Artemisinin-based combination therapy amongst medical students in the University of Benin, South-South Nigeria: A cross-sectional study

Stephen Ayinbuomwan,[1,2] Abimbola Opadeyi,[1,2] Ambrose Isah[1,2]

[1]Clinical Pharmacology and Therapeutics Unit, Department of Medicine, University of Benin Teaching Hospital, Benin City; [2]Department of Clinical Pharmacology and Therapeutics, University of Benin, Benin City, Nigeria

Correspondence: Stephen Ayinbuomwan, Clinical Pharmacology and Therapeutics Unit, Department of Medicine, University of Benin Teaching Hospital, Benin City.
E-mail: stephen.ayinbuomwan@uniben.edu

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Abstract

Since 2005, the recommended first-line therapy for uncomplicated malaria in Nigeria has been Artemisinin-based Combination Therapy (ACT). Previous research indicates that these therapies are widely accepted by health care providers and other end users. Nonetheless, few studies have examined the preferences of clinical students who will be future prescribers of these medications. This was a descriptive cross-sectional survey of medical students undergoing clinical placements at the University of Benin Teaching Hospital in Benin City, Edo State, South-South Nigeria, to assess ACT preferences, tolerability, and cost considerations. Consenting clinical medical students who were recruited sequentially were given a semi-structured questionnaire. The questionnaire collected information about the students' demographics, previous episodes of malaria symptoms, diagnosis, and treatment. Their preferred antimalarial, tolerability to ACTs, and ACT cost. The information was presented descriptively. There were 475 registered clinical students, but only 416 agreed to participate in the survey, yielding an 87.6% response rate. The students' mean (standard deviation) age was 24.3 (3.8) years, with a male preponderance of 250 (60.1%). The majority, 154 (37.0%), were in the 600 level, while the 500 and 400 levels were 130 (31.3%) and 132 (31.7%), respectively. The majority of students, 272 (65.5%), treated malaria presumptively, and the majority of students, 344 (82.7%), had treated one to five episodes of malaria in the previous 12 months. The ACTs were known to nearly all of the final year clinical students (97.4%). The majority, 289 (69.5%), had no adverse drug reactions with the ACTs. Among those who experienced adverse drug reactions, 23 (39.7%) discontinued their medication, while 2 (3.4%) required hospitalization. The mean cost of the ACT was ₦1263.4 (SD ± 529.6) (₦=Naira) (3.0 USD), with a range of ₦ 300- ₦3000 (0.72-7.2 USD). This study demonstrates a high level of acceptance for ACTs, particularly artemether-lumefantrine. However, the adverse effects of ACTs, particularly other recommended ACTs, must be evaluated on a regular basis because they may have an impact on their continued use.

Introduction

Malaria is the most common parasitic infection in the world, and it remains a major public health challenge in the tropics, particularly in Sub-Saharan Africa. According to recent WHO reports, fifteen countries in Sub-Saharan Africa and India account for 80% of the global malaria burden. Nigeria and the Democratic Republic

of the Congo account for more than 35% of global annual malaria deaths. Nigeria is responsible for 25% of these cases, with more than 76% of the population reporting more than one case per 1,000 people.[1] Although malaria transmission is holo-endemic in a significant portion of Nigeria, the country's malaria endemicity varies.[2] When compared to other regions, the South-South region of Nigeria typically receives high amounts of rainfall, providing breeding sites for mosquitoes and encouraging high malaria transmission. Other factors that have been identified as playing significant roles in modifying malaria infestation transmission within the country include education level and economic status.[3]

Malaria control has traditionally relied on two main strategies: controlling anopheline mosquito vectors with insecticides and human barriers such as insecticide-treated bed nets, and using effective chemotherapy. Unfortunately, the emergence and spread of multi-drug resistant *Plasmodium falciparum* to available antimalarials slowed initial progress in many countries, resulting in a resurgence of malaria-related morbidity and mortality.[4] The emergence of antimalarial drug resistance has significantly contributed to the global resurgence of malaria in the last 30 years.[5,6] As a result of this development, the World Health Organization (WHO) advocated in 2001 for artemisinins to become an essential component of antimalarial treatment in countries experiencing antimalarial drug resistance. Since 2005, artemisinins have been the mainstay of malaria treatment. For uncomplicated malaria, they are administered as Artemisinin-based Combination Therapy (ACT) and as injectable monotherapy for severe malaria. Nigeria adopted Artemether-Lumefantrine (AL) as her preferred ACT for uncomplicated malaria in 2005, and injection Artesunate as her drug of choice for severe cases.[7]

The initial progress made in terms of global malaria case reduction was largely due to the adoption and massive scale-up of ACT, as well as other time-tested interventions such as Insecticide-Treated Nets (ITNs), Indoor Residual Spraying (IRS), and Intermittent Preventive Treatment (IPT). However, the global malaria burden has remained stable since 2015.[8,9] In response to this development, the WHO developed a Global technical strategy for malaria spanning 2016 to 2030, with the goal of controlling and eventually eliminating malaria in malaria-endemic countries. This strategy, which was updated in 2021,[10] aims for a 90% reduction in both malaria incidence and mortality rates; it also envisions malaria elimination in 35 endemic countries by 2030, as well as preventing a resurgence of malaria cases in malaria-free countries. Among the critical tools for achieving the aforementioned strategy are system strengthening, capacity building, and surveillance, particularly among prescribers.

Most antimalarial practice surveys have primarily focused on health care providers, prescribers, and non-medical students.[11-13] However, less focus has been placed on medical students, who will be the future prescribers. The undergraduate phase of medical education is critical for acquiring proper knowledge and developing appropriate attitudes toward current malaria treatment policies, with the ultimate goal of contributing to malaria control. Thus, developing studies that elaborate pertinent information on malaria case management and antimalarial drug use practice among clinical students who will be future prescribers may help to sustain current malaria control gains. As a result, we set out to assess medical students' antimalarial preferences, tolerability, and cost considerations for Artemisinin-based Combination Therapy (ACT) at the University of Benin Teaching Hospital.

Materials and Methods

This was a descriptive cross-sectional survey among medical students of the University of Benin undergoing their clinical posting at the University of Benin Teaching Hospital (UBTH), Benin City, Edo State, South-South Nigeria. This research was conducted between February 2021 and April 2021.

Study population

All medical students from 4th to 6th year undergoing their junior and senior postings in Clinical Pharmacology and Therapeutics, Pathology, Medicine, Surgery, Paediatrics, Obstetrics and Gynaecology, Mental Health and Community Health were invited to participate.

Study instrument

All students who agreed to participate in the study were given a pretested semi-structured questionnaire. Experts in Clinical Pharmacology and Therapeutics assessed the content validity, and face validity was also assessed. The questionnaire included sections that assessed the students' demographics, previous episodes of malaria symptoms, mode of diagnosis of malaria, previous treatment of malaria, antimalarial medication preferences, ACT preference, reasons for preferred ACT, tolerability to ACTs, and cost of ACTs.

Ethical considerations

Ethical approval was obtained from the institution's research and ethics committee and written informed consent was also obtained from all the participants. Students' information were kept securely and not shared with third parties.

Statistical Analysis

Data was initially entered into Microsoft Excel (2016) spread sheet and was then subjected to statistical analysis using the Statistical Programme for Social Sciences (Version 21, Chicago, USA). Data were presented descriptively using means and frequencies. Chi-square was used to test for associations, and choice of antimalarial was the dependent variable. A p value of less than 0.05 ($p < 0.05$) was considered to be statistically significant for all analyses.

Results

A total of 416 clinical students out of 475 agreed to participate in this survey, yielding an 87.6% response rate. The majority, 154 (37.0%), were in the 600 level, with 130 (31.3%) and 132 (31.7%) in the 500 and 400 levels, respectively. The students' mean (standard deviation) age was 24.3 (3.8) years. In this study, there were 250 men (60.1%). The majority of the students, 344 (82.7%), had malaria treatment between 1 and 5 times in the previous 12 months, with 7 (1.7%) having treated malaria at least ten times (Table 1). However, 40 (9.6%) had no history of malaria in the year preceding this study.

Fever was the most common presenting symptom, accounting for 352 (84.6%), followed by headache (257 (61.8%) and generalized weakness (229 (55.0%). Few students reported night sweats (10 (2.4%), abdominal pains (8 (1.9%), yellow urine (5.2%), cold sores (4.0%), and diarrhea (2.5%).

A large number of people, 272 (65.5%), were treated for malaria presumptively. Although this was highest with 109 (70.8%) of

final year clinical students, it was not statistically significant (p= 0.16). Aside from detecting malaria parasites in blood films, 85 (21.3%) of respondents had other tests such as Widal agglutination test 26 (6.0%), full blood count 8 (1.9%), urinalysis, COVID-19 screening, and blood glucose 2 (0.4%).

When compared to students at other levels, a significant number of final year clinical students, 108 (70.1%), volunteered to take antimalarials without recommendations, as shown in Table 1. Furthermore, 75 (18.0%) of the 167 (40.1%) medical students who received antimalarial recommendations came from doctors, 59 (14.2%) from pharmacists, 19 (4.6%) from nurses, 6 (1.4%) from friends, 4 (1.0%) from sellers, and 2 (0.5%) from media/tv advertisements. 382 (91.8%) of students obtained antimalaria medications over-the-counter (OTC) from pharmacies or chemists, while 27 (6.5%) obtained them from hospitals.

Table 2 displays the antimalarial preferences, awareness of ACT, and co-administered medications of UBTH clinical students. The respondents' preferred antimalarials were mostly those containing Artemether-Lumefantrine (AL) 265 (63.6%). Lonart (91.6%), Unbranded AL (65.6%), Coartem (54.0%), Amatem (47.3%), and other AL generics are among the AL combinations. To treat malaria, a few students preferred chloroquin, 4 (1.0%), sulphadoxime/pyrimethamine (Fansidar), 3 (0.7%), quinine, 1 (0.2%), or herbs, 1 (0.2%). Almost all of the final year clinical students, 150 (97.4%), were aware of the ACTs. The most common reasons given for their antimalarial preference were effectiveness 102 (24.5%), fast action 60 (14.4%), gel formulation 38 (9.1%), tolerability 23 (5.5%), low cost 17 (4.1%), availability 15 (3.6%), and WHO recommendation 13 (3.1%). However, 140 (33.7%) of respondents said the cost of the ACTs influenced their decision. The most commonly co-administered medicine was paracetamol (320 (76.9%), followed by antibiotics (138 (33.2%), multivitamins (88 (21.2%), and haematinics (34 (3.8%).

More than half of the respondents, 292 (70.0%), had no adverse drug reactions to the ACTs. The difference was statistically significant (p=0.001). Among those who experienced adverse drug reactions, 23 (39.7%) discontinued their medication, and 2 (3.4%) were hospitalized. (Table 3) Figure 1 depicts a bar chart of system disorders experienced by respondents as a result of adverse drug reactions. The most severely affected systems were gastrointestinal disorders (59.7%), general and administrative site disorders (15.4%), and nervous system disorders (6.0%).

The mean cost of the Artemisinin-based Combination Therapy (ACT) was ₦1,263.4 (SD ± 529.6) (₦=Naira) (3.0 USD), with a range of ₦ 300- ₦3000 (0.72- 7.2 USD), and a median of ₦ 1200 (IQR-700) (2.88 USD).

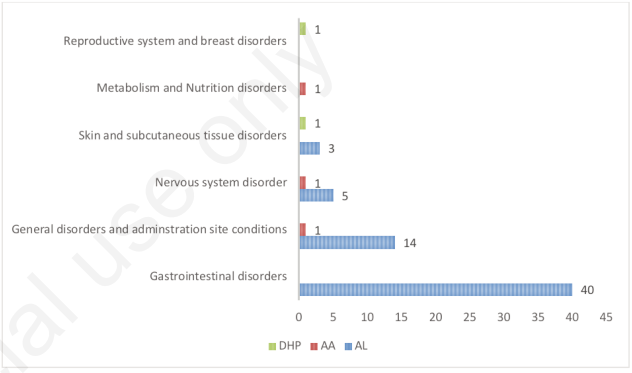

Figure 1. Bar chart showing systems mostly affected by adverse drug reactions to the ACTs among Clinical students in UBTH.

Table 1. Demographics and characteristics of malaria treatment among clinical students in UBTH (n = 416).

	Total	400L N=132	500L (n=130)	600L (n=154)	Chi square test	p-value
Sex						
Male	250(60.1)	78(59.1)	71(54.6)	101(65.6)	5.620	0.229
Female	165(39.7)	54(40.9)	59(45.4)	52(33.8)		
Missing	1(0.2)	0(0)	0(0)	1(0.6)		
Age						
Mean age(±SD)	24.3(3.8)	23.5(2.8)	22.7(3.2)	26.2(4.1)	40.235	<0.001
Frequency of treatment in the last year						
1-5 times	344(82.7)	101(76.5)	119(91.5)	124(80.5)	19.287	0.041
6-10 times	22(5.3)	7(5.3)	6(4.6)	9(5.8)		
Over 10 times	7(1.7)	2(1.5)	2(1.5)	3(1.9)		
No episode/	40(9.6)	20(15.2)	3(2.3)	17(11.0)		
No response	3(0.7)	2(1.5)	0(0.0)	1(0.6)		
Blood film for MP						
Yes	143(34.4)	46(34.8)	52(40.0)	45(29.2)	5.829	0.212
No	272(65.4)	85(64.4)	78(60.0)	109(70.8)		
No response	1(0.2)	1(0.8)	0(0)	0(0)		
Other investigations						
Yes	85(20.4)	26(19.7)	37(28.5)	22(14.3)	10.710	0.030
No	315(75.7)	100(75.8)	91(70.0)	124(80.5)		
No response	16(3.8)	6(4.5)	2(1.5)	8(5.2)		
Self - medication for malaria						
Yes	245(58.9)	79(59.8)	58(44.6)	108(70.1)	20.149	<0.001
No	167(40.1)	52(39.4)	71(54.6)	44(28.6)		
No response	4(1.0)	1(0.8)	1(0.8)	2(1.3)		

MP: Malaria Parasite.

Discussion

From 2001 to 2013, the dramatic progress made in combating the threat of malaria infestation, particularly in Sub-Saharan Africa, was based primarily on targeted interventions and significant investment in several malaria control measures, including appropriate malaria case management.[14,15] Some of the consequences of inappropriate malaria treatment on the populace include increased cases of treatment failure, the emergence of anti-malarial drug resistance, delayed parasite clearance, increased morbidity and mortality, and increased treatment costs.

This study discovered that clinical students were well-versed in the ACTs. This was especially evident in the final year clinical class, where only one student claimed to be unaware of the ACTs. Furthermore, the ACT of choice among respondents was the Artemether/Lumefantrine (AL) combination, as recommended by

Table 2. Antimalarial preferences, Awareness of ACT (Generic and Brand), and co-administered medications of Clinical students in UBTH.

	Total (n = 416)	400L	500L	600L	Chi-square	P value
Preferred antimalarial						
Unspecified ACT	36(8.7)	4(3.0)	1(0.8)	31(20.1)	129.824	0.000
Artemether-Lumenfatrine (generic)	65(15.6)	24(18.2)	6(4.6)	35(22.7)		
Amatem (AL)	47(11.3)	12(9.1)	26(20.0)	9(5.8)		
Any antimalarial	11(2.6)	1(0.8)	5(3.8)	5(3.2)		
Artemether	16(3.8)	6(4.5)	8(6.2)	2(1.3)		
Artemisinin	1(0.2)	0(0)	1(0.8)	0(0)		
Artequin (AA)	2(0.5)	0(0)	1(0.8)	1(0.8)		
Artesunate	15(3.6)	3(2.3)	8(6.2)	4(2.6)		
Camosunate (AA)	2(0.5)	2(1.5)	0(0)	0(0)		
Chloroquine	4(1.0)	3(2.3)	1(0.8)	0(0)		
Augmentin	2(0.5)	1(0.8)	1(0.8)	0(0)		
Coartem (AL)	54(13.0)	19(14.4)	13(10.0)	22(14.3)		
Combisunate (AL)	2(0.5)	0(0)	1(0.8)	1(0.6)		
Fansidar	3(0.7)	0(0)	1(0.8)	2(1.3)		
Grether (AL)	1(0.2)	1(0.8)	0(0)	0(0)		
Herbs	1(0.2)	1(0.8)	0(0)	0(0)		
Lokmal (AL)	5(1.2)	1(0.8)	1(0.8)	3(1.9)		
Lonart (AL)	90(21.6)	31(23.5)	32(24.6)	27(17.5)		
Lumapil (AL)	1(0.2)	0(0)	1(0.8)	0(0)		
P-alaxin (DHP)	10(2.4)	3(2.3)	3(2.3)	4(2.6)		
Paracetamol	3(0.7)	3(2.3)	0(0)	0(0)		
Quinine	1(0.2)	1(0.8)	0(0)	0(0)		
No response	44(10.6)	16(12.1)	20(15.4)	8(5.2)		
Have you heard of the ACTs?						
Yes	295(70.9)	79(59.8)	66(50.8)	150(97.4)	88.490	<0.001
No	109(26.2)	49(37.1)	59(45.4)	1(0.6)		
No response	12(2.9)	4(3.0)	5(3.8)	3(1.9)		
Choice of ACTs over non- ACT						
Yes	274 (65.9)	70(53.0)	68(52.3)	136(88.3)	57.099	0.000
No	15 (3.6)	8(6.1)	4(3.1)	3(1.9)		
No response	127 (30.5)	54(40.9)	58(44.6)	15(9.7)		
Does cost influence your choice of ACTs?						
Yes	140 (33.7)	39(29.5)	30(23.1)	71(46.1)	41.429	<0.001
No	180 (43.3)	48(36.4)	60(46.2)	72(46.8)		
No response	96(23.1)	45(34.1)	40(30.8)	11(7.1)		

AA: Artesunate-Amodiaquine, ACT: Artemisinin-based Combination Therapy, AL: Artemether-Lumenfatrine, DHP: DihydroArtemisinin- Piperaquine.

Table 3. Tolerability of ACTs among Clinical students in UBTH.

Characteristics	Total	400	500L	600L	Chi square	p-value
Any Adverse drug reaction with ACTs?						
Yes	58(13.9)	21(15.9)	7(5.4)	30(19.5)	34.424	0.000
No	289(69.5)	80(60.6)	92(70.8)	117(76.0)		
No response	69(16.6)	31(23.5)	31(23.8)	7(4.5)		
Any discontinuation of ACTs following Adverse Drug Reactions?						
Yes	23(39.7)	11(52.4)	2(28.6)	10(33.3)	2.273	0.321
No	35(60.3)	10(47.6)	5(71.4)	20(66.7)		
Any Hospitalization following Adverse Drug Reactions?						
Yes	2(3.4)	1(4.8)	0(0)	1(3.3)	0.360	0.835
No	56(96.6)	20(95.2)	7(100.0)	29(96.7)		

ACT: Artemisinin-based Combination Therapy, UBTH: University of Benin Teaching Hospital.

the National Antimalarial Policy. Artemether/Lumefantrine (AL), also known as Coartem, Amartem, Combisunate, and Lokmal, is the first fixed-dose to meet the WHO prequalification criteria for efficacy, safety, and quality.[16,17] It is also the most widely used ACT antimalarial treatment in Sub-Saharan Africa, including Nigeria, as the first-line treatment for uncomplicated falciparum malaria.[7] An earlier study conducted at the University of Calabar by Iwuafor *et al.*[18] discovered a lower ACT preference of 60.3% among medical students. This could be because the survey only included fourth-year clinical students, who may not have been exposed to various aspects of therapeutics and treatment guidelines at this level of training. Respondents in this study chose ACTs as the mainstay of uncomplicated malaria therapy, which is not surprising given that these medicines have eventually become both first and second-line treatments in most malaria-endemic countries.[19] These drugs are unique in their ability to significantly reduce parasite biomass, to resolve clinical symptoms quickly, to be effective against multidrug resistant *P. falciparum*, and to have gametocidal activity.

The high presumptive malaria treatment, self-medication, and frequent consumption of ACTs in this study are consistent with previous findings.[20-21] Presumptive malaria treatment increases the likelihood of overdiagnosis and ACT use. Furthermore, medical knowledge has been identified as a significant factor that may influence student self-medication.[22] As a result of this advancement, studies comparing self-medication among medical and non-medical students have been developed.[23-24] These findings support previous findings that self-medication was more common among medical and pharmacy students than other undergraduates. These factors may have played a significant role in the emergence and spread of antimalarial resistance, as seen during the chloroquine era, when chloroquine was the cornerstone of malaria treatment for decades. According to studies, artemisinin resistance is spreading throughout the Greater Mekong subregion[25] and resistance to some of the recommended ACTs is emerging in Asia.[26] There is currently a risk that ACT resistance will spread into Africa, similar to how chloroquine resistance spread into Africa from South-East Asia.

A significant number of participants in this study had no Adverse Drug Reaction (ADR) with the ACTs. Clinical trials involving artemisinin and its derivatives in various parts of the world have suggested that artemisinin derivatives have fewer major toxicities than other available antimalarial drugs,[27] but with frequent consumption of the ACTs, the half-life of the partner drugs in the combination may be prolonged, increasing the likelihood of drug-drug interactions with the potential for adverse drug reactions. Previous research has highlighted AL's tolerability profile when compared to other ACTs.[28-30] In this study, the ADRs associated with the ACTs were mostly gastrointestinal and general symptoms, which may be difficult to distinguish from the symptomatology of underlying malaria episodes. This finding was also supported by previous research.[31-32]

In this study, the average cost of ACTs was 1263.4 (SD 529.6; 3.0 USD). This had a significant impact on the type of ACT that respondents purchased. In 2015, Yakassi *et al.*[33] discovered that people with lower socioeconomic status were less likely to adhere to ACTs, as opposed to cheaper antimalarials such as chloroquine and sulphadoxine-pyrimethamine, which were 20 times less expensive. Furthermore, the high cost of the ACTs may contribute to students' unwillingness to perform a confirmatory diagnosis, as recommended by the National Antimalaria Treatment Policy.[7] This is because light microscopy, which uses blood films to diagnose malaria, is still considered expensive and thus a potential barrier to the current WHO malaria case management guidelines.[34] Nonetheless, despite its limitations, the Rapid Diagnostic Test (RDT) is increasingly being recommended as a cost-effective diagnostic tool.[35]

Conclusions

This study found that artemisinin-based combination therapy with artemether/lumefantine was widely accepted as the drug of choice for treating uncomplicated malaria. However, the respondents' frequent use of ACTs, which may have been encouraged by the high presumptive malaria treatment and self-medication practice, is a major challenge that requires immediate attention in order to promote adherence to current antimalarial guidelines while reducing the risk of drug resistance and adverse drug reactions associated with their use. Furthermore, because individuals bear the majority of healthcare costs in Nigeria, there is a need to address the high cost of ACTs in order to discourage people from switching to cheaper and less effective antimalarials. Finally, the significance of appropriate clinical student training in current disease management guidelines cannot be overstated. Incorporating clinical guidelines into medical curricula is a critical component in influencing health-care decision-making.

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