piperazine for intermittent preventive therapy in pregnancy were side

effects and forgetfulness, although these factors occurred in low percentages. These findings are similar to those reported by other self-reported studies [17, 18, 19]. The level of compliance to the scheduled three repeat regimens of dihydroartemisinin-piperazine is less than 50%, but majority of the participants took second and third scheduled regimens of dihydroartemisinin-piperazine. The assessment further showed that larger percentage of participants who completed the three multiple doses of the require regimens had high adherent scores. However, larger numbers of them were Multigravidae when compared with paucigravidae, but significant difference does not exist between gravidity ( $X^2 = 3.207, P = 0.201$ ).

This study revealed that adherence to dihydroartemisinin-piperazine for intermittent preventive therapy is high in this setting. The adherence pattern shows that majority of the participant's scored high adherence follow by moderate adherence then low adherence. Nonadherence to medication therapy is the commonest factors for therapeutic failure and can lead to medication therapy problems (20, 21). Some methods for improving medication adherence include easy dosage forms and proper counseling.

**Limitation**

1. The adherence assessment was only carried out among subjects who completed the scheduled three regimens of intermittent preventive therapy in pregnancy with dihydroartemisinin-piperazine.
2. The research was conducted among limited number of subjects who consented and participated in the clinical study. Thus, larger trials in different setting are desirable

**Conclusion**

The level of adherence to dihydroartemisinin-piperazine as intermittent preventive therapy in pregnancy in this setting is high and encouraging. However, forgetfulness was identified as major factor contributing to non-adherence. Though, less than half of the participants completed the scheduled courses of IPTp-DP, the pattern showed that majority of them had high adherence. Pregnant women on IPTp-DP will require proper counselling and education by health care providers to enhance adherence.

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