Caretakers' self adherence to artemisinin lumefantrine in Nyando district, Kenya

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Abstract

Artemisinin combination therapies (ACTs) are effective and tolerant. However, the continuous development of *Plasmodium* strains resistance to cost effective monotherapies such as chloroquine and sulphadoxine-pyrimethamine, remains the greatest setback to the global fight against malaria. Recent studies indicate that *Plasmodium* parasites are already becoming resistance to ACTs. A number of factors such as poor adherence can cause drug failure. Non-adherence is one of the major challenges facing optimal use of ACTs in real life settings. The objective of this study was to describe and identify factors associated with non-adherence to artemisinin lumefantrine (AL) among malaria-ailing caretakers seen in Nyando district hospital who also had children under the age of five ailing from malaria. From our study we concluded that the consents, follow-ups, strict adherence to the Kenya National Strategy for Control and Treatment of Malaria guidelines and availability of AL during the study may have influenced the observed high adherence rates. Therefore, it is critical to adequately stock health facilities with AL to enhance adherence. More specifically, healthcare providers need to educate malaria-ailing caretakers on the AL regimen as well as its possible side effects to promote adherence to the antimalarial at a household level.

Introduction

Kenya adopted artemisinin combination therapies (ACTs) as the first line treatment of malaria in 2004[1] at the time when numerous clinical trials had shown that ACTs were effective, efficacious and tolerant.[2] However, the continuous development of *Plasmodium* strains resistance to previous cost effective monotherapies has been the greatest setback to the global fight against malaria.[3] For instance, in spite of the decline in child mortality in Africa, the widespread resistance to previous cheap mono-therapies such as chloroquine (CQ) in early 90s and sulphadoxine-pyrimethamine (SP) in late 90s, led to the increase in malaria related child mortality in the region.[4,5]

Recent studies indicate that *Plasmodium* parasites are already becoming resistant to ACTs.[6-8] A number of factors can cause drug failure such as poor drug quality, misdiagnosis, drug interactions, erratic or poor absorption, and non-adherence.[2,9-11] Non-adherence is one of the major challenges facing optimal use of ACTs in real life settings.[12] It may lead to recrudescence, parasite resistance as well as increased mortality.[13,14] Although adherence studies have increased tremendously over the past decade,[14-19] adherence definition, levels and assessment methods differ extensively across studies.[15-27] These variations to some extent make generalization of adherence findings difficult. In essence, a number of factors do hinder adherence to ACTs.[28] These may include drugs being out of stock in public formal sector,[29] characteristics of the patient, socio economic, environmental and cultural factors.[30] Constant monitoring of ACTs is thus critical in ensuring its efficacy and long-term use.[31] Therefore, the objective of this study was to describe and identify factors associated with non-adherence to artemisinin lumefantrine (AL) among malaria ailing caretakers in Nyando district (Figure 1) in order to provide evidence for the improvement of malaria treatment strategy in the district. Aided supervision complicates adherence due to a fatalistic attitude about the treatment the caretaker brings with them in the drug administration.

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Key words: artemisinin lumefantrine, malaria, *Plasmodium falciparum.*

Conflict of interests: the authors declare no potential conflict of interests.

Contributions: JOO designed and implemented the study, did data analysis and wrote the manuscript; SOA and CAO participated in the design and coordination of the study and writing of the manuscript.

Acknowledgements: the authors thank the staffs of Nyando district hospital and all the study participants for their immense contribution in the study. The authors are grateful to the research assistants for their help in organizing and conducting the follow up visits. This work was part of a Master thesis of Public Health degree at Moi University, Eldoret, Kenya by fist author JOO.

Funding: JOO was supported by funding from Mr. Joash Ogolla Ogada and Mrs. Margaret Aoko Ogolla.

Received for publication: 28 July 2013.
Revision received: 21 November 2013.
Accepted for publication: 30 December 2013.

Malaria Reports 2014; 3:1842
doi:10.4081/malaria.2014.1842

Materials and Methods

Study site

Nyando district hospital located in Pap Onditi, lower Nyakach Division, Kabodho Sub-Location of Nyakach District in Kisumu County constituted the study area. Malaria is endemic in the district and transmission is all year round. The most predominant species is *Plasmodium falciparum*[28] and has a mean annual sporozoite inoculation rates of 90-410 infective bites *per annum*.[32] Due to its proximity to Lake Victoria, the area is relatively humid at 65%. The average temperature and rainfall is between 17-32°C and 1000-1800 mm *per annum*, respectively.

Study population

The cross-sectional study consisted of 314 randomly selected malaria-ailing caretakers who also had children under the age of five suffering from malaria. These participants had visited outpatient department (OPD) and prescribed an AL alongside their malaria-ailing children in the month of February to April 2010. The study assumed an adherence of 80%, a precision of 10%, a type 1 error of 5% and a 20% loss to follow-up in sample size determination.[28]

Data collection procedure

The study sought ethical approval from Moi Teaching and Referral Hospital and Moi University Institutional Review and Ethics Committee (Reference: IREC/2008/91, Approval Number: 000379) and informed consent from study participants prior to data collection. Home visits were conducted on the 4th day after recruitment; a day after which the patients were supposed to have completed

their AL. An interviewer-administered structured questionnaire written in English was used to collect information such as demographic characteristics of the respondents, health provider instructions to the patient at the time of dispensing the AL, and malaria treatment related health-seeking behaviour. Where necessary, the Kiswahili or Kijaluo version of the questionnaire was used.

Definition of adherence

Adherence was assessed in reference to the correct number and timing of the 3-day age specific AL tablets taken. Patients were classified as probably adherent, probably non-adherent or definitely non-adherent based on blister pack inspection and self-reports by the patients. Study participants were issued with a diary in which they recorded how they took the antimalarial on a daily basis. Respondents who had no tablets remaining in the blister pack and reported taking the medication exactly as instructed by the physician were termed as *probably adherent*. Patients who had no blister packs but reported taking the medication correctly were classified as *probably non-adherent*. Those who had tablets remaining in the blister pack or reported inconsistency in taking the AL regimen were categorised as *definitely non-adherent*.

Data analysis

Analysis was done using SPSS 17.0 for Windows. Association between each variable and adherence to antimalarial regimen was determined using univariate logistic regression. Variables with $P<0.05$ were considered as statistically significant. These variables were entered into multi-logistic regression model to assess their impact on adherence. Odds ratio (OR) with confidence interval (CI) was used to ascertain the extent of the association. Independent variables in the model included sex of the patient, age, educational level, marital status, availability of a medical cover, knowledge about malaria symptoms before treatment, effectiveness of the AL; patient perceived feeling in the course of treatment and treatment supervision.

Ethical consideration

Moi Teaching and Referral Hospital and Moi University Institutional Review and Ethics Committee (Reference: IREC/2008/91, Approval Number: 000379) approved the study. All participants were also asked for written informed consents before participating in the study.

Table 1. Odds ratios and P values for univariate logistic regression analysis of predictors of non-adherence to antimalarials.

Variables	Non-adherent		Probably adherent		OR	95% CI	P
	N	%	N	%			
Sex							0.389
Male	15	13.5	96	86.5	1.0	-	
Female	35	17.2	168	82.8	1.33	0.69-2.57	
Age (years)							0.074
18-28	14	23.7	45	76.3	1.0	-	
29-39	22	17.5	104	82.5	0.680	0.32-1.45	
≥40	14	10.9	115	89.1	0.391	0.07-1.19	
Educational level							0.001
Illiterate	25	28.4	63	71.6	1.0	-	
Primary	16	16.8	79	83.2	0.51	0.25-1.04	
Secondary	4	4.8	80	95.2	0.13	0.04-0.38	
Tertiary	5	10.6	42	89.4	0.30	0.11-0.85	
Marital status							0.904
Single	11	13.9	68	86.1	1.0	-	
Married	16	15.7	86	84.3	1.15	0.50-2.64	
Widowed	12	16.2	62	83.8	1.20	0.49-2.91	
Divorced	11	18.6	48	81.4	1.42	0.57-3.53	
Medical cover							0.178
Yes	47	17.0	230	83.0	1.0	-	
No	3	8.1	34	91.9	0.43	0.13-0.47	
Knowledge about malaria symptoms before seeking treatment							0.049
Yes	15	11.2	119	88.8	1.0	-	
No	35	19.4	145	80.6	1.92	1.01-3.67	
Effectiveness of the AL							0.000
Effective	29	11.3	227	88.7	1.0	-	
Poor	5	22.7	17	77.3	3.46	1.32-9.10	
Ineffective	16	44.4	20	55.6	6.73	3.12-15.51	
Patient's perceived feeling in the course of treatment							0.017
Improved	14	10.0	126	90.0	1.0	-	
Sick	32	19.6	131	80.4	2.198	1.12-4.31	
Better	4	36.4	7	63.6	5.143	1.34-19.78	
Treatment supervision							0.001
Self supervision	32	12.5	224	87.5	1.0	-	
Aided supervision	18	31.0	40	69.0	3.15	1.62-6.15	

OR, odds ratio; CI, confidence interval; AL, artemisinin lumefantrine.

Results

Characteristics of the respondents

Three hundred and fourteen adult patients with microscopically confirmed malaria and administered with antimalarial in the OPD from 8 am to 5 pm in the month of February to April 2010 were recruited into the study. The participants were between 18 and 51 years, with a mean age of 25.7 years. Most respondents (65%) were females. Twenty eight percent of the respondents were illiterate, 30% with primary education, 27% with secondary education, and 15% with tertiary education. Concerning marital status, 25% patients were single, 32% married, 24% widowed, and 19% divorced. Only 22% of the respondents had no medical cover.

Levels of adherence

Two hundred and eighty three patients (90%) reported completing the AL dosage as instructed by the physician during the follow-up visit. Of these 283 patients, 264 (84%) had blister packs remaining while 19 (0.6%) had blister packs missing. The 264 (84%) patients were classified as *probably adherent* whereas the 19 (6.0%) were classified as *probably non-adherent*. Of the 31 patients (10%) classified as *definitely non-adherent*, eight (3%) had tablets remaining in the blister pack while 23 (7%) reported taking the ACT incorrectly in terms of timing and dosing. The mean number of doses left at the time of the follow-up visit was 1.42 (95% CI=0.57-3.53). The sixth dose was the commonly missed dose (95% CI=3.12-15.51). The two non-adherents groups were combined into a single non-adherent group (n=50, 16%) to increase statistical power during analysis.

Variables associated with non-adherence

Univariate logistic regression model was used to perform a comparison of adherence between different subgroups. Patients who were illiterate (OR=1.0, P=0.001); had no prior knowledge on malaria symptoms before seeking treatment (OR=1.92, 95% CI=1.01-3.67, P=0.049); perceived AL as ineffective (OR=6.73, 95% CI=3.12-15.51, P=0.000); felt better before completing the dose (OR, 5.143, 95% CI=1.34-19.78, P=0.017); or were aided in AL administration (OR=3.15, 95% CI=1.62-6.15, P=0.001) were more likely to non-adhere. However, sex, age, marital status, and medical cover were comparable between the AL adherents and non-adherents (P=0.389, P=0.074, P=0.904, and P=0.178, respectively) (Table 1).

Significant factors in univariate logistic regression model were subjected in multivariate logistic regression model to analyze predictors associated with non-adherence and control for confounding factors. Only four factors fitted the model. Patients educated to secondary level (OR=0.15, 95% CI=0.04-0.51, P=0.033), those who perceived AL as ineffective (OR=6.03, 95% CI=1.89-19.29, P=0.002), felt sick during the course of medication (OR=2.64, 95% CI=1.15-6.05, P=0.022) or were aided in taking the AL (OR=2.53, 95% CI=1.01-6.36, P=0.049) when factors significantly associated with non-adherence. However, knowledge about malaria symptoms before seeking treatment was comparable between AL adherent and non-adherent (P=0.453) (Table 2).

Discussion

Perceived feeling in the course of taking medication, education level, knowledge about malaria symptoms, treatment supervision, therapeutic efficacy, availability and side effects of the treatment regimen(s) in question are just but a few factors that influence optimal use of ACTs. Side effects and antimalarial in use are major determinants affecting patient's adherence. However, perception of illness, treatment supervision, education level, knowledge about malaria symptoms, dosing of the regimen, therapeutic efficacy and availability of the antimalarial can also influence adherence.[15-28] Sub-therapeutic doses may lead to widespread drug resistance as it occurred with previously inexpensive monotherapies such as CQ and SP. Thus, continuous monitoring of adherence to ACTs is one way of ensuring the treatment remains efficacious over a long period.

As mentioned earlier, adherence definition, levels as well as assessment methods vary widely from study to study.[15-27] The assessment of adherence can take form of pill count, self-report, container inspection, or pharmacological analysis of assays. However, each of these methods has its own strengths and weaknesses.[33] In assessing adherence, this study employed the use of self-report and container inspection. Self-reports and pill counts remains the sole or complimentary methods of accessing adherence in most adherence literature. To minimise recall bias commonly associated with self-reports; participants were issued with a diary in which they were supposed to record on a daily basis how they took the AL.

Table 2. Adjusted odds ratios and P values of predictors of non-adherence to antimalarials after subjection to multivariate logistic regression model.

Variables	Adjusted OR	95% CI	P
Educational level			
Illiterate	1.0		
Primary	0.39	0.14-1.02	0.055
Secondary	0.15	0.04-0.51	0.033
Tertiary	0.36	0.11-1.16	0.087
Knowledge about malaria symptoms before seeking treatment			
Yes	1.0		
No	1.38	0.60-3.17	0.453
Effectiveness of the AL			
Effective	1.0		
Poor	1.87	0.47-7.46	0.375
Ineffective	6.03	1.89-19.29	0.002
Patient's perceived feeling in the course of treatment			
Improved	1.0		
Sick	2.64	1.15-6.05	0.022
Better	2.87	0.52-15.81	0.226
Treatment supervisor			
Self supervision	1.0		
Aided supervision	2.53	1.01-6.36	0.049

OR, odds ratio; CI, confidence interval; AL, artemisinin lumefantrine.

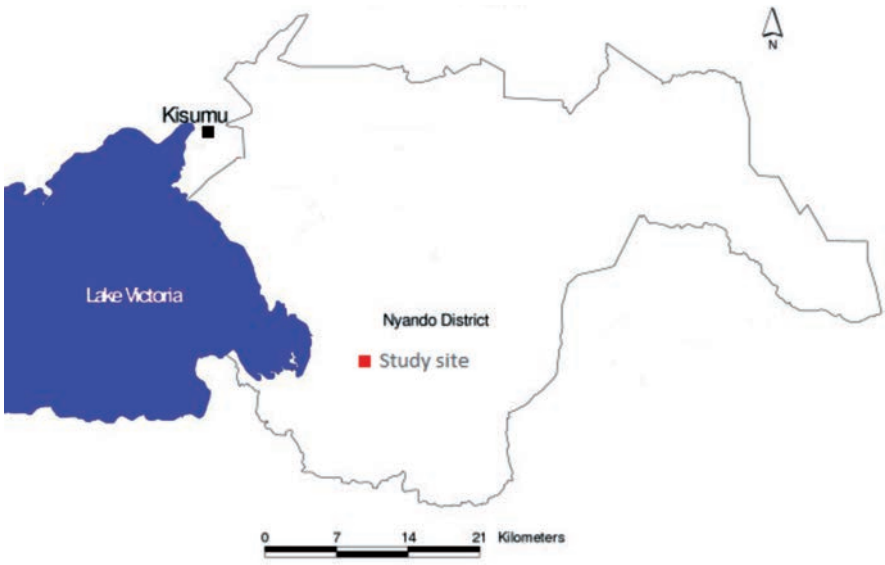

Figure 1. Map showing the location of the study site in Nyando district, Kenya.

The high number of patients who had primary level education and above (n=226, 72%), may imply that most patients did not have difficulty recording on a daily basis how they took the AL on their own. Illiterate caretakers relied on a literate member of the family record how they took the AL on a daily basis. Those who had no literate member of the family in the house were assisted by a field assistant attached to specific villages to fill in the diary on a daily basis. The field assistants visited the patients at least once a day until the end of the study period. To eliminate recall bias, the researchers subjected the caretakers' self-reports and blister pack observation to Kappa coefficient. A Kappa coefficient of 0.69 showed an agreement between the two parameters. Thus, the information recorded in most of the patients' diary alongside the blister pack inspection was reliable and formed a good basis for assessing adherence.

Adherence rate to the three day AL reported in this study was encouraging. The adherence levels correlate a similar study-assessing adherence to AL among children under the age of five in the same site.[28] However, the observed adherence rate may be an overestimation as it might have been attributed to several factors. First, in real healthcare delivery setups, there is no consenting as well as patients' follow-ups in the routine case management of malaria as provided for in the study. Second, the KNSCTM guidelines recommend that healthcare providers should explain the treatment regimen to their clients and its possible side effects; an aspect which was strongly emphasised in the study. Third, shortage of drugs is a major syndrome in public health institutions in third world countries Kenya inclusive.[31] Studies have shown that *a drug is out of stock* is a predictor of non-adherence.[29] However, the sampled health facilities had adequate stock of AL and thus none of the sampled patients missed out the AL.

With an exception of education level (OR<2), the study reported a strong association between patients' who perceived AL as ineffective, felt still sick in the course of treatment, or given aided supervision and adherence (OR>2). This implies that the true causes of adherence were identified using the employed study design. The perceived feeling of sickness in the course of taking the AL could have arose from the common side effects of the ACTs such as headache.[34] This might have brought about the feeling that the AL regimen was ineffective.

The role of a caretaker most often a family member in aided supervision further complicates adherence due fatalistic attitude about a treatment the caretaker brings with them in the drug administration. Studies have shown that, behavioural change communication interventions play an important role in promoting adherence.[35-37] Such initiatives may help increase adherence to AL and reduce the risk associated with the development of malaria parasite resistance. More specifically, healthcare providers need to educate malaria-ailing caretakers on the AL regimen as well as its possible side effects to promote adherence to the antimalarial at household level.

Conclusions

Patients educated to secondary level perceived that AL was ineffective, felt unwell during the course of medication and aided supervision factors significantly associated with non-adherence. The consents, follow-ups, strict adherence to the KNSCTM guidelines and availability of AL during the study may have influenced the observed high adherence rates.

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