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# [1]The Therapeutic Efficacy of Artemisinin Combination Therapy in Patients with Uncomplicated Malaria Attending Hasiya Bayero Paediatric Hospital in Kano, Nigeria

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**Abstract**
**Background:** Malaria is a major public health problem in sub-Saharan Africa accounting for about one hundred and ninety four million cases with Nigeria and contributing to twenty five percent of the total burden. Consequent to the wide spread of Chloroquine resistance, Artemisinin Combination Therapy (ACTs) was introduced for the treatment of uncomplicated malaria in in the country. **Aim:** This study was therefore designed to investigate the therapeutic efficacy of artemether lumefantrine among children with uncomplicated *P. falciparum* malaria in Kano state, Northwest Nigeria. **Methods**: The Artemether-lumefantrine (AL) therapeutic efficacy test was conducted at Hasiya Bayero Paediatric Hospital (HBPH), Kano state, Nigeria between August 2018 and April 2019. Children aged 6-60 months presenting symptoms of uncomplicated *P. falciparum* malaria were recruited. Parasitemia was assessed at days 0, 3, 14 and 28 for parasite density and PCR-genotyping was carried out to differentiate reinfection from recrudescence. Temperature and packed cell volume were also measured on follow up days. **Results**: A total of 200 patients were enrolled in the study and followed up for 28 days. The Day 28 PCR-uncorrected cure rate was 70.9% and the PCR-corrected cure rate 97.9%. Two cases of recrudescence were recorded, one early treatment failure (ETF) and one late treatment failure (LTF)] after merozoite surface protein-2(*MSP-2)* analysis. A significantly high rate of parasite clearance was recorded during study follow up while a significant decrease in fever over the protocol days was recorded in the subjects (P <0.05). The mean PCV also significantly increased from 26.27% to 30.31% at day 28 (P <0.05). **Conclusion**: A six-dose regimen of AL combination is still efficacious in the treatment of uncomplicated P. falciparum malaria in Nigerian under-five (U-5) children.

**Keywords:** *ACT, Efficacy, Uncomplicated-Malaria, Children*

[1] **Authors' contributions**: HA, AYM and NTD conceived and designed the study, AYM, NTD and BJ supervised the work. HA, YDJ, AIM participated in microscopy and molecular genetic analysis. HA, AA, KSB carried out data analysis and drafted the manuscript, BJ, AYM, NTD, MJG reviewed the manuscript and all authors read and approved the final manuscript.

## Introduction

Malaria still remains a disease of public health concern, about 228 million global malaria cases reported in 2018.Nineteen countries in sub-Saharan Africa and India carried almost 85% of the malaria burden with six countries accounting for more than half of all malaria case world-wide and Nigeria leading with 25% (WHO, 2019). The entire Nigerian population of >170 million is at risk of malaria, which is responsible for about 60% and 30% of outpatient visits and hospital admissions respectively and *P. falciparum* is responsible for 98% of malaria cases in the country (Muhammad et al., 2017). Artemisinin-based Combination Therapy (ACTs) are recommended by WHO as the first and second-line treatment for uncomplicated *P. falciparum* malaria.R ACT combines an artemisinin (ART) derivative with a partner drug. The role of the ART compound is to reduce the number of parasites during the first three days of treatment (reduction of parasite biomass), while the role of the partner drug is to eliminate the remaining parasites (cure) (Ajayi and Ukwaja, 2013; WHO, 2018). In 2005, Nigeria National Anti-malarial Treatment Policy (NNATP) adopted artemether-lumefantrine (AL) as the first-line drug for the treatment of uncomplicated malaria in Nigeria (Ayogu et al., 2015). Plasmodium resistance to anti-malarial medicine constitutes a major obstacle in the effort to control the disease (WHO, 2019). Artemisinin resistance in *Plasmodium falciparum* has emerged in Southeast Asia and has been reported from countries in sub-Saharan Africa but very little is known about the resistance status to ACTs of populations of *Plasmodium falciparum* in Nigeria. Mapping the geographic extent of resistance is essential for planning, containment and elimination strategies (Ashley et al., 2014). This study was therefore designed to investigate the therapeutic efficacy of artemether-lumefantrine among children with uncomplicated *P. falciparum* malaria in Kano state, Northwest Nigeria.

## Materials and Methods

**Study design:** This was a prospective cohort study conducted from August 2018 to April 2019 at HBPH Kano state.

**Study protocol:** Children with uncomplicated malaria, who met the study inclusion criteria as stipulated by the standard WHO efficacy study protocol was randomly selected and enrolled in the study (WHO, 2019). The subjects were treated with artemether-lumefantrine containing 20/120mg. The prescribed medicine was administered to the patients orally in a fixed-dose combination following the manufacturer's instructions. Each patient was then monitored for 28 days after seeking their consent. Parents/guardians were advised to administer dosage at home correctly and report if patients vomit, refuse to take the drug or any severe side effects. The follow-up consists of a fixed schedule (day 0, 3, 14 and 28) of check-up visits and corresponding clinical and laboratory examinations including the result from microscopy (parasite density). Based on the results of these assessments, the patients were classified as having therapeutic failure (i.e. early treatment failure, late clinical failure and late parasitological failure) or an adequate clinical and parasitological response (ACPR) (WHO, 2015). The proportion of the patients experiencing therapeutic failure during the follow-up was used to estimate the efficacy of the study drug.

**Study site:** Kano city is the capital of Kano state North-West Nigeria with a population of about 3,906,000 located at 11°30'N 8° 30'E and an area of about 20,131 km $^2$. The climate is tropical with an average annual rainfall of 884.4mm from June to September. The temperature is warm to hot throughout the year with a cool period (harmattan) between November to February. The vegetation is Sudan savannah and urban agriculture is very much in practice in this area (Tukur, 2010)[8]. Occupation of parents varies from small businesses, subsistent farming and in few cases civil servants.

**Sample Size Determination:** the sample size was determined using an appropriate statistical formula for estimating the minimum sample size in descriptive health studies. The number of patients included in this study was determined using the formula ($n = z^2 p q / d^2$) based on 5% proportion of treatment failure in the country and the desired levels of confidence (95%) and precision (5%) (WHO, 2009). The minimum sample size determined, including 20% attrition to cover for loss to follow up was rounded up to 200 in this study.

**Ethical approval and consent:** Ethical clearance was obtained from Kano State Ministry of Health and Aminu Kano Teaching Hospital (protocol numbers: MOH/OFF/797/T.I/679 and NHREC/21/08/2008/AKTH/EC/2299). Informed consent WAS obtained from parents/ guardians of all patients meeting the enrolment criteria.

**Study participants:** Participants were patients with uncomplicated malaria attending HBPH aged 6-60 months and with an axillary temperature of ≥37.5°C or a history of fever in the past 24 hours with *P.falciparum* count of 1,000–200,000 parasites/ L. Children were excluded if they presented with the following: severe P *falciparum* malaria documented intake of AL, or another antimalarial drug two weeks preceding enrolment, other causes of fever, evidence of underlying chronic diseases (cardiac, renal, hepatic, sickle cell disease and malnutrition), history of allergy to study drugs or known allergy to other antimalarial drugs, residence out of the study area, patient's parent/guardian unwillingness to provide written informed consent, and inability to take oral medication. Other exclusion criteria included; development of concomitant disease which would interfere with the classification of the treatment outcome (WHO, 2009). Questionnaires were given to obtain demographic data and clinical history of the participants that may be of importance to the study.

**Laboratory Procedures:** Two millilitres (2 mls) of venous blood was collected into EDTA tube and then mixed gently. The same amount was also collected on scheduled follow-up visits on days 3, 14, and 28 for parasite density and PCV. Microscopy was conducted at AKTH Microbiology laboratory. Both thick and thin blood smears were prepared and stained as described by WHO Protocol (WHO, 2015). The stained slides were examined under x100 oil immersion lens. Parasitaemia was calculated per 200 WBCs assuming 8000 WBC/µl blood Packed cell volume was estimated using a microhaematocrit centrifuge, and then read with a microhaematocrit reader and recorded in percentages. All samples were stored at -$20^0$C refrigeration.

**DNA extraction and Molecular genotyping (MSP-2):** Molecular study was conducted at the Nigeria Institute of Medical Research, Lagos. The *P falciparum* DNA was extracted from blood samples using the QIAGEN QI Amp DNA blood mini kit protocol ( Soulama et al., 2009) [11] and stored at -20 C. PCR genotyping of MSP-2 was carried out to amplify the block 3 of MSP-2 using the PCR conditions previously described (Mohammed et al., 2008; WHO, 2016). The following forward and reverse oligonucleotide primers sequences were used:

Msp2-1-F outer- ATG AAG GTA ATT AAA ACA TTG TCT ATT ATA;
Msp2-4-R-outer- ATA TGG CAA AAG ATA AAA CAA GTG TTG CTG
FC27-F- GCA AAT GGA GGT TCT AAT ACT AAT AG;
FC27-R- GCT TTG GGT CCT TCT ACT GGT GCT;
3D7-F- GCA GAA AGT AAG CCT TCT ACT GGT GCT;
3D7-R- GAT TTG TTT CGG CAT TAT TAT GA

The PCR products were analyzed by electrophoresis on 2% agarose gel stained with ethidium bromide and visualized in ultraviolet imager (UVP bio-imaging system,

New life Scientific). The sizes of the bands were estimated by visual inspection using the 100bp DNA ladder (Jena Bio-science, Germany) as a marker. The banding pattern of the post-treatment parasites was compared with matched primary parasites in each of the patients who had parasitaemia after treatment with AL. Post-treatment and primary infection parasites showing identical bands were considered true treatment failures, and non-identity band patterns were considered newly acquired infections.

**Statistical Analysis:** Data captured were entered into WHO template protocol for therapeutic efficacy studies which were then exported to SPSS version 20.0 for statistical analysis. The variables were summarized using descriptive statistics to compare clinical and biological parameters ( temperature, PCV and geometric mean parasitaemia). A difference in outcome measure was considered statistically significant when the value $\leq 0.05$. The sum of ETF, LCF and LPF gave the total treatment failure rate.

**Results:** A total of 200 children between 6-60 months participated in the study. The outcome of each phase of the research is summarized and illustrated in figure 1.

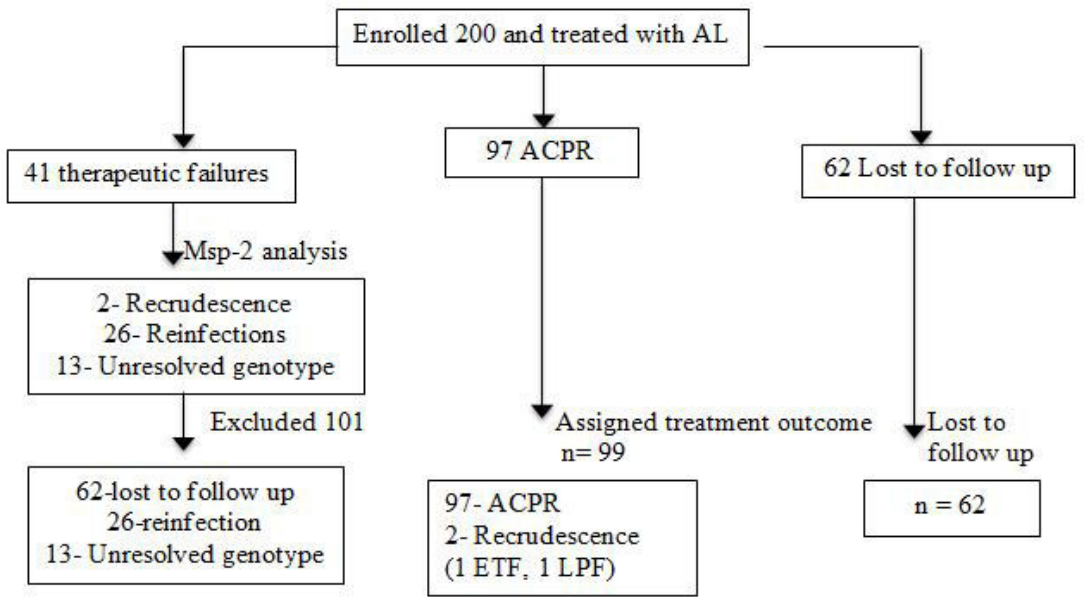


**Figure 1:** *Flow chart through the study*

The Baseline Characteristics of Study Participants Treated with AL include M/F ratio 1.3:1, having a mean age range of 35-48 months (with a median of 18 months). The mean temperature ($^0$c) was 37.7 ± 0.6, with PCV of 27.7± 9.1% and an average parasite density of 1.94x10$^4$microlitre.

**Primary Outcome**: The results of the treatment efficacy presented as PCR-uncorrected and PCR-corrected cure rates for the follow-up period and classification of treatment outcome before and after PCR adjustments on day 3, 14 and 28 were 97.6%, 82,1% and 70.9% respectively for PCR uncorrected while the PCR corrected for day 3, 14, and 28 were 97.4, 97.9 and 97.9% respectively.

**Table 1:** *Classification of Treatment Outcome on Day 28 with AL Treatment among Study Participants*

| PCR- STATUS | ACPR | ETF | LCF | LPF |
|---|---|---|---|---|
| PCR-Uncorrected | 97(70.9%) | 4(3.9%) | 18(13%) | 19(13.8%) |
| PCR- Corrected | 97(97.9%) | 1(1%) | 0(0%) | 1(1%) |

**Note**: PCR –polymerase chain reaction; ACPR- adequate clinical and parasitological response; ETF – early treatment failure; LCF- late clinical failure; LPF- late parasitological failure**.**

**Secondary Efficacy Outcome**

**Parasite clearance**: A statistically significant reduction in parasite was observed during the follow-up period (P <0.05). The mean parasitaemia on day 0 was about 20,000 parasites per microliter which significantly diminish to about 0 parasites per microliter on day 3, 14 and 28.

**Fever clearance:** On day 0, 80% of patients had presented with fever (pretreatment), this significantly decreases to about 17% on days 3 and 14 with further decrease to about 6% on day 28 of follow up.

**Packed cell volume**: Generally, there was a significant increase in the percentage of PCV with treatment (P <0.05), showing a mean increase from 26.27% at enrolment to 30.31% at day 28 (Fig 2).

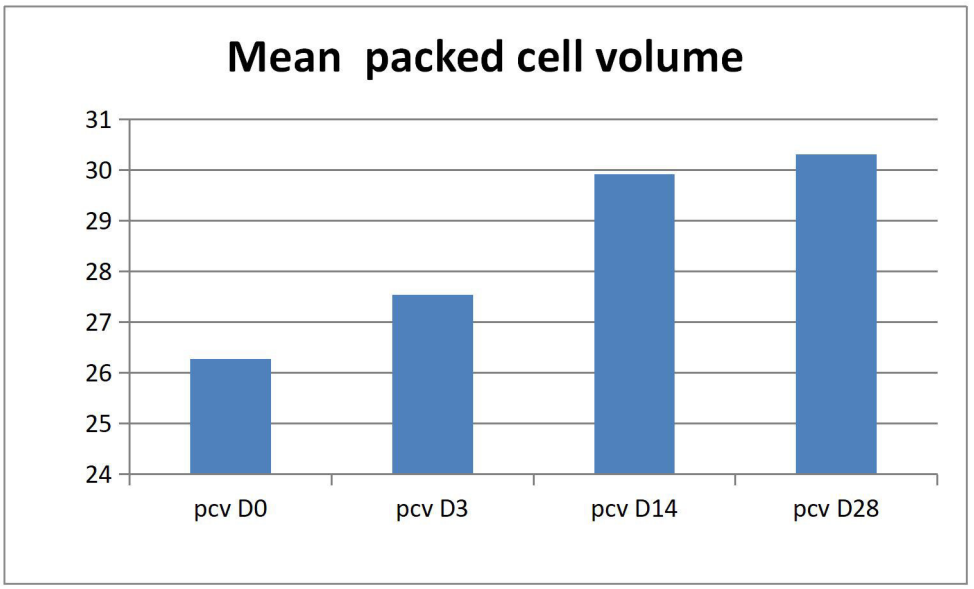


**Figure 2:** *Mean PCV in 28 Days Follow up*

**Discussion**

The results of this study showed high efficacy of AL among children visiting Hasiya Bayero Paediatric Hospital. The PCR-adjusted cure rate on day 28 was 97.9%, which was above the standard value of ≥ 90% as set by WHO (WHO, 2016 ). This high efficacy may be due to the high treatment compliance among the study participants as a result of deliberate health information and treatment counselling. Previous studies reported a close range of AL efficacy cure rates (Peko et al., 2019; Sowunmi et.al, 2016). However, some earlier studies in Nigeria reported lower cure rates of 87.0% and 90.9% in different regions of the country and this was attributed to poor compliance, drug adulteration and high cost of treatment( Djella et al 2014; Pulisinckin et al, 2015). High PCR -adjusted cure rates of 98% have been reported by Ali *et al* 2013 in Cameroon; Dorkenoo *et al. 2016* in Mali (96.6%); and Dama *et al*. 2018 (97%) in

Togo. This pattern of response to AL is supported by results of molecular epidemiologic studies conducted in Burkina Faso, Ghana, Niger and Benin which reported absence of ART-resistant *P. falciparum* strains in these countries Some et al 2016; Menard et al 2016; Tun et al 2015).

The presence of parasitemia on day 3 indicates recrudescence (drug failure) rather than reinfection (Gbotosho et al., 2011). However, in this study, only 1 out of the 4 crude PCR ETF was classified as true treatment failure (recrudescence) while the remaining 3 were considered as re-infections after PCR-adjustment. It is most probable for patients undergoing treatment to be bitten by an infected mosquito hence, acquire new infection due to the holo-endemicity of malaria in Nigeria, as well as the high entomological inoculation rate and the malaria transmission efficiency of *An. gambiae* the dominant vector species in the country (Yayo, et al., 2016)

Here we recorded two cases of recrudescence, 1 ETF and an LPF while Gbotosho et al (2011) and Plucinski et al. (2015) reported 3 and 8 cases respectively.

Also, eighteen children who had LCF in crude-PCR were classified as re-infection after PCR confirmation, and 19 LPF samples were all classified re-infections except one after PCR-adjustment. The results showed a significant high improvement in the secondary outcomes including parasite clearance, fever clearance and mean increment in PCV. The parasite clearance in this study was evaluated based on overall reduction of parasite load on each follow-up days. The mean parasite density decreased significantly from $1.94x10^4$ parasites/μL (day 0) to $4.1x10^1$parasites/μL (day 3) post-treatment. This huge difference in day 0 and day 3 parasitaemia levels affirms the rapid effect of ACT derivative in parasite clearance. Parasite clearance is the most robust measure of anti-malarial effect and is postulated to be a key component of resistance (Ojurongbe et al., 2013; White 2017) Subsequent follow up visits (days 14 and 28) mean parasitemia were $1.12x10^2$/μL and $1.01x10^2$/μL respectively. There were significant reductions in parasite load from day 0 through 14 to day 28 during the study follow-ups ($P<0.05$). Similar patterns in parasite clearance among Nigerian children and studies elsewhere have also been reported (Ali et.al., 2013; Oguche et al., 2014; Toure et al. 2018). In contrast, Ayogu *et al*. (2015) in Nigeria showed a high prevalence of delayed parasite clearance after initiation of AL therapy, suggesting emerging AL resistance in the study area, although they failed to differentiate recrudescence from re-infection. Also, studies from East Africa suggested that AL was more effective in East African regions compared to the West African regions (Ali et al., 2013; Michael et al., 2010) as corroborated by this study.

An axillary temperature of ≥ 37.5°C was used for the symptomatic diagnosis of malaria in children (Udo et al., 2013). About 80% of the subjects on day 0 had temperatures ≥ 37.5°C, this significantly decreased to 17% with fever on days 3 and 14 post-treatment and to 6% at day 28. There were significant decreases in the number of subjects with fever from day 0 to-day 28 ($P<0.05$). Subjects treated with AL showed high clinical responses, with majority cleared of fever by day 28. This high rate of fever clearance in this study correlates with the reports of clinical trials done elsewhere in Nigeria (Ayogu et al., 2015; Gbotsho et al., 2011).

Malaria is a major cause of anaemia in tropical areas. The infection causes hemolysis of infected and uninfected erythrocytes (White, 2018). The significant increase in mean PCV values (Fig 2) during the follow-up days 0, 3, 14 and 28 in the study (26.27%, 27.54%, 29.91% and 30.31% respectively) corresponds with the significant decline in parasitemia. It is assumed that ACTs may hasten recovery of malaria-associated anaemia from this endemic region as it was noted in this study, albeit complete haematological recovery often requires more than four weeks

in some malaria settings (Ali et al., 2013). Nevertheless, another study showed that failure of haematological recovery is not uncommon following ACT treatment in anaemic and non-anaemic subjects (Sowumi et al., 2016). However, AL treatment was well tolerated in this study as no serious adverse drug reactions were encountered.

**Conclusion:** A six-dose regimen of AL combination is still efficacious in the treatment of uncomplicated P. falciparum malaria in Nigerian under-five ( U-5) children. Health education and counselling should be organized appropriately to educate parents, guardians and health care workers. The use of preventive measures especially insecticide-treated bed nets and environmental sanitation should be advocated.

**Conflict of Interest**: Authors declare no potential

**Recommendation:** Use of ACT' based treatment in uncomplicated P. falcifarum malaria should be preceded by adequate health education and counselling

**Acknowledgement**: We are grateful to parents/guardians and children who participated in this study, Hasiya Bayero Paediatric Hospital, Aminu Kano Teaching Hospital microbiology laboratory staff and Nigeria Institute of Medical Research Lagos where the molecular analysis was carried out..

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