ISSN: 2754-4516

Journal of Medicine and Healthcare

SCIENTIFIC Research and Community

Research Article

Open Access

Treatment Adherence to Uncomplicated and Complicated Malaria Therapy in Two Villages of the Rural Commune of Kobiri, Mali

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ABSTRACT

Background: The adoption of Artemisinin-based Combination Therapies (ACTs) for malaria treatment in Mali has been challenged by reports of side effects potentially affecting patient adherence. This study assessed the adherence rate and its determinants to anti-malarial treatments, particularly Artesunate-Amodiaquine (AS-AQ), in two rural health centers in Mali.

Methods: A prospective observational study was conducted from April to September 2009 in the health centers of Diagala and Kobiri. Patients diagnosed with uncomplicated or complicated malaria based on clinical suspicion or Rapid Diagnostic Test (RDT) were included. Adherence was assessed during intermediate (JI) and day 7 (J7) visits. A good adherence threshold was set at >90%.

Results: Among 448 enrolled patients, the median age was 3 years, with 65.2% being children under five. AS-AQ was the most prescribed treatment (97%). The overall adherence rate for AS-AQ was 92.5% (95% CI: 89.6-94.8). However, adherence was significantly higher in children under 15 (94.4%) compared to those aged 15 and above (80%, p<0.001). The main reasons for non-adherence were side effects (55.2%) and misunderstanding of prescription instructions (27.6%).

Conclusion: While overall adherence to AS-AQ was satisfactory and above the 90% threshold, a significant adherence gap exists among adults. Side effects and comprehension issues are primary drivers of non-adherence. Targeted communication strategies for adults, improved patient education, and sustained quality assurance of medicines are recommended to optimize malaria treatment outcomes.

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Received: November 15, 2025; **Accepted:** November 20, 2025; **Published:** November 27, 2025

Keywords: Malaria, Adherence, Artemisinin-based Combination Therapy (ACT), Artesunate-Amodiaquine (AS-AQ), Mali, Rural Health

Abbreviations

ACT: Artemisinin-based Combination Therapy / Combinaison Thérapeutique à base d'Artémisinine (CTA)
AS-AQ: Artesunate-Amodiaquine / Artésunate-Amodiaquine
CI: Confidence Interval / Intervalle de Confiance (IC)
CSCOM: Centre de Santé Communautaire / Community Health Center
DEAP: Département d'Épidémiologie des Affections Parasitaires
FCFA: Franc de la Communauté Financière Africaine
FMPOS: Faculté de Médecine, de Pharmacie et d'Odonto-Stomatologie
JI: Jour Intermédiaire / Intermediate Day
J0: Jour Zéro / Day Zero (premier jour de consultation)
J7: Jour Sept / Day Seven (septième jour de consultation)
MRTC: Malaria Research and Training Center
MSF: Médecins Sans Frontières / Doctors Without Borders
PNLP: Programme National de Lutte contre le Paludisme / National Malaria Control Program
RDT: Rapid Diagnostic Test / Test de Diagnostic Rapide (TDR)
SP: Sulfadoxine-Pyrimethamine / Sulfadoxine-Pyriméthamine
USTTB: Université des Sciences, des Techniques et des Technologies de Bamako
WHO: World Health Organization / Organisation Mondiale de la Santé (OMS)

Introduction

Malaria remains a major public health challenge in sub-Saharan Africa. In Mali, it is the leading cause of morbidity and mortality, accounting for 37.5% of outpatient consultations [1]. Faced with increasing resistance of Plasmodium falciparum to conventional monotherapies like chloroquine and sulfadoxine-pyrimethamine (SP), the World Health Organization (WHO) recommended the use of Artemisinin-based Combination Therapies (ACTs) for uncomplicated malaria [2,3]. In 2007, Mali officially adopted ACTs, with Artesunate-Amodiaquine (AS-AQ) and Artemether-Lumefantrine being the first-line treatments. Therapeutic adherence is crucial for treatment efficacy, prevention of recrudescence, and delaying drug resistance. WHO defines adherence as "the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a healthcare provider" [4]. For chronic diseases, adherence rates in developing countries are often below 50% [4]. For malaria, a good adherence level is considered to be above 90% [5,6]. Following the large-scale deployment of AS-AQ in Mali, numerous patient complaints were reported, including dizziness, headaches, digestive disorders, and somnolence, linked to the high pill burden (e.g., 8 tablets/day for 3 days for adults). These factors were suspected to negatively impact adherence

[7,8]. This study, derived from a medical doctoral thesis, aimed to evaluate the adherence rate and identify the determinants of non-adherence to anti-malarial treatments, both uncomplicated and complicated, in the rural communes of Kobiri and Diagala in the Kita district of Mali.

Methods

Study Design and Setting

A prospective observational study was conducted over six months (April to September 2009) to cover the high malaria transmission season. The study took place in two health centers : the Community Health Center (CSCOM) of Kobiri and the health post of Diagala, in the rural commune of Kobiri, Kayes Region, Mali. This area is characterized by a sudano-guinean climate with seasonal malaria transmission (4-6 months per year).

Methods (Revised Version with Sample size Calculation)

Study Design and Setting

A prospective observational study was conducted over six months (April to September 2009) to cover the high malaria transmission season. The study took place in two health centers: the Community Health Center (CSCOM) of Kobiri and the health post of Diagala, in the rural commune of Kobiri, Kayes Region, Mali. This area is characterized by a sudano-guinean climate with seasonal malaria transmission (4-6 months per year).

Sample Size Calculation

The sample size was calculated using the single proportion formula for an infinite population: $n = (Z^2 \times p \times q) / i^2$, where $Z = 1.96$ for a 95% confidence level, $p = 0.90$ for the expected adherence rate, $q = 0.10$, and $i = 0.03$ for the desired precision. The calculation yielded $n = (1.96^2 \times 0.90 \times 0.10) / 0.03^2 = 384.11$, rounded to 385 participants. Accounting for an anticipated 15% loss to follow-up, the adjusted sample size was 385 / 0.85 = 453 participants. The study successfully enrolled 448 patients, meeting the minimum statistical requirements.

Study Population and Selection Criteria

The study included all patients presenting at the health centers who received anti-malarial treatment for suspected uncomplicated or complicated malaria. Diagnosis was based on clinical signs and/or a positive Rapid Diagnostic Test (RDT Paracheck®) when available.

- **Inclusion Criteria:** All patients with suspected uncomplicated or complicated malaria receiving treatment at the involved health centers.
- **Exclusion Criteria:** Patients who refused follow-up or were lost to view.

Data Collection and Variables

Data were collected using a standardized survey form at three time points: the initial consultation day (J0), an intermediate visit (JI), and a follow-up visit on day 7 (J7). Collected data included:

- Socio-demographic characteristics (age, sex, education, occupation)
- Clinical symptoms
- Prescribed anti-malarial treatment and its cost
- Treatment adherence and reasons for non-adherence
- Adverse events and complaints post-treatment

Assessment of Adherence

Adherence was assessed at JI and J7 by asking patients or their guardians if the treatment had been administered as prescribed. A patient was considered "adherent" if the treatment was taken completely and correctly as per the prescription. Good adherence was defined as a rate >90%.

Data Analysis

Data were entered using Microsoft Access and analyzed with SPSS version 12.0. Descriptive statistics (frequencies, proportions, means) were used. Adherence rates were calculated with 95% confidence intervals. The Chi-square or Fisher's exact test was used to compare proportions. A p-value < 0.05 was considered statistically significant.

Ethical Considerations

Verbal consent was obtained from all patients or their guardians. The study was part of the routine activities of the health centers. Patient confidentiality was maintained, and data were anonymized. The study protocol was approved by the Ethics Committee of the FMPOS.

Results

Socio-Demographic and Clinical Characteristics

A total of 448 patients were included. The median age was 3 years, with 65.2% (n=292) being children under 5 years. Males represented 58.5% of the cohort. Uncomplicated malaria accounted for 91.5% of cases. Fever (99.8%) was the most common presenting symptom (Table 1).

Table 1: Baseline Characteristics of Study Participants (n=448)

Characteristic	n	%	95% CI
Age Group			
0 - 4 years	292	65.2	60.6-69.5
5 - 14 years	88	19.6	16.1-23.6
≥ 15 years	68	15.2	12.1-18.8
Sex			
Male	262	58.5	53.8-63.0
Female	186	41.5	37.0-46.2
Malaria Form			
Uncomplicated	410	91.5	88.6-93.8
Complicated	38	8.5	6.2-11.4
Presenting Symptoms			
Fever	447	99.8	98.8-100
Chills	276	61.6	56.9-66.1
Muscle pain	177	39.5	35.0-44.2
Vomiting	169	37.7	33.3-42.3
Lack of appetite	148	33.0	28.7-37.6

Prescribed Treatments and Costs

AS-AQ was the most prescribed anti-malarial, representing 97% (95% CI: 94.9-98.3) of treatments when including relay therapy. Treatment was provided free of charge in 73.7% (95% CI: 69.3-77.7) of cases, primarily for children under five. For the 118 paying patients, the average cost of treatment was 2012 FCFA (approx. 3.7 USD).

Treatment Adherence and Associated Factors

The overall adherence rate for AS-AQ was 92.5% (396/428; 95% CI: 89.6-94.8). Adherence was significantly higher at J7 (95.4%;

95% CI: 93.0-97.1) than at JI (65.7%; 95% CI: 47.8-80.9, p < 0.0001). A significant difference in adherence was observed by age group (Table 2).

Table 2: Adherence to AS-AQ by Age Group

Age Group	Good Adherence, n (%)	95% CI	Total
0 - 4 years	274 (94.8%)	91.6-97.1	289
5 - 14 years	78 (92.9%)	85.1-97.3	84
≥ 15 years	44 (80.0%)	67.0-89.6	55
Total	396 (92.5%)	89.6-94.8	428

Post-Treatment Complaints and Reason for Non-Adherence
For the 29 non-adherent patients to AS-AQ, the main reasons cited were side effects (55.2%; 95% CI: 35.7-73.6) and misunderstanding of prescription instructions (27.6%; 95% CI: 12.7-47.2) (Table 3).

Table 3: Reasons for Non-Adherence to Anti-Malarial Treatments

Reason for Non-Adherence	AS-AQ (n=29)	%	95% CI
Side Effects	16	55.2	35.7-73.6
Misunderstanding of Prescription	8	27.6	12.7-47.2
High Pill Burden	2	6.9	0.8-22.8
Perceived Worsening of Illness	1	3.4	0.1-17.8
Other Reasons	2	6.9	0.8-22.8

Willingness to Reuse Treatment and Post-Treatment Symptoms
Of the 428 patients treated with AS-AQ, 9.8% (95% CI: 7.2-13.1) stated they would not use the same treatment again if they had malaria in the future. Post-treatment symptoms analysis showed increased reports of somnolence (14.5%; 95% CI: 11.3-18.2 vs 0.5% at baseline) among AS-AQ users (Table 4).

Table 4: Post-Treatment Complaints by Anti-Malarial Treatment

Reason for Non-Adherence	AS-AQ (n=29)	%	95% CI
Side Effects	16	55.2	35.7-73.6
Misunderstanding of Prescription	8	27.6	12.7-47.2
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Perceived Worsening of Illness	1	3.4	0.1-17.8
Other Reasons	2	6.9	0.8-22.8

Discussion

This prospective study conducted in rural Mali reveals an overall satisfactory adherence rate of 92.5% (95% CI: 89.6-94.8) for AS-AQ treatment, exceeding the 90% threshold considered optimal for clinical trials [5, 6]. This result is higher than those reported in other African contexts, particularly in Malawi where a study found only 73% adherence [9], and in Uganda where the adherence rate reached only 77% [12]. The significant difference in adherence between children under 15 years (94.4%) and adults (80.0%; p=0.000) constitutes the most striking result of our study. This 14.4 percentage point gap probably reflects better treatment supervision by parents in children, as well as greater tolerance to side effects in this population. Several studies have indeed demonstrated that therapeutic adherence is generally better in pediatrics, where medications are administered under parental control [13,14].

Side effects, cited by 55.2% (95% CI: 35.7-73.6) of non-adherent patients, appear as the main determinant of non-adherence. Somnolence, whose prevalence increased by 11.4% after treatment, represents a particularly problematic adverse effect for active adults. These results are consistent with those of studies conducted in Senegal and Kenya, where ACT side effects were identified as the primary cause of premature treatment discontinuation [15,16].

Misunderstanding of dosage instructions, mentioned by 27.6% (95% CI: 12.7-47.2) of non-adherent patients, highlights communication deficits between healthcare providers and patients. This rate is significantly higher than that observed in Malawi (9%) [9], suggesting the need to adapt educational messages to the local socio-cultural context. Previous studies have shown that using visual aids and repeating instructions significantly improve treatment understanding [17,18].

Free treatment for 73.7% (95% CI: 69.3-77.7) of patients, mainly children under five, probably contributed to the good overall adherence rates. Several studies have demonstrated that removing financial barriers improves access to care and therapeutic adherence in low-income countries [19,20]. However, our study reveals that 9.8% (95% CI: 7.2-13.1) of patients would not want to reuse AS-AQ in case of new malaria episode, signaling a potential risk of future non-adherence. The post-treatment symptom profile, characterized by persistence of vomiting/nausea (23.7%; 95% CI: 19.8-28.0) and emergence of somnolence (14.5%; 95% CI: 11.3-18.2), underscores the importance of strengthening pharmacovigilance in malaria control programs. These observations are consistent with literature data concerning AS-AQ's tolerance profile [21,22].

Our study also confirms the feasibility of using RDTs in rural African settings, as previously demonstrated in other contexts [23,24]. Using these tests could help rationalize ACT prescription and reduce resistance development [25,26]. The predominance of uncomplicated malaria (91.5%; 95% CI: 88.6-93.8) in our sample reflects the usual epidemiological profile of the disease in endemic areas [27,28]. The strong representation of children under 5 years (65.2%; 95% CI: 60.6-69.5) corresponds to the population most vulnerable to malaria in sub-Saharan Africa [29,30]. The main limitations of this study include the absence of systematic parasitological confirmation by blood smear, adherence collection by patient declaration potentially leading to desirability bias, and the absence of quality control of medications used.

Conclusion

Our study demonstrates that adherence to AS-AQ treatment in rural Mali is generally satisfactory but masks important disparities according to age. Interventions aimed at improving adherence should particularly target the adult population, emphasizing better management of side effects and adapted communication concerning therapeutic instructions. Strengthening pharmacovigilance and guaranteeing medication quality are also essential to maintain ACT effectiveness in malaria control.

Conflict of Interest Statement: The authors declare no conflicts of interest related to this work.

Annex 1 : Data Collection Form
Survey Form - Study Of Anti-Malarial Treatment Adherence

A) D0 : First Consultation Day
- Patient identification
- Clinical signs
- Diagnosis retained
- Prescribed treatment
- Treatment cost
- RDT result (if available)

B) Ji : Intermediate Day
- Treatment adherence
- Complaints and side effects
- Feeling of evolution

C) D7 : Seventh Day
- Final adherence
- Residual complaints
- Feeling of cure
- Willingness to reuse the same treatment

Acknowledgements
The authors thank the staff of the Diagala and Kobiri health centers, the study participants, and Médecins Sans Frontières (MSF) for their support. Special thanks to the Diagala Mali Association and all supervisors and colleagues from the Malaria Research and Training Center (MRTC) and the Department of Epidemiology of Parasitic Diseases (DEAP). This work was carried out as part of a medical doctoral thesis defended at FMPOS in Bamako.

Funding
This study did not benefit from specific external funding. Material support was provided by Médecins Sans Frontières (MSF) and the Diagala Mali Association.

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