

Community Perception of Antimalarial-Associated Weakness

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ARTICLE INFO

Article history:

Received 30th April 2026

Revised 22nd September 2026

Accepted 26th September 2026

Keywords:

Malaria,
Antimalarial therapy,
side effect,
Weakness,
Asthenia,
Nigeria

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ABSTRACT

Background: Weakness (asthenia) is frequently reported by patients following antimalarial treatment. However, the prevalence and pattern of perceived antimalarial-associated weakness in the community, as well as its potential influence on subsequent antimalarial use, remain poorly evaluated. We assessed the occurrence of weakness attributed to antimalarial therapy among adults and explored its effect on treatment-related decisions.

Methods: A cross-sectional survey using a structured questionnaire was conducted among adults aged 18–60 years with a history of malaria episodes and previous use of antimalarial therapy. Participants were randomly recruited from three population groups in Ibadan, southwest Nigeria: traders at a marketplace, undergraduate students in a university community, and medical doctors at a tertiary hospital. The questionnaire assessed participants' history of malaria and antimalarial treatment, experience of weakness following antimalarial therapy, perceived severity of weakness, treatment discontinuation, and the effect of the experience on subsequent choices of antimalarial medications.

Results: A total of 330 adults participated in the study, comprising 110 traders, 110 undergraduate students, and 110 medical doctors. There were 202 males and 128 females. Overall, 239 (72.4%) participants reported experiencing weakness that they attributed to antimalarial therapy. The reported prevalence was 66.4% among traders, 77.3% among students, and 73.6% among medical doctors. Weakness was attributed to all formulations of antimalarial therapies. Among participants reporting weakness, the experience was perceived as mild to moderate in 82.1%. One hundred and eighty-nine (84.8%) reported that the experience of weakness had resulted in discontinuation of antimalarial therapy. Furthermore, 73 (32.7%) reported avoiding the antimalarial regimen they suspected had caused weakness when subsequently purchasing antimalarial medications.

Conclusion: Perceived antimalarial-associated weakness was highly prevalent among adults surveyed across community, university, and healthcare settings in Ibadan. The experience may adversely affect adherence to antimalarial therapy and influence subsequent treatment choices. Further studies are warranted to better characterize antimalarial-associated weakness, identify contributing factors, and determine its implications for malaria treatment adherence and effectiveness.

Introduction

Malaria remains a major global public health challenge, with the greatest burden occurring in sub-Saharan Africa, which accounted for approximately 94% of global malaria cases and 95% of malaria deaths in 2024. Globally, an estimated 282 million malaria cases and 610,000 deaths occurred in 2024, underscoring the continuing need for

effective case management and access to safe, efficacious antimalarial medicines¹. Effective antimalarial treatment is central to malaria control, and artemisinin-based combination therapies (ACTs) remain the recommended first-line treatment for uncomplicated *Plasmodium falciparum* malaria because of their rapid parasite clearance and high therapeutic efficacy². ACTs combine an

artemisinin derivative, such as artemether, artesunate, or dihydroartemisinin, with a longer-acting partner drug, with the artemisinin component rapidly reducing parasite biomass during the initial days of treatment and the partner drug eliminating residual parasites^{2,3}.

Current WHO recommendations require ACT regimens to provide three days of treatment, with dosing selected to achieve adequate drug exposure and maximize clinical and parasitological cure while minimizing the risk of treatment failure and drug resistance². Although ACTs have contributed substantially to the successful treatment of malaria and remain highly effective in many endemic settings, their continued effectiveness depends on appropriate dosing, adherence, drug quality, and preservation of antimalarial susceptibility^{2,4}. Consequently, assessment of antimalarial therapy extends beyond parasitological efficacy to include tolerability and drug safety. Adverse effects experienced during or following treatment may influence patients' willingness to complete therapy, perceptions of treatment, subsequent medication choices, and ultimately the effectiveness of malaria case management. Understanding patients' experiences of antimalarial-associated adverse effects is therefore important for optimizing the safe and effective use of these essential medicines.

Weakness is a known, but under-reported, adverse effect of many medications, including antimalarial therapies. Occasionally, after taking prescribed antimalarial medications, patients have reported experiencing different grades of physical debility and lack of energy (asthenia)⁵. There are anecdotal reports of this experience, with claims that the experience is disturbing. While this complaint is reported in clinical trials⁶, community studies on the perceptions of different populations regarding antimalarial-associated weakness are scarce. In the assessment of adverse events, many clinical trials do not routinely evaluate the pattern, grade, and effect of weakness as an adverse event due to antimalarial therapies. In addition, it remains to be fully evaluated how the experience of weakness attributable to the use of antimalarial therapies affects compliance and choice of antimalarial regimens.

A 2014 report of a cohort-event monitoring study describing the profile of adverse events in patients receiving treatment for malaria in urban Ghana showed that the most commonly reported event was asthenia, often described by patients as 'weakness' or 'generalized weakness', which was reported by 10.1% of those evaluated⁷. The investigators also noted that the adverse

event was reported more frequently in patients prescribed Artesunate-Amodiaquine combination (ASAQ) and was also more associated with females than with males. In an open-label trial of three dosage regimens of a fixed-dose combination of artemisinin and naphthoquinone in Calabar, Nigeria, weakness was the most commonly reported adverse effect in up to 14% of the study participants⁸. A systematic review of different artemisinin-based combination therapies in children reported that artemether lumefantrine (AL) treated children had a higher risk of body weakness (64.9%) than those on artesunate-mefloquine (58.2%)⁹. In all these studies, details of the nature of the weakness were not described.

Our study, reported here, was conducted to evaluate the perceptions of three groups of participants in the community with regard to weakness that they attributed to antimalarial therapies. The major objective of the study was to characterize the experienced weakness attributed to the use of antimalarial therapies.

Methods

Study site and groups: The survey was conducted at three purposively selected sites in Ibadan, Oyo State, southwestern Nigeria, representing community, university, and tertiary healthcare settings. The first site was Agbowo, a densely populated commercial and residential community located directly opposite the University of Ibadan main campus, where traders and other members of the surrounding community were recruited. The second site was the University of Ibadan community, where undergraduate students were recruited. The third site was the University College Hospital (UCH), a major tertiary teaching hospital affiliated with the University of Ibadan, where medical doctors were recruited. These sites were selected to capture participants from different sociodemographic and occupational backgrounds and to provide perspectives on experiences with antimalarial therapy across community, academic, and healthcare settings. The study was conducted from March to September, 2016. A pre-tested, structured questionnaire was used to obtain data at the sites selected for the study. Adults aged 18 - 60 years, with a history of past episodes of malaria infection and use of antimalarial therapy, were interviewed at three selected sites. The three sites selected for the study were a university community, a busy marketplace, and a tertiary hospital in southwest Nigeria. Prospective participants were informed of the project and assured that their personal details would be protected. Every aspect of the study, the definition and grades of antimalarial-associated weakness, and the questionnaire were thoroughly explained to prospective participants.

Individuals who agreed to participate went ahead to fill out the questionnaire under the guidance of the investigators. Inclusion to participate in the study was based on their meeting the age range (18 - 60 years) and previous use of antimalarial therapy.

Study groups: Three groups of participants were interviewed:

Group 1 - Traders who were interviewed at a popular market in southwest Nigeria. This group was selected to cover a good cross-section of adults living in the community and representing those of low economic status.

Group 2 - Students (undergraduates) of a tertiary institution in southwest Nigeria. The students were enrolled and interviewed on campus at random.

Group 3 - Medical Doctors at a teaching hospital in southwest Nigeria. These were doctors who attend to patients and the outpatients' clinics of the hospital. They were randomly selected with no restriction to sub-specialty. This group was included because of their knowledge of malaria treatment, antimalarial therapies, and side effects of antimalarial therapies.

Study Questionnaire: A twenty-item questionnaire was generated and pre-tested on a small population of randomly selected adults. The questionnaire evaluated past episodes of malaria, past antimalarial treatment, experience of weakness following antimalarial treatment, and how the experience of weakness has affected their choice of antimalarial medications. During the study, the questionnaire was explained in detail to all participants. Literate participants were allowed to fill the questionnaire without much assistance. The questionnaire was explained in Yoruba, the local language, to those who could not read. They filled the questionnaires with assistance from the study team.

Evaluation of Nature and Grade of weakness: The questionnaire assessed the nature of weakness experienced by the participants. Antimalarial-associated weakness (Asthenia) was defined as a general weakness of the body, lethargy, or listlessness, which commenced after the ingestion of antimalarial medication(s), and which the individual attributes to the ingestion of antimalarial therapy. Participants were asked to describe regions of the body affected by the weakness, effect on daily activities, duration, severity of the weakness, and how they were affected by the weakness. Participants were asked to grade their experience of weakness on a scale of zero to ten, with zero representing no weakness and ten representing the inability to move. On this scale, weakness was graded as

mild when the score was 1 – 3 (not really bothered by weakness), moderate for scores of 4 – 6 (weak, affected usual daily activities but did not discontinue medication), and severe for scores of 7 – 10 (could not move around or conduct daily activities).

Data Analysis: The data were entered and analyzed using Statistical Package for the Social Sciences version 17 (SPSS Inc, Chicago, IL, USA). Data obtained during the study were categorical. Proportions and frequencies were generated for relevant variables.

Ethical Considerations: This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. All participants were provided with comprehensive information about the study objectives, procedures, and their rights as participants. Informed consent was obtained from each participant to inclusion in the study. Participation was entirely voluntary, and participants were assured of their right to withdraw at any stage without any consequences. To ensure privacy and confidentiality, data were anonymized, and no personal identifiers were collected or stored. The completed questionnaires were securely stored, and access was restricted to authorized research personnel. Additionally, the study posed minimal risk to participants, as the survey was based solely on their retrospective accounts and did not involve any invasive procedures. This study involved the collection and analysis of anonymized, non-identifiable information. No clinical intervention was administered and no personally identifiable participant information was retained in the study dataset. Participant confidentiality was maintained throughout the study. Formal Institutional Review Board/Research Ethics Committee approval was not obtained prior to study commencement, which was an oversight by the research team. We acknowledge the absence of prior formal ethical review as a limitation of the study. The study was conducted with attention to the principles of confidentiality, respect for persons and responsible use of human participant information, consistent with the ethical principles of the Declaration of Helsinki.

Results

Study population: The study was conducted from March to September, 2016. Three hundred and thirty (330) adults agreed to participate and were interviewed. Each group comprised 110 adults. In the three groups (Traders, Students, and Medical Doctors): 202 males (61.2%) and 128 females (38.8%). For the groups of traders, students, and doctors, the male-to-female ratios were 65:45, 69:41,

and 68:42, respectively. All the participants had taken antimalarial therapy in the past. The five most commonly used antimalarial therapies for the treatment of acute malaria episodes mentioned by the respondents were Artemether–lumefantrine, Amodiaquine-Artesunate, Sulphadoxine-Pyrimethamine, Artemether injection, and Chloroquine (Table 1).

Participants' experience of antimalarial-associated weakness: All participants stated that they used antimalarial therapies during past episodes of malaria infection. All participants also responded to the question on whether they had experienced antimalarial-associated weakness. Ninety-one (91/330, 27.6%) participant responded that they did not experience weakness attributed to their use of any antimalarial therapy. Two hundred and thirty-nine participants (239/330, 72.4%) reported that they had experienced weakness which they attributed to the antimalarial therapy. Among them, 73 (66.4%) of traders, 85 (77.3%) of students, and 81 (73.6%) of medical doctors responded that they had experienced antimalarial-associated weakness. Not all participants responded to other questions on details of the weakness they experienced. Sixteen of the 239 (16/239, 6.7%) participants could not recollect details of the weakness; the other participants (223) were able to describe the experience.

Antimalarial-associated weakness sub-analysis was done on the 223 participants who could recollect details of the weakness. The majority of respondents said the weakness was generalized and affected the entire body. Respondents also described the duration of the weakness. The majority (211/223, 94.6 %) stated that the experience of weakness lasted from one to three days before complete resolution. The antimalarial therapies mentioned by respondents believed to be responsible for weakness were Artemether-lumefantrine, Amodiaquine-artesunate, Sulphadoxine-pyrimethamine, Chloroquine, and amodiaquine. These results are shown in tables two and three.

Grades of antimalarial-associated weakness: Participants graded their experience of weakness attributed to antimalarial therapy. Thirty five participants (35/223, 15.7%) stated that the weakness was mild, one hundred and forty-eight (148/223, 66.4 %) stated that the weakness was moderate, while forty participants (40/223, 17.9 %) stated that the weakness was severe. Among the traders, fourteen (14/67, 20.9%), thirty-nine (39/67, 58.2%), and fourteen (14/67, 20.9%) graded the experience as mild, moderate, and severe, respectively; fifty-six (56/67, 83.6%) of them responded that the experience led to their discontinuing the

antimalarial therapy. Among the students, thirteen (13/80, 16.3%), fifty-four (54/80, 67.6%), and thirteen (13/80, 16.3%) graded the experience as mild, moderate, and severe, respectively; seventy-one (71/80, 88.8%) of them responded that the experience led to their discontinuing the antimalarial therapy. Among the medical doctors, eight (8/76, 10.5%), fifty-five (55/76, 72.4%), and thirteen (13/76, 17.1%) graded the experience as mild, moderate, and severe, respectively; sixty-two (62/76, 81.64%) of them responded that the experience led to their discontinuation of the antimalarial therapy before completion. Overall, on whether the experience of weakness led to discontinuation of antimalarial therapy, one hundred and eighty-nine participants (189/223, 84.8%) answered yes while thirty-four (34/223, 15.2 %) said no.

Experience of antimalarial weakness and choice of therapy: Participants responded how the experience of weakness affected their choices of antimalarial therapy during subsequent episodes of malaria infection. Seventy-three participants (73/223, 32.7%) stated that the experience of weakness made them avoid the antimalarial therapy suspected to have caused the weakness during subsequent purchases of antimalarial therapies; sixty-seven (67/223, 30.1%) and eighty-three (83/223, 37.2%) answered no and not sure, respectively.

Willingness to use Antimalarials perceived as causing weakness for subsequent malaria episodes: participants responded to the question of their willingness to continue using antimalarials perceived to be responsible for weakness during subsequent episodes of malaria. Analysis of responses from the three groups showed that among the traders, 25 (37.3%), 16 (24.6%), and 26 (38.5%) responded yes, no, and not sure, respectively. Among the students, 20 (25.0%), 34 (42.5%), and 36 (32.5%) responded yes, no, and not sure, respectively. Among the medical doctors, 38 (50%), 25 (32.9%), and 13 (17.1%) responded yes, no, and not sure, respectively.

Table 1: Demographic characteristics and five most preferred antimalarial therapies of the three groups evaluated

	Group 1 Traders	Group 2 Students	Group 3 Medical Doctors
Number of participants	110	110	110
Male: Female ratio	65:45	69:41	68:42
Proportion that are male (%)	59	62.7	61.8
Age range (years)	18 – 60	18 – 60	18 – 60
Number that provided responses on antimalarial-associated weakness	110	110	110
Number that responded that they had experienced antimalarial-associated weakness (n, %)	73 (66.4)	85 (77.3)	81 (73.6)
Number (%) that described their experience of antimalarial-associated weakness	67	80	76
Five most commonly used antimalarial therapies	n (%)	n (%)	n (%)
Artemether – lumefantrine	72 (65.5)	102 (92.7)	102 (92.7)
Amodiaquine-Artesunate	33 (30)	29 (26.4)	41 (37.3)
Sulphadoxine-Pyrimethamine	12 (10.9)	10 (9.1)	23 (20.9)
Artemether- injection	20 (18.2)	25 (22.7)	27 (24.5)
Chloroquine	33 (30)	25 (22.7)	49 (44.5)

Table 2: Frequency of weakness perceived to be associated with specific antimalarial therapies.

	Traders n = 67 (%)	Students n = 80 (%)	Medical Doctors n = 76 (%)	Total N = 223
Artemether-lumefantrine	24 (35.8)	48 (60)	16 (21.1)	88 (39.5)
Amodiaquine-artesunate	18 (26.9)	17 (21.3)	24 (31.6)	59 (26.5)
Sulphadoxine-pyrimethamine	10 (14.9)	10 (12.5)	13 (17.1)	33 (14.8)
Chloroquine	12 (17.1)	4 (5)	10 (13.2)	26 (11.7)
Amodiaquine	3 (4.5)	1 (1.6)	13 (17.1)	17 (7.6)

Table 3: Duration of experience of antimalarial-associated weakness reported by study participants

Duration (Days)	Traders	Students	Medical Doctors	Total n (%)
< 1	15	23	30	68 (30.5)
1 – 2	22	29	26	77 (34.5)
> 2 – 3	26	27	13	66 (29.6)
> 3 – 7	3	1	7	11 (4.9)
> 7	1	0	0	1 (0.5)
Total	67	80	76	223

Discussion

In this community-based survey of 330 adults across three distinct groups in southwest Nigeria, a substantial majority (72.4%) reported having experienced weakness that they personally attributed to antimalarial therapy. This perception was common across all three groups, though it was somewhat more frequently reported by students (77.3%) and medical doctors (73.6%) than by traders (66.4%). Among those who described their experience in detail, weakness was predominantly mild-to-moderate (82.1%) and self-limiting, resolving within one to three days in the large majority of cases (94.6%). Notably, the behavioral consequences were substantial: 84.8% of affected participants reported discontinuing antimalarial therapy because of the perceived weakness, and about one-third (32.7%) said the experience led them to avoid the suspected regimen on subsequent purchases. Willingness to reuse a regimen associated with prior weakness varied markedly by group, being highest among medical doctors (50%) and lowest among students (25%), which may reflect differences in health literacy, risk tolerance, or access to alternative regimens. Weakness was attributed to all major antimalarial classes in use, including artemether-lumefantrine and amodiaquine-artesunate, the two most commonly used regimens in our cohort.

In pharmacovigilance terminology, an adverse event (AE) is any untoward medical occurrence temporally associated with drug use, regardless of whether a causal relationship is established, whereas an adverse drug reaction (ADR) implies a suspected or established causal link between the drug and the event, typically assessed using structured causality tools (e.g., WHO-UMC criteria or the Naranjo scale) within clinically monitored settings. Our study measured neither in the strict pharmacovigilance sense. Rather, we captured self-attributed, retrospectively recalled weakness - that is, what community members themselves believed, often long after the exposure, to be linked to antimalarial use. This is a distinct and complementary data type: it reflects lay perception and its behavioral consequences (non-adherence, treatment-avoidance), rather than a clinically verified safety signal.

While antimalarial drugs are generally safe and effective, some antimalarials have side effects such as nausea, vomiting, abdominal pain, headache, dizziness, malaise, body pain, diarrhea, cough, fever, skin rash, itching, and body weakness¹⁰. While these side effects are usually mild, they can be disturbing and may affect adherence to therapy. More recently, growing concern over emerging artemisinin partial resistance in parts of East Africa has renewed

international attention on the durability of current ACT-based treatment policy, and on the need to safeguard adherence to existing first-line regimens while alternatives are developed⁴. A Nigerian pharmacovigilance surveillance study similarly found that weakness and fatigue were significantly more frequent among patients on artesunate-amodiaquine than artemether-lumefantrine, reinforcing that regimen-specific differences in perceived weakness are not confined to our study population¹¹.

Reports of the incidence and nature of antimalarial-associated side effects, to an extent, are available. In a study on travelers using malaria chemoprophylaxis, Hoebe, de Munter and Thijs in 1997¹² reported that the use of Mefloquine was associated with side effects which included depression, dizziness and itching. They also reported that adverse effects of proguanil included dizziness and nausea. They added that the adverse effects were mostly mild to moderate and occurred mainly during the time the travelers they evaluated were abroad. On whether the side effects were linked with adherence, they reported that 22% of mefloquine users were non-compliant, while 35% of proguanil users were non-compliant. They explained that adverse effects experienced were the most often reported reason for mefloquine users to stop or even not to start taking the drug. In a study on leading causes of methotrexate and antimalarial drug discontinuation in Iranian patients with rheumatoid arthritis, Bita Anvari in 2016¹³, reported that among 271 patients who received antimalarial agents (chloroquine and hydroxychloroquine), 41.3% discontinued treatment. He stated that 51.3% of drug withdrawals were because of ophthalmological consultations and the presence of retinopathy, macular pigmentation, and keratopathy. However, there was no report of persistent or serious ocular complication such as blindness. The author stated that ocular toxicity (which occurred in 41.3 % of those who took chloroquine and hydroxychloroquine) was the major reason for discontinuation of therapy. In 2017, Diallo and colleagues in Burkina Faso¹⁴ conducted a cross-sectional study that explored spontaneous reporting of adverse effects of antimalarial drugs sent to the pharmacovigilance center from January 1, 2009 to December 31, 2013. They reported that the artemisinin-based combination therapies (ACTs) were used in 77.8% of the reports evaluated. The authors stated that several categories of adverse effects were observed, including skin and annexes disorders (34.6%), disorders of general health conditions (29.8%), central nervous system disorders (29.8%), and gastro-enterological disorders (23.0%). The authors added that most of the adverse effects were mild (67.3%).

Despite reports of antimalarial-related side effects, Peto, in a review article on toxicities of antimalarial drugs, concluded that there are very few reliable data on the frequency of serious adverse effects with antimalarial drugs¹⁰. He added that such data are very difficult to obtain and will never be available for newly marketed drugs. He advised that great caution should be exercised before new drugs are recommended for widespread use by routine travelers who may have only a low risk of death from malaria without chemoprophylaxis. To date, studies continue to show that side effects of antimalarial therapies deserve attention whenever and wherever they occur. Many side effects that are experienced by users of the medications are mild and transient. A side effect of antimalarial drugs that remains relatively under-reported is weakness.

In a longitudinal, single-blind, randomized clinical trial of children conducted by Catherine Maiteki-Sebuguzi and colleagues to determine the safety and tolerability of combination antimalarial therapies for uncomplicated falciparum malaria in Ugandan children¹⁵, weakness was a major adverse event experienced by the study participants. The authors reported that during the first 14 days after therapy, a total of 2,496 adverse events, defined as any untoward medical occurrence, irrespective of suspected relationship to study medications, were detected. They stated that most of the events were mild, 1747 (70%), while 749 (30%) were of moderate or greater severity. Weakness constituted 93 (23.5%), 89 (24.6%), and 47 (13.0%) of adverse events in those who received amodiaquine plus sulphadoxine-pyrimethamine, artesunate plus amodiaquine, and artemether-lumefantrine, respectively. There are no detailed reports of the characteristics of weakness associated with the use of antimalarial therapies. While malaria remains prevalent in malaria-endemic countries, there remains the need to conduct epidemiological and mechanistic, well-controlled studies on the complaints of antimalarial-related weakness. In the same vein, the pathophysiological mechanisms underlying weakness associated with antimalarial therapy remain largely unknown and poorly investigated.

Weakness (asthenia) has been reported in other disease conditions. In a review article on Asthenia in Patients with Advanced Cancer by Eduardo Bruera and R. Neil MacDonald published in 1988¹⁶, the authors stated that the asthenia syndrome is clearly multi-causal and that in most cases the cause of asthenia remains undetermined. They also stated that most of the evidence suggests that the cancer itself, and not other contributing factors, was the principal cause of asthenia. They concluded that the underlying mechanism for the syndrome remains unknown. Brotto et

al in their review of effects of malaria infection on skeletal and cardiac muscle activity^{17, 18} concluded that malaria in humans leads to muscle weakness and muscle fatigue, with demonstrable biochemical and structural changes. There are other reports of detrimental effects of malaria on cardiac and skeletal muscles^{19, 20}. The reports suggest that malaria may be associated with cardiac complications and considerable morbidity. However, the effects of antimalarial therapies on the function and structure of skeletal and cardiac muscles remain largely unexplored.

It is imperative to state that the study, being questionnaire based, has limitations. Participants might have provided inaccurate or biased information, either unintentionally (due to memory issues, i.e., recall bias, particularly since some participants were reporting on episodes that occurred some time before the survey) or intentionally (to present themselves in a favorable light). They may also have provided responses they perceive as socially acceptable rather than reflecting their true opinions or behaviors. In addition, there may be difficulty in separating weakness caused by the malaria infection itself from that attributable to antimalarial therapy, as our design could not disentangle the two. This study also did not include a control group of individuals who had malaria but did not attribute weakness to treatment, or of antimalarial users without a preceding malaria episode; the absence of such a comparison group limits our ability to estimate the true incremental contribution of antimalarial therapy to the weakness reported, beyond what would be expected from malaria illness alone. These limitations may introduce bias at different levels of participants' responses to the questions and constrain causal interpretation of our findings. Despite these limitations, the results suggest that weakness due to malaria therapy plays a significant role in treatment choices and outcomes and that there is a justifiable need for more studies on weakness attributed to antimalarial therapy - ideally using prospective, controlled designs capable of distinguishing drug effect from disease effect.

Conclusion

In conclusion, side effects of antimalarial therapies are common. Weakness appears to be an adverse effect that, though common, has received little attention. The adverse effect affects adherence to therapy and may be a factor that affects the choice of antimalarial therapy. This concern is not merely historical: ACTs remain the WHO-recommended first- and second-line treatment for uncomplicated *P. falciparum* malaria, and their continued effectiveness is central to global malaria control efforts even as artemisinin partial resistance emerges in some

regions. In this context, poor tolerability that undermines adherence to current first-line regimens carries policy-relevant consequences, potentially contributing to incomplete treatment courses, treatment-seeking delays, and pressure toward drug switching or self-directed regimen changes - all of which have implications for both individual outcomes and the broader effort to preserve ACT efficacy. More studies on antimalarial therapies and associated weakness are required, particularly prospective and mechanistic studies; there is also a need to explore the pathogenesis of antimalarial-related weakness and to incorporate structured assessment of this adverse effect into routine pharmacovigilance for current ACT regimens.

Conflict of interest declaration

Authors have no conflict of interest to declare.

Acknowledgements

We are grateful to the participants who generously contributed their time and insights into the study.

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